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The Biocompatibility Challenges in the Total Artificial Heart Evolution

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Abstract

There are limited therapeutic options for final treatment of end-stage heart failure. Among them, implantation of a total artificial heart (TAH) is an acceptable strategy when suitable donors are not available. TAH development began in the 1930s, followed by a dramatic evolution of the actuation mechanisms operating the mechanical pumps. Nevertheless, the performance of TAHs has not yet been optimized, mainly because of the low biocompatibility of the blood-contacting surfaces. Low hemocompatibility, calcification, and sensitivity to infections seriously affect the success of TAHs. These unsolved issues have led to the withdrawal of many prototypes during preclinical phases of testing. This review offers a comprehensive analysis of the pathophysiological events that may occur in the materials that compose TAHs developed to date. In addition, this review illustrates bioengineering strategies to prevent these events and describes the most significant steps toward the achievement of a fully biocompatible TAH.

Contents

1. INTRODUCTION

Heart failure (HF) is a complex clinical condition that impairs the heart's function as a pump. It is associated with a wide spectrum of symptoms, sometimes nonspecific, and may result from any cardiovascular disease. The incidence of HF in the developed world is around 900,000 new cases per year and has recently increased significantly, even in developing countries. A recent estimation of HF prevalence (1) predicted a dramatic increase of 46% between 2012 and 2030, due to population aging and survival of patients with both cardiac and noncardiac pathologies.

Unfortunately, HF prognosis remains poor, despite advances in medical therapy, and a diffuse culture of prevention and donation has slightly improved the rate of overall survival. HF is a high-mortality disease: The rate of survival 1 year after diagnosis is around 50% and decreases dramatically at 5 years (2, 3). Moreover, HF has a large economic impact due to direct medical costs, such as long-lasting hospitalizations and subsequent readmissions. For these reasons, new targeted strategies, whose costs can be amortized by savings from conventional medical therapies, are urgently required (4).

At present, cardiac transplantation is the only definitive solution for refractory end-stage HF. However, the use of this well-established surgical procedure is limited by organ shortage, mortality associated with increasing waitlist time, and adverse effects of lifelong immunosuppressive therapies.

The urgent need for alternative treatments for the failing heart has led physicians to collaborate with engineers in an ambitious scientific project. Ventricular support and whole replacement of the biological heart with mechanical pumps, namely ventricular-assisted devices (VADs) and total artificial hearts (TAHs), have the potential to increase patient survival and quality of life (5). In recent years, these devices have proved their feasibility. At present, 80 years after the first reported TAH implantation in an animal model (6) and almost 50 years after the first human implantation

(7), the number of implanted pumps is increasing as both a bridge to transplantation (BTT) and a destination therapy (DT) (8).

The use of circulatory mechanical supports inevitably has some disadvantages. Although TAHs have evolved to include several prototypes and countless attempts at advancement, there has been no significant technological breakthrough since the 1980s. Advances in this field practically ceased for more than 20 years, resulting in only one TAH currently approved for clinical use. The main drawbacks are related to pump geometry (i.e., dimensions, fitting, weight), power supply (i.e., drivelines and noise, battery duration), and physiological (i.e., cardiac output, stroke volume, adaptation of venous return) and biological factors.

Despite impressive recent progress in medical and material sciences, the nature and progression of blood–material interactions are still not completely predictable. Blood pumps can give rise to several concerns regarding blood compatibility (e.g., hemorrhages, hemolysis, thrombosis, thromboembolism), calcification, and infections that, depending on their site, extent, and severity, can cause the device to fail. The goal of this review is to discuss these issues and the strategies applied to date in order to design more effective and affordable TAH prototypes.

2. BLOOD COMPATIBILITY: CATASTROPHE OR ILL-POSED PROBLEM?

2.1. The Problem of Hemocompatibility

For all materials intended for use in blood-contacting applications, such as TAHs, VADs, vascular substitutes, heart valves, oxygenators, catheters, and many others, blood compatibility is the most important requirement. Blood compatibility does not simply mean the absence of hemolysis, platelet activation, consumption of blood cellular components and plasma coagulation factors, and activation of coagulation pathways. It is also involved in complement activation and immune response (9–12). Furthermore, complete knowledge of the phenomenon requires integration with principles of structural (13) and chemical (14, 15) properties, biological behavior of the interfacing surfaces, and flow dynamics (16), as well as the design of the whole device. Indeed, adoption of hemocompatible materials does not automatically entail blood compatibility of the entire device.

Blood–biomaterial interactions are very complex and can be regulated by different mechanisms that lead to a precise sequence of events. The first consequence is protein adsorption controlled by the Vroman effect (17), a competitive process in which molecular dimensions, concentration, and surface affinity play a key role (18). Subsequently, the adsorbed protein layer activates the intrinsic pathway of coagulation (platelet activation, coagulation, fibrinolysis) and complement that will influence both short- and long-term outcomes.

The only surface known to be fully blood compatible is the natural healthy endothelium lining the lumen of the blood and lymphatic vessels. This continuous monolayer, made up of endothelial cells (ECs), constitutes a smooth barrier between the bloodstream and the luminal surfaces, with few exceptions. The natural endothelium plays an active role as both anti- and prothrombogenic layer (19). ECs directly regulate the expression of binding sites and the release of anticoagulant or procoagulant factors on their surface (20). Furthermore, vascular endothelium is negatively charged, just like the blood elements that are electrostatically repulsed.

Studies on blood compatibility date to the 1960s. By 1981, the inherent drawbacks of implantable devices had already become clear, but the difficulties of overcoming them made the experimental studies not fully satisfactory (21). In 1993, Ratner (22) described the interaction between biomaterials and blood as a "catastrophe," an observation based on the lack of general agreement regarding definition, proving tests, and certified blood-compatible materials. More

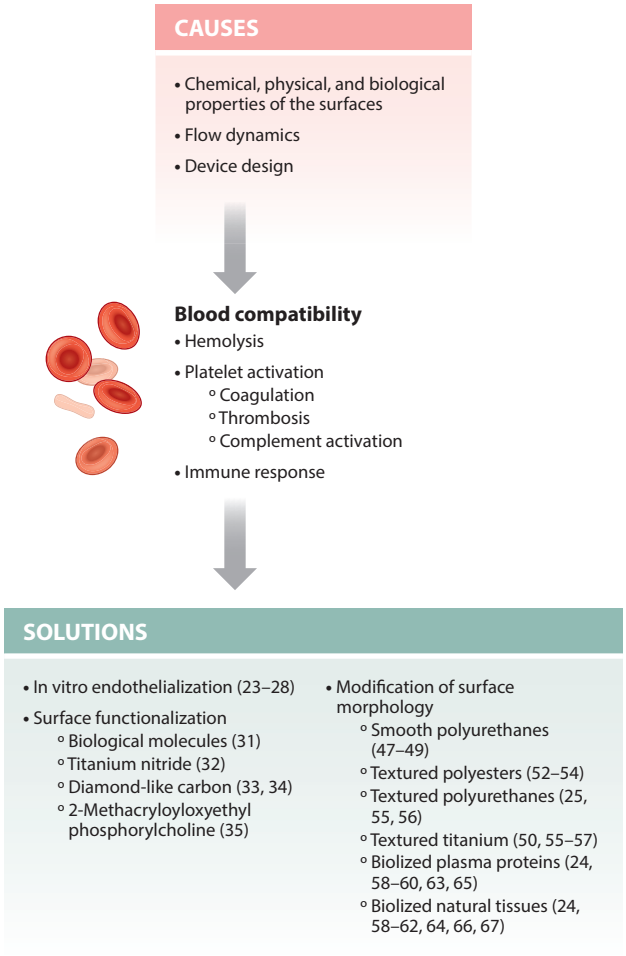

Figure 1

Factors contributing to blood compatibility in total artificial hearts and strategies to improve it.

than 20 years later, despite recent progress in biomedical science and the number of devices needed each year for blood-interfacing implants, the quest for blood compatibility remains an open issue.

