Polyurethanes and their application in cardiovascular surgery- a review

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Abstract:

Polyurethanes are a broad family of polymers. These materials have a significant position in the medical industry. The use of polyurethanes is unlimited. But it should be kept in mind that polyurethanes are actually the best materials for producing devices for specific applications (Figure 1). Accordingly, we provide an overview of some applications, which may not be exhaustive, but focus on specific processes, debatable results, and potential for future developments.

Cardiac surgeons' equipment shows no significant role for polyurethanes in intra-aortic balloons, blood bags for ventricular assist devices (VADs), catheters, and pacemaker leads as the most important. The results of testing polyurethanes as blood vessels are not yet complete due to the lack of long-term resistance to degradation. Breast implants covered with PU foam are part of the scientific debate. The use of polyurethane is limited, but these materials have interesting properties. Cardiac dressings and tissue engineering scaffolds enable new developments.

Keywords: ***Polyurethane, application of polyurethane, cardiovascular surgery, surgical equipment, tissue engineering, polymer***

Introduction

Most industrially produced polymers possess relatively simple structural designs, typically synthesized from one or two monomers, resulting in either homopolymers or copolymers. Notable examples of such polymers include polyethylene terephthalate, polytetrafluoroethylene, polystyrene, polyethylene, polypropylene, and polybutadiene. In contrast, polyurethanes exhibit more complex chemical structures, as they are derived from three components: diisocyanates, oligomeric macro monomers known as polyols, and a chain extender. The synthesis of polyurethanes provides "three degrees of freedom," resulting in a remarkable diversity of materials characterized by varying physicochemical and mechanical properties. This distinctive capability leads to polyurethane structures that significantly diverge from those of other polymers.

Polyurethane elastomers typically display a two-phase architecture, comprised of hard domains dispersed within a soft segment matrix. The hard domains are predominantly formed from diisocyanates and chain extenders, while the soft segments consist of polyol sequences.

Consequently, polyurethanes are frequently classified as segmented block copolymers. This specific molecular architecture, combined with the intrinsic properties of the materials utilized in polyurethane synthesis, endows these

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polymers with unique characteristics that distinguish them from others within the polymer family.[1,2]

Despite certain claims found in the extant literature, polyurethanes have gained traction in biomedical applications primarily due to their exceptional mechanical properties rather than their biological responses. While numerous studies corroborate the assertion that polyurethanes exhibit "biocompatibility" and "blood compatibility," several publications indicate that these materials can degrade within the human body, displaying inferior compatibility with blood relative to alternative materials employed in vascular surgery. Nonetheless, the distinctive mechanical properties of polyurethanes render them highly advantageous for specific applications, particularly in scenarios where tissue resilience is paramount.

Polyurethanes exemplify a diverse family of polymers that play a critical role in medical treatments. On one hand, they offer substantial benefits due to the feasibility of tailoring their characteristics through synthesis. On the other hand, there is potential for unwarranted generalizations regarding this polymer family. For instance, the blood response to polyurethane surfaces can vary significantly among different polyurethane formulations. Therefore, the meticulous selection of a specific polyurethane for a particular application is essential.[3]

It is evident that the development of newly designed polyurethanes is required for many applications, rather than relying exclusively on commercially available types. Historically, many successful applications of synthetic materials have emerged outside the biomedical realm, yet preliminary tests in biomedical settings often lack a solid scientific rationale, relying instead on empirical evaluations. Today, the advancement of polyurethane development necessitates a collaborative approach grounded in clearly defined biomedical engineering requirements and an enhanced understanding of material interactions.

Such collaboration facilitates the targeted synthesis of polymers, enabling the production of prototype medical devices tailored to meet specific demands. Additionally, establishing robust correlations between implant outcomes and polymer properties is imperative for optimizing polyurethanes for designated applications. This methodological approach not only enhances the efficacy of polyurethanes but also deepens our understanding of their limitations. The inherent versatility of this category of materials holds tremendous promise, and specialized polyurethanes are anticipated to play a pivotal role in the advancement of numerous future biomedical engineering devices (Figure 1).

Polyurethane

Polyurethane materials first made their debut in the medical field in the late 1950s. In 1958, Pangmann introduced a composite breast prosthesis encapsulated in polyurethane foam. However, this polyurethane polyester foam proved susceptible to hydrolysis, presenting challenges for implantation within the human body.

In the same year, Mandrino and Salvatori employed a rigid polyurethane foam known as Ostamer for bone stabilization. By 1961, Dreier and colleagues proposed the application of a polyurethane polyester termed polyurethane VC for components in heart valves and aortic grafts. The mid-1960s witnessed Cordis Corporation commercializing polyurethane polyester diagnostic catheters,[4-6] garnering scientific interest in the quest for an ideal biomaterial. Unfortunately, early cardiovascular applications of these polyurethane esters yielded unsatisfactory outcomes, as investigations revealed their hydrolytic instability, leading to a broad characterization of polyurethanes as unsuitable for implantation.

This unfortunate conclusion erroneously condemned the entire category of materials commonly referred to as polyurethanes, based on the shortcomings of a particular subclass, despite their significant industrial relevance.

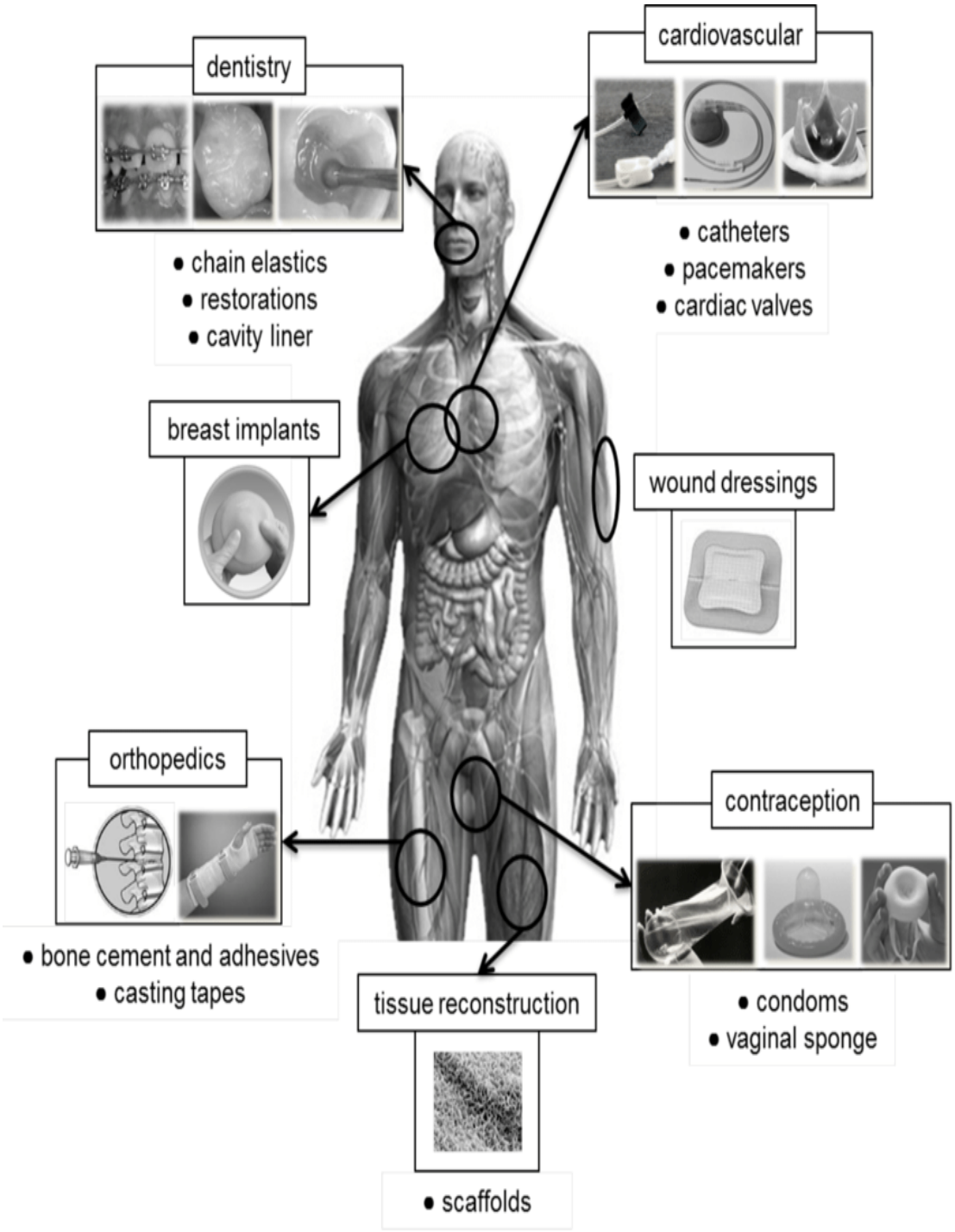

Figure 1 - Some applications of polyurethane in medical engineering

This generalization stemmed from a limited understanding of the materials at the time, which inaccurately classified all polyurethanes as inherently degradable. Today, this characterization is widely acknowledged as an oversimplification, particularly in light of the success of hydrolytically stable polyurethane ethers, which have rekindled interest in polyurethanes as potential biomaterials. Reflecting on the industry's past, one might question why the hydrolysis of polyurethanes was not foreseen by early manufacturers.

Notably, in 1954, textile chemists at DuPont developed Lycra as a superior alternative to natural rubber for elastic yarns, patented by Stober in 1960. Renowned for its exceptional properties, including resistance to degradation during laundering, Lycra quickly found adoption in the textile industry as a form of polyether urethane. In 1967, Bortus and Pierce introduced Lycra as a biomaterial for the first time, having produced a "bucket" polymer solution at DuPont. This material was initially used as elastomeric components in heart assist pumps and their arterial conduits.

By 1971, the hybrid polyurethane/silicone known as Avocatan 51 was specifically designed for medical applications. The following year, Ethicon introduced a DuPont-licensed variant of Lycra called Biomer. Both Avocatan and Biomer were synthesized from a solution and were not conducive to fabrication methods such as dipping, spraying, or casting. Nevertheless, these polymers were extensively studied as pioneering biomedical polyurethanes.[7] Avocatan was clinically utilized in the first intra-aortic balloon pump in 1971, and this product continues to be in use today under the name Cardiotone 51, owned by Arrow International. Components derived from Biomer played an instrumental role in the development of the "Jarvik heart," the first artificial heart transplanted in 1982. At that time, both Avocatan and Biomer demonstrated a combination of thrombosis resistance, durability, and flexibility—properties critical to the safety of heart assist devices. Their introduction represented a significant advancement, as earlier polymers lacked these essential characteristics, which hindered the progress of applications such as heart balloon pumps and ventricular assist devices throughout the 1960s.

In 1977, the chemical company Upjohn commercialized the first thermoplastic polyether urethane, Pelthane 2363, for medical applications.[8] This material became the first polyurethane utilized in an implant, specifically as a catheter for the Avocatan heart balloon pump, while still classified as a testing material. As the integration of polyurethane into medical devices expanded, research addressing toxicity and stability within the body gained momentum. The hydrolysis issues observed with polyurethane polyesters motivated early research efforts, leading to studies by Parins and colleagues, who published initial findings on the degradation of Pelthane 80-2363, followed by Lem, who noted relative stability across various polyurethane formulations. Subsequent investigations identified the susceptibility of polyether urethanes to oxidation, alongside significant concerns regarding the potential carcinogenicity of polyurethane materials. Through continuous research and development, the understanding of polyurethanes' role in medical applications has evolved, paving the way for innovations and enhancements in biomaterials capable of meeting the complex requirements of contemporary medicine.

Developments in Polyurethane Biomaterials: A Historical Perspective

In 1978, a seminal publication by Baxter and Travounol disclosed that certain sterilized blood bags, identified as Texin, contained methylene dianiline. This revelation raised significant concerns within the medical community, which escalated in 1988 when Blais from the Canadian Ministry of Health highlighted issues pertaining to gel-filled silicone breast prostheses coated with polyurethane foam, referred to as the Mim prosthesis. The concerns raised by Blais were substantiated by research conducted by Batich and Williams, alongside Goudon and

colleagues, thereby prompting a renewed focus on the stability and potential toxicity of these materials.[9] Although the potential carcinogenicity of polyurethanes is still a subject of debate, there have been no documented cases to date. In the early 1990s, manufacturers began to reassess their production and sales policies regarding medical polyurethanes, largely in response to liability concerns linked to Teflon, polyurethane, and silicone used in breast implants. In 1991, DuPont and Coritech discontinued production of Ethicon and divested Biomer. During the same year, Pelthane, which is now under the ownership of Dow, was restricted to implantation periods of less than 29 days.[10]

Anticipating these developments, Toratech Laboratories had already commenced production of an alternative polyurethane, designated 215 SPB, specifically engineered for the Pierce-Donachy ventricular assist device. Although 215 SPB exhibited performance comparable to that of Biomer, it presented different chemical properties. In 1991, the Polymer Technology Group, based in Berkeley, Canada, and the United States, began producing "cloned" polymers that were chemically identical to original materials, thus facilitating transitions for manufacturers of existing devices without necessitating comprehensive redesigns. A noteworthy example is the polyurethane Biospan, which was formulated to possess equivalent stabilizer content and similar physical and chemical properties to Biomer. This strategic approach not only simplified material substitutions but also streamlined regulatory processes, particularly those mandated by the Food and Drug Administration (FDA), which typically require extensive testing for material modifications in clinical devices. The emergence of Biospan and 215 SPB coincided with the initial clinical applications of ventricular assist devices and artificial hearts,[11] leading to numerous clinical implants utilizing these newer polymers as opposed to the original "legacy" materials. Soft segment-based polyether urethanes, especially those incorporating PTMO due to their exceptional flexural performance in blood flow applications, have emerged as strong candidates for blood pumps. Nonetheless, various devices and implanted prosthetics have unique requirements that necessitate the ongoing development of new material formulations. Factors such as metal ion oxidation and fluctuations in ambient pressure can adversely affect performance. Established manufacturers, such as Medtronic, address these challenges by implementing stringent production protocols and meticulously controlling processing parameters.[12]