2.2. Strategies to Improve Blood Compatibility

Figure 1 illustrates the factors contributing to blood compatibility in TAHs and possible strategies to improve it.

2.2.1. Endothelialization. The goal of research on novel biomaterials intended for blood-contacting use has always been to reproduce the innate properties of living endothelium or to induce formation of the so-called natural pseudoendocardium or pseudoneointima (PNI) (23, 24). The formation of PNI on the luminal surface of TAHs is influenced by surface properties, flow conditions, and relative position between the natural tissue and the device itself (24); this is the first possible solution to the challenge of enhancing the blood compatibility of both short- and long-term implants, although the potential detachment of a not-well-stabilized layer might cause embolic events. The possibility of seeding cells onto the internal surfaces of blood pumps prior

to their implantation has also been investigated. However, doubts have been raised regarding immunological compatibility between the donor and recipient cells, the possibility of obtaining stable coverage on flexible components or in the case of critical flow conditions, and blood compatibility itself (24).

Szycher et al. (25) seeded allogeneic fetal bovine cells obtained from the nuchal ligament onto textured pumps prior to implantation in a calf model for at least 30 days. The seeded intima was collagen based, stable, firmly adherent, and thin. Conversely, the PNI grown during implantation onto nonseeded controls appeared fibrin based and thick. Fasol et al. (26) seeded human ECs from the saphenous vein onto polyurethane and silicone rubber and evaluated the effects of surface tension in cell adhesion and growth. Even though cell resistance to shear flow conditions was not yet proven, the experiment confirmed the feasibility of creating a living endothelial monolayer on polyurethane. Unfortunately, the length of time required for in vitro creation of the biological layer was prohibitive for clinical implementation. More recently, a fast method to coat sintered titanium blood pumps with autologous blood-derived cells was developed. The procedure took only 45 min and could be performed in the operating room, just before implantation of the pump. When explored in an animal model (27) and in an in vitro study using human cord blood–derived ECs (28), this approach led to reduction of platelet adhesion compared with the noncoated control.

2.2.2. Surface functionalization. Blood compatibility is related to materials' chemical properties (functional group distribution) and physical properties (surface charge, surface tension, hydrophilicity/hydrophobicity, wettability) (29, 30), hemodynamic conditions, and contact duration. In light of these parameters, several strategies have been employed to improve the blood compatibility of implantable devices. In general, surface modifications are widely used for prosthetic vascular grafts and, in cases of mechanical assistance, for VADs, resulting in various solutions such as coating with heparin (31), titanium nitride (32), carbon material [diamond-like carbon (DLC)] (33, 34), and polymer [2-methacryloyloxyethyl phosphorylcholine (MCP)] (35). Heparin coating has been successfully used in the Berlin Heart (36), Excor (37), and Incor pumps (38) (Berlin Heart, Berlin, Germany) by immobilizing its unfractionated form on polyurethane. This treatment is named Carmeda BioActive Surface (Carmeda, Upplands Väsby, Sweden). DLC coating has been applied to a titanium alloy substrate used on the Sun Medical pump (Sun Medical, Nagano, Japan) (39), VentrAssist (VentraCor Inc., Foster City, California) (40), and Eva Heart (Sun Medical) (41), the last of which was originally coated with MCP (42).

2.2.3. Surface morphology modification. Strategies to achieve blood compatibility in TAH design have focused mainly on surface morphology. There are three main categories of blood-contacting surfaces: smooth, textured or rough, and biolized.

2.2.3.1. Smooth surfaces. In initial studies on blood compatibility, a surface was defined as smooth if it was able to prevent molecule adsorption or if its discontinuities and defects could be assumed to be smaller than the adsorbed molecules (24). The postulated association between smooth surfaces and blood compatibility derived from observations of vascular intima smoothness.

Practically, it is very difficult to obtain a smooth surface; its production requires advanced manufacturing technologies, since the smallest imperfection can trigger blood reactivity (43). The fabrication of the materials themselves, and certain process parameters such as dipping rate, drying time, and temperature, can affect the extent of defects and, as a consequence, the thrombogenicity of the surface (44).

Among all the biomaterials selected for manufacturing blood pumps, polyurethanes have been the most favorable. Their suitability arises from their unique combination of optimal long-term

mechanical properties (durability, elasticity, compliance, and fatigue resistance in both static and dynamic conditions) and good biological characteristics (biostability, biodurability, biocompatibility, and hemocompatibility). These features can be modulated by using different processing methods and by functionalizing their bulk and/or surface (45).

Polyurethane synthesis was first achieved in the 1930s, but the original material was prone to calcification and degradation when exposed to the biological environment; therefore, it had to be further modified for biomedical applications. The properties of thermoplasticity and segmentation were introduced in order to modulate the material's mechanical and biological performance (46). Drawbacks of the use of polyurethanes can be related to protein adsorption, poor mechanical durability in flexible applications, possible release of degradative factors or additives (plasticizers and antioxidants), biodegradation (hydrolysis, cracking, and oxidation), and calcification (29). Zartnack et al. (47) investigated the chemical stability and durability of different types of polyethers (Biomer, Pellethane, and Avcothane) and polyesters (Plathuran and two types of Platilon). Their analysis showed that hydrolysis and degradation were due to the sterilization technique employed rather than to the interactions with the biological milieu. Furthermore, the inherent chemical stability of these materials did not automatically result in mechanical durability and fatigue resistance. Polyurethanes, unlike rougher surfaces, are not an optimal support for cell growth and proliferation, as demonstrated by the poor adhesion of ECs and fibroblasts to both coated and noncoated polycarbonate and polyether urethanes (48, 49).