Researchers have explored alternative soft segments to enhance performance and longevity, focusing on methods to eliminate or minimize ether and ester linkages. One notable strategy involves the blending of stable and hydrophobic polydimethylsiloxane (PDMS) with soft polyester or polycarbonate segments in the formulation of polyurethanes. In 1988, Pinchuk and colleagues published findings on PDMS covalently bonded to polyurethanes and proposed an end-group approach informed by experiences with Avocatan 51. More recently, Gantillack and Mejz reported the development of a new series of polyurethanes exhibiting high biocompatibility and superior properties attributable to elevated siloxane content in both the hard and soft segments. Additionally, Zicher introduced aliphatic polyurethane polycarbonates, branded as "biodegradable polyurethanes" (Crownflex), which have demonstrated increased biodegradability compared to their previously introduced aromatic counterparts. The Cortans developed by Pinchuk at Corvita received a patent for biomedical applications in 1992; however, polycarbonate polyurethanes remain commercially successful as stable elastomers and coatings. These materials present a viable alternative to biological polyurethane materials derived from polyether, particularly when oxidation is considered the primary mode of degradation. When copolymerized with silicone polyols, polycarbonate polyurethanes have been found to combine

the hydrolytic stability of PTMO-based polyurethanes with the oxidative stability associated with the soft polycarbonate segment. The Polymer Technology Group has secured patents for these innovative formulations. Furthermore, Mejz and Gantillack have developed a range of macrodiols with fewer ether linkages than PTMO, wherein polyurethanes derived from materials such as poly(hexamethylene oxide), poly(octamethylene oxide), and poly(dekamethylene oxide) demonstrate significant improvements in stability. Kuri and his colleagues at Medtronic have introduced biocompatible polyurethanes utilizing dimer acid soft segments, which have yet to achieve commercial viability. Currently, efforts to enhance biological stability in vivo are being actively pursued by several research groups through various innovative modifications. Despite these advancements, PTMO-based thermoplastic polyurethanes and polycarbonate soft segments remain the principal classes of polyurethanes employed for chronic implantation, owing to their extensive documentation and historical performance concerning adverse events, thereby ensuring their continued centrality in biomedical applications.[13,14]

1. Biocompatibility of Polyurethanes

The biocompatibility of polyurethanes has been extensively investigated through both in vitro and in vivo studies, focusing on the enzymatic and tissue responses elicited by these materials. Understanding the interactions between cells and the kinetics of these biomaterials is essential for their application in organ replacement and tissue maintenance. In vitro testing is imperative for assessing the biocompatibility of any material; common methodologies include cytotoxicity tests that evaluate the effects of extractable substances from a biomaterial on cell viability and morphology. Direct contact assays, frequently utilizing fibroblasts and endothelial cells, are standard approaches for assessing the toxicity of these materials. Fibroblasts and endothelial cells are typically favored for cytotoxicity testing; however, other cell types, such as neutrophils, lymphocytes, monocytes, and epithelial cells, may be employed based on specific applications involving skin, blood, tympanic membranes, and the cornea when interfacing with the biomaterial.

In vivo studies further evaluate the cellular and tissue responses to polyurethanes, often through implantation at subcutaneous, intramuscular, or intraperitoneal sites. Additional recommended sites for implantation encompass the cardiovascular system (including grafts and synthetic vessels), stents, sinkhole valves, catheters, tympanic membranes, intraocular lenses, the esophagus, ureters, biliary tract stents, and other internal prosthetic applications.[15]

2. Blood Compatibility of Polyurethanes

In the late 1960s, Bortis, followed by Lehmann in the early 1970s, established the blood compatibility of urethane polyurethanes, which have since found extensive application in the medical field. Notably, these materials are utilized in the fabrication of artificial hearts, intra-aortic balloons, pacemakers, heart valves, and hemodialysis membranes. The first comprehensive studies examining the blood response characteristics of polyurethanes emerged in the early 1980s and were primarily concerned with the influence of chemical composition on predefined segmented polyurethanes. This research employed three distinct polyether soft segments—poly(tetramethylene oxide), polypropylene oxide, and poly(ethylene oxide)—in conjunction with two diisocyanates: tolylene diisocyanate and diphenylmethane diisocyanate.[16] To mitigate the thrombogenic potential of polyether urethanes, Lala and colleagues investigated the role of ionic domains in influencing the adsorption of platelets and fibrinogen on polyurethane surfaces. Their research focused on utilizing the chain extender N-methyl diethanolamine within zwitterionic, anionic, and cationic polyurethanes, contrasting these findings with those related to neutral urethanes. The results indicated

that the ionic segregation within the material and the preferential presence of anionic end groups on shorter side chains at the surface significantly impacted protein adsorption. This suggests that the synergistic effects of both charges contribute to an enhanced surface environment that promotes blood compatibility.[17,18]

Furthermore, the 1980s marked the advent of discussions regarding hydrophobicity in polyurethanes, defined as the polymer's capacity to absorb water upon contact with blood, thereby reducing platelet adhesion and enhancing blood compatibility. However, Lala and her colleagues reported counterintuitive findings, indicating that while cationic hydrophobic polyurethanes exhibited elevated levels of platelet and fibrinogen adsorption, neutral hydrophobic variants did not follow this trend.

Subsequent investigations in the late 1980s demonstrated that small vascular constructs fabricated from hydrophobic polyether urethane displayed low hemolysis rates alongside heightened thrombosis levels in vivo. An array of studies has since delved into the chemical, morphological, and structural transformations within polyurethanes and their respective blood responses. Modern methodologies, including synthesis and surface modifications such as variations in chemical composition and coating techniques, have been implemented in efforts to enhance blood compatibility.

2.1. Heparin

A critical advancement in augmenting the blood compatibility of polyurethanes involves the covalent attachment of heparin, a well-known anticoagulant. Various studies have established that the stabilization of heparin on polyurethanes through differing reaction patterns can effectively inhibit material-induced clotting.

Unlike other biomolecules, such as albumin, which may depend on surface adsorption, heparin necessitates the formation of covalent bonds to maintain its efficacy, as heparin adsorbed from polyurethane surfaces is prone to dissipation within hours due to its high solubility and low affinity for surfaces in comparison to aqueous environments. Several stabilization methods have been explored. For example, covalent bonding facilitated by a hydrophilic polyethylene oxide (PEO) spacer, achieved through a diisocyanate reaction, has proven effective in enhancing the coverage of heparin and increasing the density of reactive stabilization sites. Narayanan and colleagues utilized a polyethylene imine spacer to attach heparin to polyurethane after activation in a water/oxygen plasma environment, employing a water-soluble carbodiimide. Their approach modified both the internal and external surfaces of the tubes to bolster performance. Similarly, Lindau and colleagues employed carbodiimide to covalently bond heparin to partially hydrolyzed polyacrylamide, effectively delaying thrombin production on the surface. Furthermore, Kang and collaborators advanced the field by stabilizing heparin through carbodiimide on carboxylic acid or amino groups derived from tri-azole acrylate grafted onto oxygen plasma-modified polyurethane. This contributes to a comprehensive suite of methodologies aimed at enhancing the blood compatibility of polyurethane materials.[19]

Recent work by Gravinger and Park, along with their research teams, has concentrated on innovative strategies to improve the blood compatibility of polyurethanes by applying heparin-PEO-PDMS coatings or block copolymers of PEO with Biomer™ heparin to polyurethane substrates. In these systems, the hydrophobic blocks effectively adhere to the substrates, while the hydrophilic heparin-PEO segments expand upon exposure to aqueous environments. In particular, in the latter copolymer, 4,4’-Diphenylmethane diisocyanate (HDMI) is linked to the Biomer™ through an aliphatic/biuret reaction, with PEO binding via terminal hydroxyl groups. The remaining hydroxyl groups on the PEO chains react with HDMI to facilitate the attachment of heparin through isocyanate groups formed during the reaction. The resultant terpolymer exhibits the bioactivity associated with heparin, with studies indicating that a PEO molecular weight of 3.4

kDa is optimal for heparin binding to the surface. The efficacy of surface-immobilized heparin is profound.[20]

Research conducted by Ito and colleagues demonstrated that electrostatic repulsion occurs between platelets and the anionic surface of immobilized heparin, rather than as a direct physiological response attributable to the heparin itself. Protein adsorption studies further elucidated that surface-bound heparin inhibits the adsorption of both albumin and fibrinogen, exhibiting a low affinity for thrombin. Conversely, proteins such as fibronectin and antithrombin III still exhibit binding to this coating, indicating that immobilized heparin establishes a protective barrier against the adsorption of various proteins. Consequently, the efficacy of this coating is not exclusively reliant on the protein-repellent properties of PEO. Critical evaluations by Winterton and colleagues have assessed the biological activity of surface-bound molecules, investigating how these can diminish protein adsorption when applied as coatings using PEO and polysaccharides other than heparin. It is noteworthy that heparin interacts with several proteins characterized by specific heparin-binding sites; its highly ionic nature can precipitate non-specific adsorption of various plasma proteins. Given that fibronectin is essential for platelet adhesion and activation, the absence of fibrinogen in certain coatings represents a potential limitation in achieving long-term biocompatibility. Understanding the interactions among proteins, such as fibronectin and antithrombin III on heparin-immobilized polyurethane, is critical for extrapolating findings from single-protein model studies to real in vivo applications. Numerous investigations have identified fibrinogen adsorption on blood-compatible coatings, underscoring the complexities within biological pathways governing hemostasis.

It is imperative to recognize that immobilized heparin may degrade under in vivo conditions, leading to a gradual decline in coating effectiveness over time—an occurrence that is applicable to all molecules subject to hemostatic, immunogenic, or metabolic influences. An intriguing alternative involves synthetic polymers that mimic natural biomolecules. For instance, Ito and colleagues explored the utilization of poly sodium vinyl sulfonate, a synthetic compound that activates antithrombin III. This polymer was stabilized through atmospheric plasma modification and graft polymerization on polyurethane, resulting in diminished interactions with proteins and platelets in both in vivo and in vitro settings.[21]

A noteworthy investigation by Gorman and colleagues tested the hypothesis that heparin-coated perfusion circuits could mitigate the formation and activity of thrombin, along with fibrinolysis and the activation of platelets, complement, and neutrophils in 20 adult patients undergoing cardiopulmonary bypass. Various blood tests were conducted, and post-operative sampling of the tubing was performed. While the heparin-coated circuits demonstrated reduced platelet adhesion, they did not confer significant advantages in other clinical evaluations. The study concluded that heparin-coated circuits, when employed alongside standard systemic heparin dosages, diminished platelet adhesion and improved platelet function but did not yield a remarkable anticoagulant effect during cardiovascular bypass procedures. These conclusions have been further validated by subsequent research.

Moreover, Winterton and colleagues raised an important consideration regarding the application of heparin coatings in medical devices, such as intraocular lenses (IOLs). If it is indeed true that immobilized heparin reduces clot formation via specific biological mechanisms, it prompts questions about its capability to prevent the occurrence of secondary cataracts.[22] Conversely, the adsorption of fibronectin—a cell-adhesive glycoprotein—onto immobilized heparin suggests that cell colonization on heparin-coated IOLs may occur through a fibronectin-mediated mechanism. Hence, a coating characterized

by minimal bulk may present a more effective approach for preventing cell re-colonization. This consideration emphasizes the challenges inherent in designing medical coatings that succeed in one specific context yet face hurdles in other medical engineering applications. Ultimately, numerous instances indicate that a coating, devoid of a comprehensive understanding of its biological functions and the molecular interactions between the coating and associated proteins across varied medical applications, may yield unexpected outcomes.

3. Biodegradability of Polyurethanes

Another critical challenge in the investigation of polyurethanes for medical applications pertains to the preparation of recovered samples for analysis. The comprehensive removal of inhibiting tissues, cellular material, absorbed blood clots, or residual protein layers from medical devices is imperative for accurately assessing alterations in both the surface and bulk properties of polyurethanes. However, medical devices are frequently subjected to fixation using formaldehyde or glutaraldehyde, resulting in extensive networking and the formation of strong chemical bonds with the device structure. This fixation process complicates the thorough removal of implants, and methods aimed at cleaning can introduce artifacts that distort material analyses. For instance, should residual tissues, lipids, or protein attachments persist, it becomes infeasible to rigorously evaluate the changes induced by biodegradation through a detailed examination of surface chemistry or mechanical properties. In such situations, only macroscopic observations—such as dimensional changes, discoloration, cracks, and fissures—can be conducted, thus constraining the understanding of the underlying biocompatibility and performance of the materials under in vivo conditions.

To analyze the chemical intricacies of device degradation following implantation, it is essential to eliminate any attached tissues. Various methods have been explored for this purpose, including the application of sodium bicarbonate, a range of washing agents, and pancreatin. However, these cleaning procedures do not consistently suffice in removing sufficient fixed tissue, thereby hindering sensitive surface analyses of polyurethane materials. Alternative techniques, involving acidic or basic conditions, have also been examined; nevertheless, some methods may be excessively harsh, potentially inflicting significant damage to the polymer structure. For example, Zhang and colleagues reported that aggressive cleaning methods applied to vascular grafts resulted in a notable reduction in carbonate group content near the surface of Vascugraft™ implants, adversely affecting both molecular weight and urethane content. Furthermore, these studies indicated that exposure to elevated temperatures, approaching boiling point, led to substantial alterations in the micro-porous morphology and micro-fibrosis of polyurethane vascular grafts. To accurately assess the effects of implantation and cleaning agents, it is advisable to conduct control cleaning tests on intact materials under conditions that replicate those experienced by devices post-extraction from the body.[23]

3.1. Degradation in In Vivo Applications

3.1.1. Cardiac Pacemaker Insulators

In 1986, Pirzada and colleagues published the first long-term study of polyurethane-coated unipolar electrodes in patients, reporting the absence of observable surface cracking leading to insulation failure, except at sutured sites. However, this investigation focused exclusively on macroscopic properties and overlooked deeper chemical analyses.

Subsequent research by Chawla and colleagues examined polyurethane cardiac pacemaker leads, which exhibited significant electrical disturbances upon removal from the body, employing techniques such as optical microscopy, scanning electron microscopy (SEM), and Fourier-transform infrared (FT-IR) spectroscopy. Their findings revealed extensive damage to the

polyurethane insulation, characterized by prevalent cracking. Many retrieved leads displayed dull, rough, and uneven surfaces. Examination of lead insulation at 30x and 300x magnifications using SEM revealed patterns of transverse erosion as well as areas of diminished grading. Evidence of wear and cracking was particularly pronounced near the electrode, with material shrinkage contributing to further degradation at the electrode junction, suggesting that stress and strain accelerated the degradation process. FT-IR analyses demonstrated that for the retrieved leads, specific spectral regions—2800-3000 cm^{-1} (C-H bonds), 1730 cm^{-1} (C=O), 1368 cm^{-1} (CH_3), and 1105 cm^{-1} (C-O)—exhibited a reduction in intensity compared to a reference polyurethane tube, indicating significant destructive alterations in the polyether components.[24,25]

Internal insulation damage was also observed in leads retrieved from human patients, occasionally accompanied by degradation of the inner surfaces of the outer coaxial lead conductor (Figure 2).