2.2.3.2. Textured surfaces. Textured blood-contacting surfaces were introduced to promote the formation of a stable PNI lining the internal chambers of mechanical pumps. In order to avoid embolic complications, the adsorbed material, consisting mainly of fibrin and blood elements, was entrapped onto the synthetic surfaces, promoting the growth of a nonthromboembolic autologous endothelial layer (24, 50). In addition to introducing a physical barrier composed of fibers and cavities, these surfaces can promote the growth of PNI by enabling exposure of a larger surface area to the bloodstream. The goal of this approach is to achieve hemocompatibility of all blood-contacting surfaces through dynamic and progressive replacement of this initial support with fibroblasts and ECs from the patient (51). These surfaces were produced through various strategies, such as the use of polyester (52–54) or polyurethane fibrils or casting on a negative flocked mold (25, 55, 56), titanium microspheres (50, 55–57), and deposition of dissolvable salts on a polyurethane surface. Regardless of the method employed, the outcome was the progressive smoothening of the surfaces due to the deposition of biological molecules. The textured surfaces were uniformly covered by PNIs of varying thickness depending on the location on the surface in the pump. In the presence of flocked fibrils, their lengths and movements during pump activity can lead to PNI disruption or instability (52). The rupture of the biological layer and detachment of thrombi from incorporating fibrils might cause embolic events (43, 53). Metman et al. (54) compared textured and smooth surfaces of artificial ventricles and reported similar hematological outcomes and hemolysis due to surface contact. In all of the devices investigated, thrombosis affected the inflow tract, sparing the outflow one, which was likely correlated to the high turbulence occurring in that region.

2.2.3.3. Biolized surfaces. In the 1970s, the Department of Artificial Organs of the Cleveland Clinic Foundation developed a new approach based on the observations that protein adsorption on blood-contacting surfaces was unavoidable and that hemocompatible properties of biological tissues were related to their components (proteins and other molecules) (58). Imai et al. (59) observed increased blood compatibility in devices that passed through several consecutive implantations, following fixation of the adsorbed protein layer with formaldehyde. This insight led

to the concept of biolization. Biolized surfaces consist of biological tissues (such as homologous or heterologous pericardium, dura mater, and aorta) and synthetic materials (polyether-based elastomers) coated with albumin, heparin, and skin gelatin. These biological surfaces are treated with alcohols and aldehydes to prevent the in vivo immune response and create durable layers by means of insolubilization and cross-linking (58, 60). In the first in vivo proof of concept in a sheep model, biolized valves were used in both inflow and outflow tracts of polyester fabric ventricles of the pump, and woven Dacron tubes were inserted as vascular connections. No evidence of paravalvular thrombi was reported (61).

Biolized surfaces lining the whole pump were first developed in 1971 (62) as a result of in vitro testing of several combinations of treatments, materials, and biological molecules (59). Nosé et al. (60) created the first totally biolized artificial heart out of formaldehyde-treated bovine pericardium. Each ventricular chamber was sutured to two aortic valves and dipped into a solution of natural rubber. This study was the first to employ a hybrid material, overcoming the limitations of individual synthetic and biological materials. Successive studies employed an aldehyde-treated, gelatin-coated, Dacron velour fabric backed with rubber. This surface supported the growth of PNI, but the diaphragm was prone to thickening and frequent ruptures. These drawbacks led to the replacement of the material with textured polyolefin rubber directly coated with aldehyde-treated gelatin, which allowed survival for more than 100 days (63).

The development of PNI on biolized surfaces lining TAHs was analyzed in detail in 1976; adhesion of endothelial-like cells on each of the aldehyde-treated surfaces was confirmed (64). Cell attachment appeared to be related to the presence of a stable fibrin meshwork, since PNIs are fibrin rich, especially the PNI grown on the treated pericardial surface. The smooth, gelatin-coated, biolized and textured polyester–flocked surfaces were compared; in all cases, rapid PNI development was impaired by extensive calcification (65). Five-year-long experiments resulted in effective and stable endothelialization of biolized surfaces in blood pumps, starting from the second week of implantation, even though the origin of these cells was unknown (24).

In 1996, Chatel (66) proposed a new biventricular model of TAH. Each ventricular internal surface was made of an intact porcine pericardial sac treated with glutaraldehyde. This biomaterial was inserted into a polymeric sac (Pebax; Elf Atochem Inc., Paris, France) joined at the inflow and outflow orifices of an animal heart used as a mold. A thin layer of lubricant filled the empty space. A computational model revealed the hemodynamic suitability of the artificial ventricle thus realized (67).

3. CALCIFICATION IS AN UNDERRATED ISSUE

Until long-term experiments were performed, blood pump calcification had been neither observed nor expected. Calcification became a significant problem when gradual improvements in surgical techniques and selection of materials, design, and fabrication methodologies increased the survival of animals with implantations.

The mineralization of textured blood pumps was first reported in 1975 (68). Four years later came the first report of calcification of a diaphragm with a polymeric smooth surface (69). Blood pump calcification is a problem common to several cardiovascular devices and affects a broad spectrum of materials (segmented polyurethane, polyester fibrils, glutaraldehyde-treated skin gelatin, bovine pericardium) as well as textured, smooth, and/or biolized surfaces.

3.1. Mineralization in Total Artificial Hearts: Typologies and Causes

Nucleation and growth of calcium phosphate crystals can be defined as a self-sustaining process; once initiated, it continuously increases by taking up salts from the bloodstream (70). Notably, the

relevance and seriousness of this phenomenon depend strictly on the location of the calcific lesions. Calcification of nonmoving parts (i.e., pump housing) may not be a concern, whereas formation of calcium phosphate deposits on moving elements (i.e., valves, diaphragm) gradually causes stiffening and loss of compliance of flexible components, compromising the device performance and eventually leading to complete pump failure (71). Other effects related to calcification include systemic embolization, deformation, abrasion, thinning, and perforation of pumping surfaces and linings (70, 72, 73).

Calcification is commonly acknowledged to be one of the main factors that cause the degeneration of glutaraldehyde-treated heart valve bioprostheses and seriously limit their long-term durability in vivo. However, the mechanisms regulating this phenomenon have not yet been completely elucidated, leading to the formulation of different hypotheses.

A morphologic analysis performed on xenograft porcine valve ultrastructure has highlighted the relationship between prosthesis mineralization and calcific cellular organelles, collagen breakdown, and loss of proteoglycans. The presence of carboxyglutamic acid with high affinity for calcium has also been documented (74). The similarity between mineralization of porcine aortic valves and bovine pericardium has been demonstrated despite the different architectures of these tissues. The pathological process normally begins with dead cells (mainly their nuclear cellular debris and residues of membrane phospholipids) and then involves collagen (75). The age of the recipient (for both animals and humans), chemical modification of the tissues, and mechanical stress play an important role in promoting calcification of bioprostheses, independently of the biomaterial considered (76).

Mineralization might affect both treated biological tissues and synthetic materials, in the latter case through neither cellular nor connective tissue involvement. The starting point of the mineralization process has been identified as the adsorption of calcium and the formation of its complexes on the material surface (77, 78).

3.1.1. Biological and mechanical causes of calcification. Whereas the selective deposition of insoluble crystalline calcium phosphate salts is a physiological feature of growth and remodeling in bone, teeth, and cartilage, soft tissue ectopic calcification and biomaterial-associated mineralization are considered pathological events (79). Biomaterial mineralization can be divided into two main classes (51, 80): metastatic and dystrophic. Metastatic calcification is a primary type of mineralization that occurs when the serum calcium-to-phosphorus ratio is altered (hypercalcemia). Dystrophic calcification is a secondary process that arises when the serum calcium-to-phosphorus ratio is normal (normocalcemia), and it affects necrotic tissue, degenerated or injured cells, and thrombi. Vaškù & Urbánek (70) described another type of primary calcification, calciphylaxis, that occurs when the local environment supports the deposition of calcium salts on soft tissues.

The calcification of TAHs and VADs is usually dystrophic because it is triggered by damage to the cells adhered to the device surface (51, 81) and/or can be introduced by dead bacteria debris left behind after sterilization (82). As for biological tissue mineralization, the mechanisms underlying nucleation and growth of calcium phosphate crystals on the blood-contacting surfaces of mechanical circulatory supports are poorly understood. At present, there is no agreement on the etiopathogenesis, and several often-conflicting explanations have been proposed, correlating calcification with both cell-mediated mechanisms (e.g., degradation of blood elements onto the surface, disruption and degeneration of spontaneously grown biological linings) and cell-free factors (e.g., surface morphology and related imperfections, precipitation of calcium phosphate on adsorbed lipids and proteins, direct binding with polymer molecules). It is not yet clear whether mineralization of these devices can be defined only as a secondary event, following thrombi or necrotic tissue formation, or whether it can also be primary, with direct calcification of the surfaces due to adsorbed proteins and phospholipids.

Most calcific lesions in blood pumps were found on moving parts and regions subjected to high cyclic strain. By contrast, lesions were totally absent or minimal on nonflexing components (72). These findings confirmed that mechanical stress, such as flexure movements and flow, is one of the most significant factors underlying calcification in TAHs and VADs (57, 71, 82, 83).

3.1.2. Calcification of textured surfaces. As described above, PNI formation is favored with the use of textured surfaces, but its growth can be very slow and unpredictable, and its thickness can be nonuniform among different parts of the pump. A diffuse thickening of PNI has been reported on high-flexing and stagnation areas as well as in cases of infection (51, 71). PNI can also be affected by mineralization.

One type of calcification that affects PNI is directly caused by mechanical stress. Research has demonstrated that cyclic stimuli can detach and/or disrupt the PNI grown on regions of stress concentration, causing calcification of wounded cells (57, 84).

Another type of calcification is related to pseudointimal thickening and was considered to be an early event, limited to the deepest portions of layers exceeding 500 μm (51, 57, 71, 72). At this depth, efficient diffusion, oxygenation, and nutrient supply into PNI are precluded. Cell death is the outcome, with subsequent release of phosphatase and other molecules commonly involved in calcium precipitation and crystallization. However, calcification can also occur in thinner PNI, as reported for long-term implants (51).

3.1.3. Calcification of smooth surfaces. Fabrication methodologies, prolonged mechanical stimuli, and wear of smooth surfaces may induce a broad spectrum of microscopic defects, ranging from microbubbles and fiber contaminants to surface folds and cracks. These imperfections on the blood-contacting surfaces of pumps might serve as foci for dystrophic calcification due to calcified thrombi or injured blood elements (71–73, 85). Nevertheless, the pathogenesis of calcified smooth surfaces cannot be exclusively dystrophic; it is also related to the accumulation of calcium-binding proteins or lipids into these discontinuities, without previous formation of thrombi (72, 73, 84, 86).

Calcification of polymers can also be facilitated by their molecular structure. In particular, the soft segment of polyurethanes may provide binding sites for salt and phosphate deposition (87). These regions are highly flexible and subjected to deformation and loosening. They can be covered by adsorbed proteins and phospholipids with high affinity for calcium and phosphorus (88).

3.1.4. Calcification of biolized surfaces. Similar to what has been observed in prosthetic valves, biolized surfaces undergo calcification as well. Harasaki et al. (71) reported calcification of the deepest layers of glutaraldehyde-treated bovine pericardium lining the internal surface of blood pumps, without any cellular reactions. These findings confirmed the influence of material structure and chemical modifications on the promotion of calcification. The same study also reported calcium deposition on several diaphragms, due to the presence of degraded and necrotic blood cells adhering to the glutaraldehyde-treated calf-skin gelatin after its detachment from polyolefin rubber.

3.2. Possible Strategies to Prevent Calcification

Several ways to avoid calcification of bioprosthetic heart valves have been proposed. These include the use of inhibitors of hydroxyapatite formation and calcium diffusion, methods for eliminating calcific materials, and/or improvements in fixation techniques (76). So far, none of these approaches have been applied to TAHs (**Figure 2**).

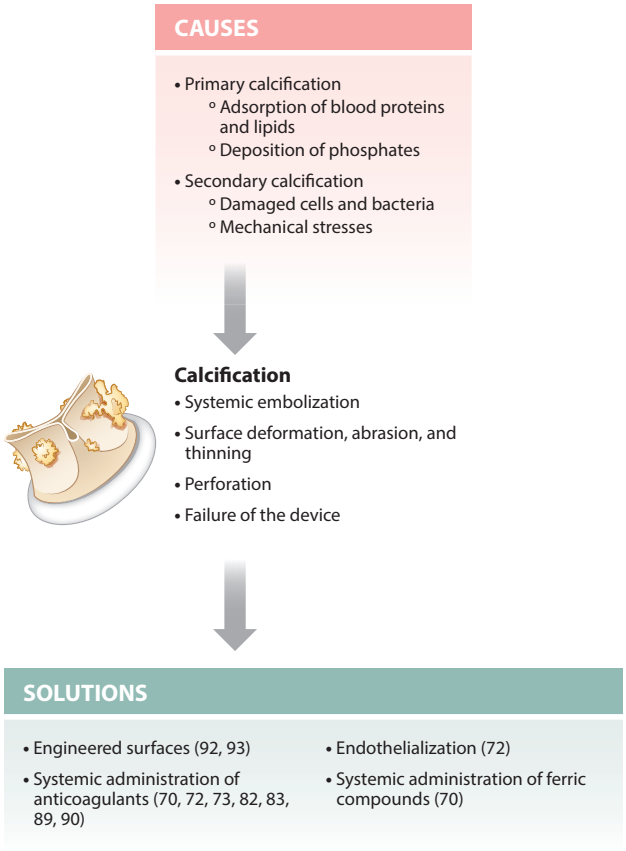

Figure 2

Causes and effects of calcification in total artificial hearts and strategies to prevent its occurrence.

Warfarin sodium (Coumadin), an antagonist of vitamin K, inhibits blood pump calcification (82, 83), following two possible blocking mechanisms. The first involves osteocalcin, a vitamin K–dependent protein that contains γ-carboxyglutamic acid, which has a strong calcium-binding affinity (89) and is distributed in considerable amounts in calcific deposits (73). In the second, warfarin sodium, as an anticoagulant, acts by preventing thrombus formation and hence dystrophic calcification (51). Nevertheless, these effects have not been confirmed on textured and smooth surfaces. In long-term experiments, use of the anticoagulant reduced the number of calcific deposits and the severity of lesions, but all devices eventually developed mineralization (70, 72, 73, 89, 90).