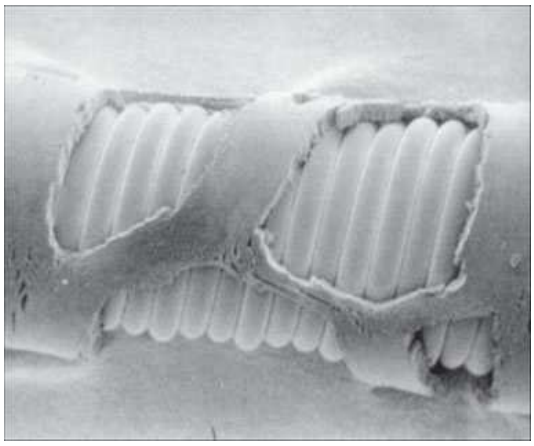

Figure 2 - A cardiac pacemaker lead removed from the body 14 months after implantation. Residual stress in the insulation led to cracks perpendicular to the longitudinal axis of the device.

Moreover, Stokes and colleagues noted that the visual appearance of degraded polymers varied, ranging from colorless to amber and even to darkened shades resembling soft, resin-like materials. Degraded segments were typically small, affecting only a few millimeters along a 58-centimeter length of the device. A noticeable decrease in PTMO ether content was documented in the extracted leads. Additionally, Stokes and colleagues reported the occasional presence of cubic crystals near decomposition sites, identified as silver and chlorine. This finding indicated that metals had leached from conductive coils, contributing to the biodegradation of the polyurethane.

Notably, the concentration of transition metals within the polyurethane insulation of leads corresponded with the duration of implantation, even in the absence of bulk degradation. Nickel, in particular, was detected near degradation sites, along with other metals such as silver, cobalt, iron, and chromium. The impact of these metals on biodegradation varied, as the degree of damage to Pellethane™ 2363-80A was ranked in severity as follows: >Ni >PtCo >>Fe, MP 35 N >DBS, Mo, Ag >304 SS, Cr, Ti >Elgiloy. This evidence, combined with observations of corrosion in metallic components, strongly suggests that these metals play a pivotal role in the polymer degradation process.

For instance, after one year of subcutaneous implantation in rabbits, Pellethane™ 2363-80A tubing exhibited severe degradation at cobalt rod contact points, with cracks observed throughout the material's thickness in three samples.[26]

3.1.2. Heart Valves

In animal studies, polyurethane heart valves predominantly encountered challenges such as calcification, coagulation, and mechanical failure. McKay and colleagues determined that the initial generation of polyurethane valves exhibited poor performance in durability tests, failing to withstand over 100 million cycles—approximately equivalent to 2.5 years of physiological cycling. In contrast, advancements in valve technology have led to the development of polyurethane valves constructed from C156Lycra®, which

successfully endured over 400 million cycles, equating to nearly 10 years of in vivo operation. Remarkably, certain PEUU valves surpassed 800 million cycles without failure, indicating over 20 years of clinical viability. Comparatively, valves fabricated from traditional PEU materials exhibited shorter lifespans and failed earlier than their PEUU counterparts.[27]

McKay and colleagues also observed that calcium deposits tended to accumulate in areas subjected to mechanical stress and near surface defects. Plaque-like formations on the leaflets of the heart valves contained both calcium and phosphorus. Two distinct forms of calcification were identified: one associated with the polyurethane surface or the interface between the leaflet and smaller blood clots or fibrous capsules, and the second characterized by extensive calcification and cellular destruction. Hilbert and colleagues reported that the calcification process occurred independently of changes in the physicochemical properties of the polyurethane, coexisting with surface coagulation, fibrous capsule formation, and cellular damage. Notably, calcium deposits were frequently associated with microbubbles observed on the polyurethane leaflets, while surfaces that remained immobile exhibited no signs of clot formation or calcification.[28]

3.1.3. Vascular Prosthetics

Considerable progress has been made in the development of artificial blood vessels, particularly small-diameter vascular grafts. Polyurethanes have garnered significant attention due to their favorable mechanical properties; however, prolonged implantation durations necessitate meticulous investigation into their biostability to ensure device success. For example, the biostability of a hydrophilic micro-porous vascular prosthetic fabricated from Mitrathane®, a polyurethane based on PTMO, MDI, and ED, was assessed. Pinter and colleagues reported that after six months—the longest implantation period studied—all vascular grafts had been occluded with clots and exhibited varying degrees of degradation on their external surfaces. Importantly, the in vivo surface degradation observed in Mitrathane® prosthetics was not attributed to simple chemical hydrolysis, as the polymer exhibited stability when immersed in water at 37 degrees Celsius for up to 11 months. Furthermore, Mavrin and colleagues noted small cracks in implanted Mitrathane® components after just 15 days, suggesting that these defects might arise from cycles of swelling and deswelling.[29]

3.1.4. Calcification / Mineralization

Calcification, defined as the deposition of calcium-containing minerals, occurs in a wide range of cardiovascular and non-cardiovascular medical devices. It is a primary macroscopic cause of defects in bioprosthetic heart valves and a limiting factor for the longevity of both laboratory-made mechanical blood pumps and polymeric heart valves, including those incorporating polyurethane components.

While calcification is a normal physiological process in the formation of bone, dentin, and enamel, calcium deposits in soft tissues are uncommon; nevertheless, they can manifest on biomaterials implanted within the bloodstream or under specific conditions, as well as within connective tissues. Ashun and colleagues indicated that the determinants of mineralization encompass factors related to the host's metabolism as well as the structural and chemical properties of the implant. The nucleation and growth of mineral deposits generally occur at interfaces involving either implanted components (internal) or elements associated with surrounding tissues, such as blood clots, adjacent cells, or pseudo-intima (external). In the context of blood flow across smooth surfaces, such as in polymeric trileaflet heart valves, most deposits are linked to external calcification mechanisms.

Calcium-containing deposits frequently correlate with surface defects, which may arise during manufacturing or degradation processes. Mineralization typically does not occur in areas devoid of defects, as these surfaces represent high-energy sites that facilitate the adsorption of ions, proteins, and other molecules, thereby serving as

nucleation sites for crystal growth. Both the hard and soft segments of polyurethanes develop surface defects; however, findings from Bornak et al. using FT-IR spectroscopy indicate that the hard segment components may play a more significant role in the calcium mineralization of PEUU compared to PEU. This observation suggests that the ether components in the soft segment contribute less significantly to the mineralization processes.

A critical factor in evaluating calcium mineralization associated with biomaterials is the age and species of the animal utilized in such studies. The dynamics of calcium turnover in young, growing animals significantly differ from those in adult specimens, potentially resulting in accelerated mineralization within medical devices. Additionally, the mechanical loading conditions and the frequency of loading cycles vary with the age of the animal. Furthermore, the implantation site exerts a considerable influence on the rate of calcium mineralization. For instance, Bornak et al. noted that samples of polyethyleneurethanes (PEUU) exhibited lower levels of mineralization than those subjected to a subcutaneous implant model tested in prairie dogs, particularly at the pericardial implantation site in bovine subjects.[30]

As previously discussed, calcium mineralization associated with biomaterials represents a complex interaction influenced by intricate metabolic processes. Consequently, it remains ambiguous whether calcium mineralization is a direct consequence of polyurethane (PU) degradation, a side effect of such degradation, or a distinct molecular phenomenon altogether. Nonetheless, it is critical to note that device defects can also contribute to processes of calcium mineralization.

3.1.5. Electric Stresses

Given the prevalent use of polyurethane materials as insulation for pacemaker leads, it is imperative to acknowledge the potential effects of electrical discharge on the dielectric properties of the insulation sheath. When an insulating material comprises two or more distinct phases or contains dispersed macroscopic regions, the formation of space charges at these interfaces occurs due to discrepancies in conductivity and dielectric permittivity. Such accumulation of space charge leads to field distortion and may result in dielectric losses. Interfacial polarization can arise from various factors. In biomedical polyurethanes, such as those used in pacemaker insulation, the limited solubility of water may contribute to the onset of interfacial polarization effects. Numerous studies have indicated a correlation between interfacial losses and the presence of water. Additionally, ionic conductivity, which can arise from trace amounts of catalysts or other ionic impurities in commercially available polymers, further contributes to dielectric loss.

Moreover, the "treeing effect," a phenomenon characterized by initial electrical degradation commonly observed in polyethylene cable insulation, can manifest when materials are subjected to electric stress, particularly in pacemaker applications. This microscopic damage progresses through a dielectric section under electrical stress, leading to localized changes in dielectric properties that may facilitate further damage along field lines. This phenomenon resembles miniature electrical discharges occurring at sites of least resistance, despite the fact that the applied voltage in pacemaker leads is typically no more than 5 volts. Notably, the treeing effect can occur under low electric stress in the presence of moisture, even in the absence of discernible partial discharges.

Several factors—including water adsorption, polymer morphology, localized structural defects, and mechanical stresses—play critical roles in the mechanisms that give rise to treeing effects. The microphase structure of polyurethanes is conductive and contributes to the dielectric conditions that facilitate treeing. Although initial degradation may exacerbate treeing conditions, research on this aspect within polyurethane applications, particularly in conjunction with metallic conductive

materials, remains limited. Further investigation is warranted to address this significant concern.[31]

4. Polyurethane Configurations in Medical Applications

Polyurethane materials are integral to a variety of medical applications, necessitating that each configuration exhibits a comprehensive set of mechanical properties tailored to its physical and chemical environment.

4.1. Tubing

Biomedical polyurethane tubes can be fabricated using three primary methods: extrusion, solvent casting, and fiber methods. In the extrusion process, temperature control is paramount, as excessive heat may lead to polymer degradation. Although extrusion is generally the preferred method for tube fabrication, solvent casting can be advantageous for producing smaller quantities of specialized tubes. Typically, these tubes are formed around a polymer band—often derived from polyolefin or polyvinyl chloride—with a segment of the tube positioned on a metallic mandrel that is subsequently removed. It is essential to completely eliminate residual solvent, as it can adversely impact the performance of the final product. This can be achieved through various methods, such as gas flow, low-heat drying, or vacuum drying. Following the drying process, the products should be washed with water to ensure the removal of solvent residues. However, caution is warranted during the washing process, as water exposure may result in undesirable side reactions, underscoring the necessity for meticulous solvent selection.

To produce thicker sections, multiple iterations of this process may be executed. Conversely, porous tubes can be fabricated using fiber methods, wherein strands obtained through spinning are woven or assembled into cylindrical sections. This fibrous winding can also be applied directly by adjusting the rotational pattern on a screw mandrel, thus providing the advantage of controlling porosity, pore size, and orientation through variations in rotational speed.[32] Additional fabrication methods, such as lamination and spraying, have also been explored and are discussed in greater detail elsewhere.

4.2. Coatings

Polyurethane coatings are employed to alter the surface properties of various biological materials. These coatings are versatile, offering benefits such as flexibility, toughness, excellent electrical insulation, and strong adhesion. While traditional solvent and spraying methods remain the most commonly utilized techniques, plasma spraying is gaining traction as an alternative approach.

The selection of solvent in the solvent method is critically important, as only a limited number of solvents are compatible with polyurethanes. Due to both scientific and economic considerations, a high polymer concentration is preferred to minimize solvent usage; however, this must be balanced against the viscosity of the mixture and the desired properties of the coating post-solvent removal. Cleanliness is paramount in the preparation of the coating surface; it must be devoid of contaminants, and moisture levels can often be improved through etching processes, whether liquid or plasma-based. Other methods, including hot melt deposition, the use of surface-modifying additives, and fluidized bed techniques, have also been investigated and are discussed in greater detail elsewhere.[33]

4.3. Foams

Polyurethane foams are primarily produced through the reaction of water with isocyanate, resulting in the generation of carbon dioxide.

This preparation process involves the formation of gas bubbles within a liquid mixture, which subsequently polymerizes, causing the bubbles to grow and stabilize into a solid polymer structure. Foam formation occurs in three critical stages: the colloidal characteristics of the bubbles, the dynamics of bubble growth governed by diffusion, and the solidification and curing processes that produce the final product via

heat and mass transfer. In addition to the essential components—polyisocyanate, polyol, water, and catalysts—foam production often necessitates the inclusion of additives such as nucleating agents, secondary blowing agents, and surfactants. The influence of these additives on biological responses remains largely unclear and requires thorough evaluation.[34]

4.4. Fibers, Sheets, and Films

Polyurethane fibers are predominantly manufactured through extrusion and fiber spinning methods, which rely on isocyanates and chain extenders. In specific cases, the solvent reaction method, as described by Lamba et al., may be utilized to produce fibers with irregular cross-sections. Following fiber production, various components can be woven together using textile machinery. For comprehensive insights into polyurethane fiber applications, formulations, and production processes, existing literature provides extensive documentation. The primary methods for producing polyurethane sheets are extrusion and casting, both of which can be executed continuously and require subsequent forming equipment to finalize dimensions. In the casting method, the process typically occurs on a conveyor belt coated with Teflon or glass sheets to prevent sticking. This approach, known as slab stock, can be implemented using either the transfer or pass-through technique, which differ primarily in their methods of depositing reactive components. In the transfer method, the mixture is evenly spread onto the conveyor belt, whereas, in the pass-through method, the mixture is deposited directly onto the moving conveyor. After traversing a specified distance, the materials are subsequently cut to the desired shape. Laminating techniques are also employed to produce multi-layer sheets with varying properties. Films differ from sheets in that they are not simply thin sheets (less than 0.25 mm in thickness); rather, they are predominantly composed of rigid urethane and serve applications including packaging or surface modification to regulate vapor permeability. The gas permeability characteristics also vary with increased network connectivity and are dependent on the specific type of polyurethane employed (e.g., polyether, castor oil-based, or polyester). Films are typically created using solution casting methods. To achieve films that are clear and devoid of bubbles, it is essential that the polymer is fully dissolved to yield a transparent solution. In the dipping process, achieving consistent thickness necessitates meticulous control over the solution's adhesion and solid content concentration. Viscosity primarily influences the thickness of the wet coating, while the solid content concentration governs the thickness of the dry coating.[35]

5. Sterilization

Sterilization is a paramount requirement for all medical polymers, ensuring their integrity while effectively eliminating microbial life. This process encompasses three principal methods: heat, gas, and radiation. The effectiveness of sterilization is primarily contingent upon the chosen method rather than the materials themselves. Should a specific material not conform to the parameters of a selected sterilization process, it is advisable to consider alternative methods. Adjustments to sterilization parameters have a direct impact on the efficiency of the process.

Two methods may be employed to assess this effectiveness. The first involves immersing the equipment in a liquid microbiological culture; in instances where the device remains sterile, no microbial growth will be observed. The second, a more efficient and widely adopted method, determines the Sterility Assurance Level (SAL), defined as the probability of observing fewer than one instance of non-sterility per million implanted devices.

This technique includes a bioburden assessment, which quantifies the number of viable microorganisms present on the implant prior to sterilization, followed by the execution of sterilization checks to graphically delineate the assurance level, typically ranging from 6 to 10.[36]

6. Cardiovascular Applications of Polyurethanes

The conditions required for polymeric materials in the production of various cardiovascular devices depend significantly on their intended duration of application, methods of application, and performance criteria. Generally, these devices can be categorized into three classifications: transient, intermediate, and permanent.