Polyurethane calcification may be prevented by covalent immobilization of bisphosphonates, a class of drugs currently employed in the settings of vascular calcification and osteoporosis (91). These molecules can be stably and permanently associated with the soft segment of polyurethanes without altering their mechanical properties (92). In other studies, bisphosphonates were chemically bound to the hard segment of polycarbonate urethanes and polyurea polyurethanes. Upon evaluation in a sheep model for 60 days following implantation, the modified materials composing the leaflets of a pulmonary valve showed no evidence of calcification (93). Also, the formation of a stable PNI with healthy ECs lining the internal surfaces of the pumps prevented calcification (72). For the case of calciphylactic calcification,

systemic administration of iron compounds in form of ferric saccharate has been suggested as a solution (70).

4. THE SPECTER OF BIOMATERIAL-ASSOCIATED INFECTIONS

4.1. The Clinical Relevance of Total Artificial Heart Infections

Infections are among the most common causes of severe septic complications and death in patients with mechanical pumps. In general, bacterial and (less frequently) fungal colonizations may affect all types of biomaterials or biomedical devices.

Low concentrations of these pathogens, which are commonly present in the environment, are normally eliminated by the immune system. Still, host response, and even the use of antibiotics and antimycotics, is insufficient when analogous infections are associated with a biomaterial (94, 95). Bacteria have glycocalyxes that allow their survival in extremely adverse microenvironments (96), and they can aggregate in persistent structures known as biofilms (97). The consequences of these observations first became evident in the biomedical field when antibiotic-resistant biofilms of *Staphylococcus aureus* were discovered on the pacemaker leads of a patient with recurrent bacteremia (98).

Biofilms are formed on both biotic and abiotic surfaces by several types of bacteria, such as group A streptococci, *Escherichia coli*, and *Pseudomonas aeruginosa*. Infections caused by biofilm-forming bacteria are particularly difficult to eradicate. Due to the adherent extracellular matrix they secrete, bacteria can live in an insulating milieu, able to protect themselves from antibiotic treatment (99, 100).

Bacterial infections have always been considered a significant challenge for the successful outcome of any TAH tested on animals. One of the first studies on TAH and VAD implantation in calves, published in 1983 (101), reported an incidence of infection equal to 52.9%, independent of the applied sterilization process. The contaminants were bacteria of intestinal origin, prone to colonizing smooth rather than rough surfaces. Furthermore, debilitation and weakness during the first preoperative days might increase the early onset of these infections. Infections within TAHs are frequently observed, especially with vegetative bacteria. Depending on their evolution, the bacteria can have occlusive capacities or lead to embolic complications due to the possible detachment of agglomerated materials.

Two other regions can be affected by infections: percutaneous drivelines and discontinuities in the external surface of the TAH (102). Although mediastinal colonization is less probable, other factors need to be considered, such as medical routes of access to the body (i.e., vascular cannulae, tracheal tubes, drainages, and urinary catheters), prolonged HF-induced debilitation, or certain properties of the materials (e.g., selective adhesion and sequestration of contaminants) (103). Poor survival as a result of contamination was initially confirmed in humans, and the severity appeared to be strictly correlated to implant duration (104). By contrast, a more recent and optimistic retrospective study by Sivaratnam & Duggan (105) reported that in recent years survival was improved, except in cases of *Pseudomonas aeruginosa* infection.

TAH contamination may also be fungal in nature because of reduced host resistance. Fungi possess a strong natural affinity for synthetic surfaces, often forming biofilms (106). Although uncommon, fungal infection is a severe chronic complication and may cause death (107, 108).

4.2. Possible Solutions

In both bacterial and fungal contamination, prevention and use of effective sterilization procedures are crucial (**Figure 3**). Infections acquired through contaminated percutaneous drivelines can be

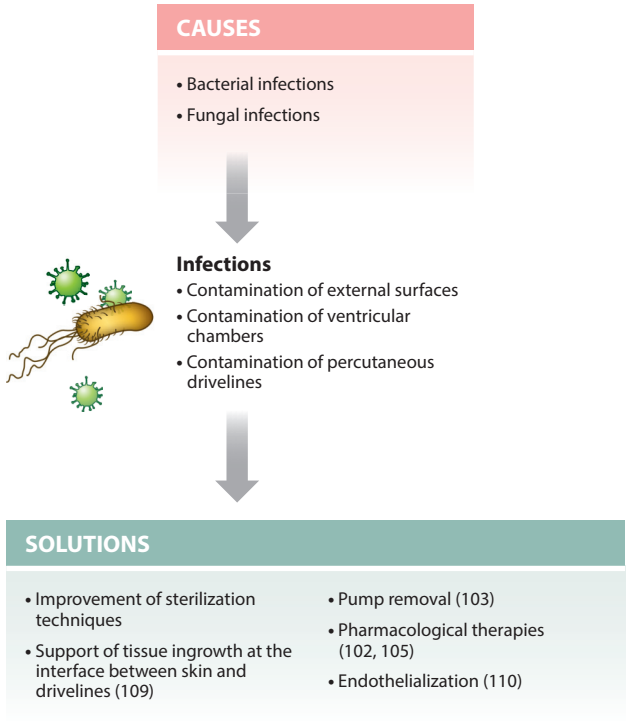

Figure 3

Causes and effects of infections in total artificial hearts and strategies to prevent their occurrence.

inhibited by use of specific connectors (buttons) through the skin, allowing tissue ingrowth and, thus, wound healing (109). Unfortunately, in the case of internal chamber contamination, the blood pump must be removed (103) and pharmacological therapies administered (102, 105), given the necessity for long-term treatment and prevention of the infection in a transplanted organ. In 2007, a study by Asai et al. (110) on polyurethane patches implanted in murine abdominal aorta showed that in vivo adhesion of ECs can reduce *Staphylococcus aureus* colonization of the graft. Nevertheless, this strategy has not yet found clinical translation.

5. FROM AN UNCERTAIN PAST TOWARD A PROMISING FUTURE: ADVANCES IN MATERIAL SCIENCES FOR TOTAL ARTIFICIAL HEART DEVELOPMENT

The fate of each implantable device is strictly dependent on its constituting materials. In addition to the presence of comorbidities, biomaterial selection plays a crucial role in the above-mentioned events.

A different perspective on the evolution of mechanical circulatory supports comes from materials science (5, 111, 112). Early in the development of TAHs, knowledge about biomaterials was extremely limited; the terms biomaterial and biocompatibility were not clearly defined; and prosthetic implants failed because of the lack of adequate sterilization techniques (113). Most materials were borrowed from the mechanical industry and, therefore, were not suitable for medical purposes, which required contact with one of the most hostile and aggressive environments (i.e., the human body). Furthermore, few aspects of TAHs' mechanical behavior and biological

stability were known or tested, even though the fundamental requirements had already been identified (114, 115).