- Transient cardiovascular devices are commonly utilized in emergency scenarios, typically for durations ranging from several days to a few weeks. This category encompasses intra-aortic balloon pumps, temporary left ventricular assist devices (LVADs), and biventricular assist devices, all designed for removal once the heart has sufficiently recovered.
- Intermediate cardiovascular devices are utilized for patients awaiting heart transplants due to suitable donor organs. Common examples include ventricular assist devices and total artificial hearts, which serve as critical bridges to transplantation. In cases of transplanted heart failure, these devices provide essential support but are generally intended for use of less than one month, thereby negating the need for permanent implantation.
- Permanent cardiovascular devices, such as implantable total ventricles, artificial hearts, blood conduits, and access routes, are designed for long-term implantation, typically exceeding two years. The demand for these devices raises significant considerations regarding long-term stability, blood compatibility, and material properties.

The success of cardiovascular devices is contingent upon appropriate polymer selection, a thorough comprehension of processing methodologies, proper user training, and rigorous clinical evaluation.[37]

Polyurethanes are frequently favored for their potential blood compatibility; however, despite promising outcomes associated with intra-aortic balloons and ventricular assist devices (VADs) or artificial hearts, there have been instances of unreliable scientific extrapolations and overly optimistic expectations, prompting a reevaluation of biocompatibility concepts. Throughout this discourse, the limitations of polyurethanes for long-term cardiovascular applications have become increasingly evident. Specifically, the mechanical properties of polyurethanes are critical for applications such as vascular grafts.

6.1. Intra-Aortic Balloon

The advent of open-heart surgery in the early 1950s was made feasible by the development of heart-lung machines, which maintained cardiopulmonary function during surgical procedures. This advancement effectively addressed acute and recurrent left ventricular systolic dysfunction, whereby temporary unloading of the heart's preload, facilitated by assistive pumps, permitted recovery from left ventricular failure.

The relationship between diastolic aortic blood pressure and coronary flow gave rise to the counterpulsation concept, initially introduced by Moluopoulos and colleagues utilizing intra-aortic balloon devices. Following the work of Kantrowitz and his team in 1967, the intra-aortic balloon emerged as a vital tool for supporting circulation in patients during recovery from cardiopulmonary bypass. The intra-aortic balloon, in conjunction with conventional heart-lung machines, enhances blood return to patients in a pulsatile manner, deploying a predetermined volume of gas during diastole and releasing it during systole.[38]

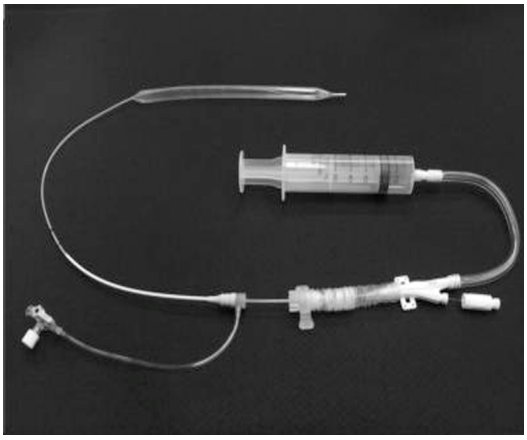

Figure 3 (A) - Intra-aortic balloon: general view

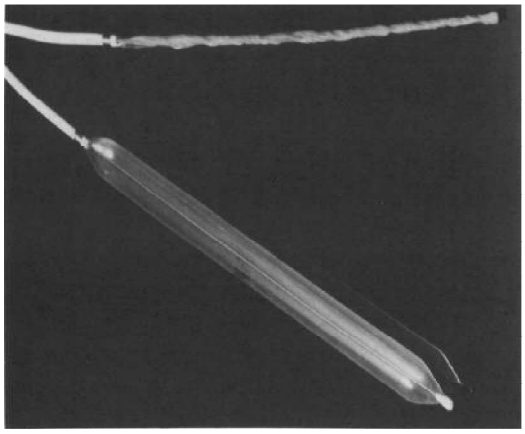

Figure 3 (B) - Intra-aortic balloon: details of the polyurethane balloon

Its primary advantage lies in its capacity to improve myocardial oxygen supply, while its inherent simplicity offers several benefits, including ease of placement and removal, minimal patient discomfort, avoidance of anticoagulant therapy, and cost-effectiveness. Presently, information regarding the properties of polyurethane intra-aortic balloon devices remains limited.

Our evaluation encompassed 112 devices, revealing that microscopic analyses disclosed no significant changes in shape or color, with no discernible wear or fractures detected. However, it was noted that 61% of the polyurethane intra-aortic balloons exhibited collapse, with 40% displaying substantial flexural defects in the central conduits and 21% in the sheaths. Additionally, breakage of organic components was observed.

Challenges associated with intra-aortic balloon utilization include catheter placement difficulties, incorrect positioning, balloon degradation, hemolysis, infections, and neurological or vascular injuries. Only a few of these complications are attributed to the polyurethane membrane, which demonstrates appropriate blood compatibility and stability during counterpulsation. Some studies suggest that this device enhances coronary flow and decreases myocardial oxygen demand, thereby improving the supply-demand ratio in the left ventricle. Nonetheless, these benefits are not consistently observed in cases of severe heart failure. Research in canine models indicated a rise in microforms of platelets due to normal-sized platelet separation, as well as signs of platelet activation and plasma membrane alterations. Findings by Bulock reported that prolonged use of intra-aortic balloons in patients resulted in decreased red blood cell and platelet counts.

Common chemicals such as acetone, ether, and Vi-Drape spray can damage polyurethane intra-aortic balloon catheters, leading to hardening and rupture of the polyurethane material. It is critical to prevent contact with these substances during dressing changes or while preparing sterile surfaces. In contrast, isopropyl alcohol has been demonstrated to be safe for these applications.

The implantation of intra-aortic balloons is a well-established procedure that effectively increases coronary artery pressure while reducing left ventricular pressure, thus serving as an indispensable tool for patients following open-heart surgery. Polyurethane balloons are considered satisfactory, reflecting a degree of maturation in this technology.

Over the past 25 years, there has been a notable increase in cardiac surgeons' satisfaction with these devices. Currently available intra-aortic balloons exhibit adequate blood compatibility, flexibility, biocompatibility, and durability for clinical applications that last several weeks. Minor improvements may still be anticipated; however, no fundamental changes are deemed necessary given the low defect rate. Emerging issues are likely associated with manufacturing defects or friction against calcific plaque. It appears that a single manufacturer currently dominates the market for these devices, adequately meeting the needs of the medical community. Prospects for new developments or the introduction of competing polymers in this well-established field appear minimal.[39]

6.2. Heart Valve

Research into prosthetic heart valves utilizing polyurethane commenced in 1958 with the introduction of a polyurethane film, which was sandwiched between solid Teflon anchoring rings and semi-circular sections for connections. From 1960 to 1962, aortic valve prostheses were developed, culminating in the first successful replacement of an aortic valve with a Teflon leaf valve in April 1960. Despite these innovations, such valves became less competitive compared to mechanical valves and bioprostheses in cardiac surgery. This limitation also extended to their application in replacing Björk-Shiley and Hall valves, which were associated with clotting complications and mechanical failures. Moreover, their high costs impeded their selection as viable artificial devices. To address these limitations, engineers developed a cost-effective valve design reminiscent of a parachute. This design features a simple structure with a thin circular polyurethane membrane mounted on a fixed polyurethane plate, incorporating numerous cavities or pores. These innovations serve to reduce flow resistance while assisting in membrane stabilization during the diastolic phase. Although this valve utilizes circumferential flow rather than central flow, its overall flow characteristics are comparable to those of the Björk-Shiley valve. Notably, retrograde flow characteristics demonstrated improvement, with no stagnant points identified around the membrane, thereby facilitating effective anticoagulation.[40]

Currently, Pellethane™ is recognized as the polymer of choice for polyurethane tri-leaflet semi-mechanical valves. The primary advantages of polyurethane valves include their cost-effectiveness and reliability for short-term applications. During the development of the polyurethane open-cell mitral valve, it was anticipated that thin and flexible leaflets would minimize flow resistance while posing a risk of inversion during systole. To optimize stress on the chordae tendineae in a beating heart, a novel prosthetic design (J-3) was created within an open environment, facilitating a transition from a nearly flat position to a cone shape, in which the leaflets can maintain stable open and closed positions. Hydrodynamic evaluations revealed minimal pressure drops and exceedingly low energy losses compared to existing valves, with downstream shear stresses remaining remarkably low.