Little attention was paid to the selection of appropriate materials for the first TAH implantations in animals. At that time—that is, the very beginning of in vivo experiments—blood compatibility was not a major concern. The most pressing concerns were to demonstrate mechanical pump performances and to achieve animal survival.

With increased long-term survival and scaling up of animal models, several TAH prototypes were developed. The prevalent material adopted for fabricating atria and ventricles in both sac- and diaphragm-type devices was Silastic (i.e., Silastic Medical Grade Sheeting 372; Dow Corning, Midland, Michigan), a natural silicone rubber with enhanced blood compatibility in comparison to other available polymers, but with inadequate mechanical features. The Silastic was reinforced with a Dacron mesh to increase diaphragm durability. Unfortunately, the ruggedness and stiffness of the Dacron led to damage and increased tearing of the silicone component; therefore, other techniques (e.g., injection molding instead of layering) were preferred. Moreover, the prosthetic valves positioned at the inlet and outlet of the devices varied among TAH models. At first, only mechanical prostheses were used, independently of their configuration (i.e., caged-ball and monoleaflet valves made of Silastic, and polyethylene-, polypropylene-, or graphite-coated polycarbonate and polymethylmethacrylate). These valves were usually the primary cause of stagnation and turbulence, frequently resulting in thrombus formation (115).

Table 1 lists several TAH prototypes that represent the most innovative devices in terms of materials used. Five of these are discussed in the following subsections.

5.1. Liotta

The first biventricular pump, the Liotta TAH, was first implanted in a human in 1969. The Liotta was a diaphragm-type blood pump made of Dacron-impregnated Silastic. The blood-contacting surfaces (i.e., ventricular chambers, atrial cuffs, and outflow tracts) were lined with reticular Dacron fabric in order to promote PNI formation. Hingeless tilting-disc valves (i.e., Wada–Cutter prostheses) were used at the inlet and the outlet. These Wada–Cutter prosthetic valves were composed of a titanium inner ring with a single polyethylene disc. These valves were chosen mainly because of their large orifice area and the low clinical incidence of thromboembolic events. The drivelines were made of Silastic tubes wrapped in Dacron fabric.

The first Liotta TAH was implanted as a BTT for 64 h. Once explanted, it showed smooth internal surfaces covered by a fibrin mesh with entrapped blood cells and a complete absence of thrombotic formations. Early hemolysis was reported, probably because of both the unsatisfactory performance of the valves and the roughness of the Dacron lining the ventricular blood-contacting surfaces (7, 116).

5.2. Akutsu III

In 1964, Akutsu et al. (117) reported the implantation of a one-piece (but not seamless) sac-type TAH, made of Dacron mesh embedded in Silastic, in a dog model. The use of this device was hampered by unsolved problems with thrombogenic stitching lines. In 1977, Akutsu and colleagues (118) proposed a new TAH prototype: a one-piece, entirely seamless, diaphragm-type pump made of Avcothane 51 (Avco-Everett Corporation, Waltham, Massachusetts). This multisegmented elastomer was a polyether urethane/poly(dialkylsiloxane) block copolymer. The success of Avcothane 51 was due to its blood compatibility, which precluded the use of anticoagulants (118, 119). In 1981, this TAH was implanted in a human as a BTT.

Table 1 General overview of materials adopted in prominent TAHs

Device	Manufacturer	First human implantation	Atria	Valves	Ventricles	Diaphragm	Vascular grafts	Housing	Drivelines	Selected reference(s)
Liotta	Texas Heart Institute	1969	Dacron, Silastic	Titanium, polyethylene	Dacron, Silastic	Dacron, Silastic	Dacron, Silastic	Silastic	Silastic covered by Dacron	7
Akutsu III	Texas Heart Institute	1981	Silastic, Dacron	Pyrolytic carbon	Avcothane 51	Avcothane 51	Dacron	Avcothane 51	Dacron	120
Kwan-Gett	University of Utah	None	Dacron, Silastic	Polypropylene or titanium, polyethylene	Dacron, Silastic	Dacron, Silastic	No data	Dacron and Silastic	Metal	121
Jarvik-3	University of Utah	None	Silastic housing, Biomer sac	Pyrolytic carbon	Dacron, Silastic	Dacron, Silastic	No data	Dacron and Silastic	No data	122
Jarvik-5	University of Utah	None	Dacron	Pyrolytic carbon	Avcothane 51 or Biomer	Dacron, Avcothane 51, or Biomer	Dacron	No data	No data	123–124
Jarvik-7	University of Utah	1982	Dacron	Pyrolytic carbon	Biomer	Biomer	Dacron	No data	Polyurethane, Silastic	125
CardioWest SynCardia TAH[a]	SynCardia	1993	Dacron mesh, polyurethane, velour	Titanium, pyrolytic carbon	Polyurethane, Dacron	Polyurethane	Polyurethane, Dacron, velour	Polyurethane, Dacron	Polyvinyl chloride, polyurethane, velour	127
AbioCor	Abiomed	2001	Dacron	Angioflex	Angioflex	Angioflex	Dacron	Polycarbonate	No data	135
CARMAT[b]	CARMAT	2013	Bioprosthetic flanges	Bioprostheses	ePTFE	Glutaraldehyde-treated bovine pericardium backed with polycarbonate urethane	Dacron	No data	No data	145

[a] The SynCardia TAH is the only TAH in clinical use.

[b] The CARMAT TAH is currently under clinical validation.

Abbreviations: ePTFE, expanded polytetrafluoroethylene; TAH, total artificial heart.

The Akutsu III comprised two seamless, smooth ventricular chambers made of Avcothane 51 (120). Four Björk–Shiley convexo-concave monostrut prosthetic valves with a tilting disc in pyrolytic carbon were positioned at the inflow and outflow tracts. The criteria for the selection of the valves were similar to those used for the Liotta TAH. Silastic and velour were used for the atrial connectors and cuffs, respectively, and the vascular grafts were made of porous Dacron preclotted with autoclaved autologous plasma. The blood pump successfully bridged the patient toward transplantation for 55 h. After explantation, the absence of thrombi and material failure was confirmed, and the internal surfaces appeared smooth and shimmering.

5.3. SynCardia

In the 1970s, the University of Utah began development of a device that went on to become the only TAH fully approved for clinical use. The evolution of the CardioWest TAH (SynCardia, Tucson, Arizona) proceeded through a hemispherical heart and several versions of the Jarvik model. Between 1967 and 1971, Kwan-Gett et al. (121) designed a simple, pneumatically driven, diaphragm-type TAH, laying the foundation for the development of the Jarvik heart. The Kwan-Gett heart comprised two hemispherical ventricles with an aluminum base. Dacron-reinforced Silastic velour was used to line the ventricles and the atrial cuffs and to create the housing and diaphragm. The inflow and outflow tracts used Hammersmith and Wada–Cutter valves, respectively (121).

Improvements in both the pumps and the outcomes of animal trials led to the development of the Jarvik-3 model. Its materials and fabrication techniques were very similar to those used for the Kwan-Gett heart. The Jarvik-3 housing was composed of two layers of Silastic reinforced with a Dacron mesh, and the diaphragm was made from the same materials but in a thinner version. During layering of the ventricles, aluminum rings were integrated to allow valve attachment and atrial connections. Atrial chambers were composed of molded Silastic with the inclusion of a Biomer (segmented polyether urethane; Ethicon Inc., Somerville, New Jersey) dip-molded membrane separating the blood compartment and the compliant chamber. Atrioventricular connections were established through four Björk–Shiley prosthetic valves (122). The materials used to coat the ventricular chambers of the Jarvik-3 heart were modified in order to increase blood compatibility. However, when anticoagulated and nonanticoagulated calves were implanted with this device, with either textured (Dacron-fibrilized silicone rubber) or smooth (polyurethane) surfaces, the limits of the device design became apparent. Although the hemocompatibility of smooth polyurethane appeared slightly higher than that of fibril coating, most of the animals died as a result of thromboembolic events generated in areas of turbulence and stagnation (68).

The Jarvik-5 device was developed to improve the diaphragm–housing connection (D–H junction) and, therefore, to overcome thrombosis in these critical sites. Innovations in smooth-surface fabrication allowed the production of inner linings free from discontinuities: Each ventricle was realized as a single element. The blood-contacting surface of the ventricles was made of polyurethane (Biomer or Avcothane 51), and the diaphragm was composed of a Dacron mesh interposed between two layers of polyurethane. Another modification involved pouring the chosen polymer inside the device in order to simultaneously coat the internal surfaces of the housing and the diaphragm, as well as to eliminate the discontinuity at their junction (123). A rigid polycarbonate connection system was used to join mechanical tilting-disc Björk–Shiley valves to both the atrial cuffs and the woven Dacron vascular grafts (when autologous pulmonary and aortic valves were not retained in situ). Artificial atria, originally fabricated with smooth polyurethanes, were improved with Dacron felt cuffs (124). The new design of the D–H junction led to a reduced rate of thrombosis in this area, although thrombosis still occurred around the connection between the polycarbonate support of the valves and the ventricles (123).

Between 1976 and 1980, the Jarvik-7 TAH was implanted in calves, demonstrating the feasibility of long-term implantation. In comparison to Jarvik-3 and -5, Jarvik-7 offered improvements in the atrial cuffs (in polyester felt, dura mater, or polyester felt–lined Biomer), outflow tracts (in Avcothane 51 or Biomer, both lined with polyester velour), and heart valves (Hall–Kaster pivotal disc valves; Medtronic Inc., Minneapolis, Minnesota). The Dacron mesh was removed from the layers of the diaphragm, and the number of polyurethane layers was increased from two to four, with graphite as an internal lubricant. Despite success in terms of implant duration, all of these combinations of materials led to calcification of diaphragms and, in some cases, to vegetative endocarditis (109).

The final version of Jarvik-7 underwent its first in-human implantation in 1982. This device was composed of smooth segmented polyurethane ventricles, Dacron felt cuffs, Björk–Shiley valves, a polycarbonate quick connector, and Dacron vascular grafts. Polyurethane drivelines emerged at a flank through a velour skin button (125). After 112 days, the pump was explanted, and investigation confirmed the absence of thrombi and infections (126).

By changing hands, Jarvik-7 underwent commercial renaming and is now known as the SynCardia TAH. This device began a validation study as a BTT in 1993 (127) and received approval from the US Food and Drug Administration (FDA) in 2004 and CE marking from the European Union in 2006. In 2012, it was approved as a DT for humanitarian use by the FDA (128). The version of this device known as the CardioWest TAH was composed of a semirigid lower part made of engineered thermoplastic polyurethane (Isoplast; Lubrizol, Orlando, Florida) and a dome fabricated using a segmented polyurethane solution, reinforced with Dacron mesh, as done for the velour-lined inflow cuffs and vascular grafts. The blood-contacting surface of the ventricles comprised a single layer of poured segmented polyurethane solution, whereas the diaphragm was made of four different sheets, lubricated with graphite microparticles. Medtronic-Hall pyrolytic carbon monodisc valves were fitted between Isoplast quick connects at both inflow and outflow tracts.

More than 1,100 SynCardia TAHs were implanted worldwide until 2013, but studies of the device's blood compatibility are limited to in vitro evaluation of platelet activation and computational modeling of fluid dynamics (129). Hemocompatibility remains a concern in long-term implants: A study considering a follow-up period longer than 1 year reported thromboembolic events in 19% of patients, despite the adoption of anticoagulation strategies (128).

5.4. AbioCor

The AbioCor TAH (Abiomed, Danvers, Massachusetts) was the first mechanical pump specifically designed to eliminate the risk of infection associated with percutaneous drivelines. This device could be completely implanted into the body thanks to the adoption of transcutaneous energy transfer (TET).

The development of the AbioCor TAH began in 1988. Its material formulation remained substantially the same in the different versions released over the years. The blood-contacting surfaces of the smooth ventricles and trileaflet valves were fabricated using Angioflex, a proprietary polyether urethane. As observed in Jarvik-3 (68), junctions and discontinuities might promote thrombus formation due to stagnation and turbulence. To prevent such problems, valves and outflow grafts were inserted into the body pump through the application of solution-casting techniques. The result of this design was a continuous smooth surface from the inflow to outflow regions. Domes were reinforced using an industrial epoxy resin (STYCAST; Emerson & Cumming, Woburn, Massachusetts). The trileaflet valve design was preferred over the mechanical tilting-disc design because of its lower hemolytic rate. Connections between the inflow tracts and cuffs were specifically designed to discourage occlusive tissue ingrowth. The artificial atria and vascular grafts were made of Dacron.

The second model of the AbioCor TAH was tested both in vitro (130) and in vivo (131, 132) by demonstrating the feasibility of long-term experiments. Implantation in a calf model for 47 days revealed the absence of blood cell damage and thromboembolic events. PNI formation on the textured surfaces of the inflow tract and cuffs was present. The pump was entirely encapsulated by a fibrotic tissue.

The dimension of the pump was reduced in the third model, while materials and design were maintained unaltered (132). Even with these changes, no evidence of blood damage was demonstrated in calves surviving for 30 days (133). Between 1998 and 1999, only 4 of 12 calves implanted with the AbioCor TAH survived for more than 1 month. Death occurred due to bleeding, respiratory alterations, malposition of the primary TET coil, and other complications. In animals that survived for a longer period, no sign of pannus ingrowth was observed. No information about thrombus formation, embolic events, or blood damage was reported (134).

The first implantation of the AbioCor TAH in a human occurred in 2001, when the FDA approved a multicenter trial (135). Early results from these studies reported device failure due to thrombus formation on the plastic cage struts atop the artificial atrial orifice, even when anticoagulation and antiplatelet therapies were administered. This problem had not been observed in the preclinical testing phase. Conversely, the pump's blood-contacting surfaces appeared completely clean; no infection or tissue damage was disclosed (136). The AbioCor TAH received FDA approval for humanitarian use as a DT in 2006 (137).

5.5. CARMAT

Among the most recently developed pumps, one was created specifically to overcome the crucial issue of low hemocompatibility and to reduce the need for anticoagulation therapies. Development of this device, the CARMAT TAH (CARMAT, Velizy, France), began in 1993 (138). It represents the first successful attempt to incorporate a hybrid (biological/synthetic) membrane into TAHs.

Along with his colleagues, Carpentier is considered a pioneer in the use of natural tissues to realize bioprosthetic valves (139, 140). These researchers employed the same technology used for the manufacture of valve substitutes to develop a diaphragm blood-contacting surface in glutaraldehyde-treated bovine pericardium backed by polycarbonate urethane using a proprietary process. The remaining nonmoving parts of the artificial ventricles were fabricated with expanded polytetrafluoroethylene (ePTFE) (141). The atrial cuffs were made of bioprosthetic flanges, and Dacron tubes were used as arterial grafts (138). Commercially available Carpentier–Edwards bioprosthetic heart valves (Edwards Lifesciences, Irvine, California) were placed between the ventricles and the artificial atria or outflow conduits (142). The composite membrane and ePTFE were tested in vitro for blood compatibility, demonstrating close similarity with the negative control (i.e., heparin-coated polyvinyl chloride tubes). The authors found no change in plasma fibrinogen, low platelet and blood cell adhesion, and inferior thromboxane B2 release with respect to the positive control in silicone rubber (141).

Animal studies in calves have been performed since 2013. Implants were short term (10 days), and in order to verify the in vivo hemocompatibility of the device, no anticoagulant was used. Only one animal reached the maximum duration of 10 days; the others suffered from respiratory problems, gas embolisms, paralysis, sepsis, and hemorrhages. In all of the explanted TAHs, there were no thrombi and no evidence of hemolysis. Fibrin deposits were found covering the blood-contacting surfaces of the diaphragm, dome, and leaflets. In longer-term implants (7 and 10 days), PNI formation was observed (143). These favorable results in terms of blood compatibility were recently confirmed in an analogous short-term study (144).

In December 2013, the first human implantations of the CARMAT TAH were reported. The electronics of the device failed, causing the death of the first two patients. They survived for 74 and 270 days, respectively, without developing thromboembolic events, even in the absence of anticoagulant therapy (one case). The diaphragm surfaces showed no thrombi, while the formation of a thin layer of proteins was detected (142).

These two cases were part of a feasibility study that included a total of four subjects suffering from end-stage HF in acute life-threatening conditions. The third patient survived for 254 days and the fourth for only 20 days, for reasons not related to the implanted device (145).

In 2016, CARMAT began the process of obtaining CE marking. In the same year, a pivotal study was approved in France. A patient in that study passed away for reasons related to the handling of the power-supply system. For this reason, the study was temporarily suspended. In May 2017, the French Agency for the Safety of Health Products authorized CARMAT to restart the clinical trial. The company plans to perform 20 new implants in France and in other countries (i.e., Kazakhstan, Czech Republic, Denmark) in order to obtain CE marking by 2019 (146).

6. CONCLUSION

The shortage of biological organs underlies one of the most complicated (but intriguing) challenges in modern medicine: the search for affordable and effective mechanical substitutes for failing hearts. These efforts have culminated with the creation of TAHs.

Clinical application of TAHs has been limited for several reasons. The most notable is blood compatibility, one of the crucial and well-investigated issues in biomaterial science. Possible solutions for hemocompatibility had already been tested at the outset of TAH development; nevertheless, a fully hemocompatible material has not yet been identified, and some potential options are moderately tolerated by the body only in association with aggressive anticoagulant and antiplatelet therapies.

Calcification of mechanical blood pumps is another critical issue, which has been investigated extensively. Given that mineralization is not an acute reaction but rather a chronic process, time is crucial. Therefore, mineralization should not be underestimated in efforts to create a long-term functional mechanical substitute, especially when glutaraldehyde-treated mammalian tissues are used for blood-contacting surfaces. Indeed, fatigue-induced exposure of xenoantigens from animal-derived biomaterials can elicit an immune response that may evolve into calcification (147–149).

In addition, advanced sterilization techniques are currently being used to avoid microorganism contamination, but considerable improvements are needed to reduce driveline-derived infections. New devices aim to bypass this limitation by means of a transcutaneous energy supply. This issue therefore remains partially unresolved.

Over the last few decades, several TAH prototypes have been released, but only the newest one (CARMAT) demonstrates improved hemocompatibility. Despite the multitude of studies performed in this area, the search for the perfect, or most appropriate, biomaterial for blood-contacting surfaces remains a challenging task.

Clinical translation of TAH prototypes can only occur once the requirements established by the International Organization for Standardization (ISO) have been fulfilled. In particular, ISO 10993 regulates the evaluation of biocompatibility of medical devices; together with ISO/TS 10993 and ISO/TR 15499, this requirement offers guidance for the realization of systematic biological assessments with regard to cytotoxicity, hemocompatibility, degradation, and risk management (150).

Blood compatibility is necessary but not sufficient for a truly biocompatible and affordable TAH. Several other basic specifications must be satisfied: a simple geometrical configuration of

the inner chambers, in order to prevent flow turbulences and blood stagnation; easy automation, to avoid software failure; and the presence of minimal moving components, such as valves, to reduce the risk of malfunction. Therefore, a novel TAH characterized by small dimensions, an advanced actuator system, and innovative materials should be manufactured in order to overcome the drawbacks of the systems conceived so far. With an effort to guarantee the survival, as well as a respectable quality of life, of treated patients, our group at the Padua Heart Project is facing this challenge (5). Although the goal is still arduous to achieve, we firmly believe that recent steps toward the creation of novel medical devices will soon result in the development of a more biocompatible TAH.

To date, TAHs represent the most concrete, effective, and immediate answer to the lack of suitable donor organs. However, no artificial pump has been able yet to fully reproduce the complex physiology and everlasting performance of a native functional heart. Therefore, these devices must be considered short-term therapeutic responses [our group has reported one of the longest experiences (i.e., 1,374 days) with a CardioWest TAH (151) for BTT indication].

In the middle term (10–15 years of treatment), heart transplantation remains the gold standard. Currently, several groups are focusing on the development of new technologies aiming at improving graft preservation before transplantation and/or enlarging the pool of possible donors (152).

For a lifelong treatment, the greatest hope is now placed on cardiovascular regenerative medicine and tissue engineering in order to create less artificial solutions for HF. Several cell-based methods and/or the use of specific biomaterials able to support in situ cardiac regeneration has been investigated to ameliorate impaired heart function, not always with satisfactory outcomes (153). Through a combination of decellularized natural cardiac extracellular matrix and patient-derived cardiovascular cells, the whole bioengineered heart is anticipated to become the ultimate biocompatible, personalized solution for the long-lasting replacement of the failing heart (154).

DISCLOSURE STATEMENT

S.T.G.S. and G.G. are inventors of a TAH actuator (EP3082898A1). The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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