Polyurethane heart valve prostheses are crafted from solvent-cast polyurethane sheets, shaped under heat to achieve the desired leaflet geometries. Alternatively, dipping techniques are employed, wherein stainless steel molds are submerged in a polyurethane solution to fabricate the valve leaflets.

Results from studies utilizing the dipping technique indicated a more uniform distribution of average circumferential velocity and normal Reynolds stresses from the central orifice produced by the dipped leaflets.

In a study involving a tri-leaflet heart valve prosthesis implanted in a young sheep, significant calcification occurred in the mitral position over a 21-week period, adversely impacting both hemodynamic performance and the durability of the biomaterials. Hoffman and colleagues explored a tri-leaflet semi-mechanical PU valve positioned in the mitral area, reporting initial defects primarily attributed to leaflet rupture and calcification. However, the overall performance of the valve was deemed satisfactory, leading the authors to recommend its use for temporary left ventricular assist devices (VADs).[41]

Luo and colleagues evaluated a new valve design utilizing dipping mold techniques with various polyurethane materials, demonstrating that two specific polyurethanes (Pampul and PUR 1025/1) exhibited survival times that surpassed those of bioprostheses under comparable implantation conditions.

Numerous challenges related to heart valves stem from their dynamic behavior and the resultant unstable flow patterns. A well-established correlation exists between the level of disturbance and the severity of stenosis. Laser Doppler anemometry measurements conducted in a pulse-

replicating system assessed the distal section of PU heart valve prostheses implanted in both the mitral and aortic positions, revealing maximum disturbance levels corresponding to the severity of stenosis. Moreover, the morphology of velocity and disturbance waveforms was closely associated with the geometry of stenosis and the specific valve position (aortic vs. mitral).

In terms of hydrodynamic characteristics, tri-leaflet PU valves demonstrated superior in vitro performance compared to larger or similarly sized prosthetic valves. While some studies suggest that these prostheses hold potential for valve replacement, others indicate satisfactory hemodynamic properties, with minimal platelet aggregation observed on the surface of the PU material (Avcothane™). Despite these encouraging results, acceptance among surgeons for heart surgery has been relatively limited, resulting in primarily restricted application to VADs and artificial hearts.

Currently, the use of polyurethane-based heart valves remains confined to short-term applications within VADs and artificial hearts serving as bridges for transplantation. Due to their susceptibility to rupture and calcification, these PU valves are not deemed suitable for long-term implantation. Nevertheless, for temporary applications, they offer an economical solution with adequate hemodynamic performance. Given the current stage of their development, these valves should be restricted to extracorporeal devices, rendering implantation within the body unsuitable.[42]

6.3. Vascular Grafts

At the commencement of the 20th century, research findings indicated that both homologous and heterologous arteries and veins could effectively serve as arterial substitutes in canine models, with implanted autologous vein materials also proving suitable for arterial replacement in human subjects. However, early developments in graft technology primarily concentrated on the use of non-biological tubular constructs. The introduction of Vinyon-N in 1952 signified a pivotal advancement in the realm of porous tissue arterial prostheses, particularly in light of challenges encountered with smooth-walled tubes. As time progressed, more resilient materials such as polyethylene terephthalate (PET) and polytetrafluoroethylene (PTFE) emerged, exhibiting considerable durability. While the exploration of polyurethane (PU) blood conduits garnered attention owing to their adaptable properties, the results have been inconsistent. Bovine heterografts and human umbilical cord allografts, which were once utilized in vascular surgery, have since diminished in popularity.[43]

Polyurethane grafts are distinguished by a broad spectrum of physical properties, which can be modified by varying the concentration of polyurethane, altering the freezing temperature, and adjusting the methods of freezing employed. Given that porosity is crucial for the long-term performance of small synthetic vascular prostheses, increased graft permeability has been associated with enhanced tissue integration. Implants exhibiting pore sizes ranging from 10 to 45 microns facilitated the internal growth of fibrohistiocytic tissue and capillaries, while those possessing pore sizes greater than 45 microns resulted in organized fibrous tissue development with minimal cystic response. Consequently, micro-porous vascular prostheses that retained elasticity several months post-implantation demonstrated limited internal or fibrohistiocytic tissue growth.

Several PU vascular prostheses have advanced to industrial production as substitutes for small-diameter arteries, exemplified by Corvita®, Thoratec®, Pulse Tec®, Biomer™, Mitrathane™ (available in both hydrophilic and hydrophobic forms), and Vascugraft®. Each of these prostheses showcases distinct characteristics worthy of attention.

The Corvita® prosthesis, fabricated from polyurethane carbonate, features a flexible fibrous structure with interconnected open fibrous spaces; however, it necessitates careful coating to prevent blood loss during implantation. The Thoratec® prosthesis, composed of polyether-urethane-urea,

requires no sealing or initial coagulation and promotes minimal tissue ingrowth (Figure 6). Conversely, the Pulse-Tec® prosthesis presents the fewest openings on its exterior surface, offering resistance to collapsing forces while inhibiting tissue ingrowth (Figure 7).

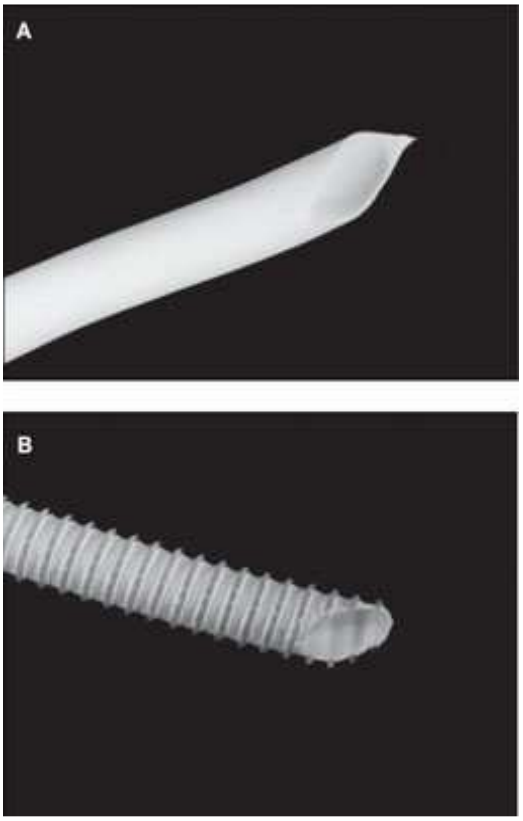

Figure 4 - Polyurethane grafts (A) without external support; (B) with external support

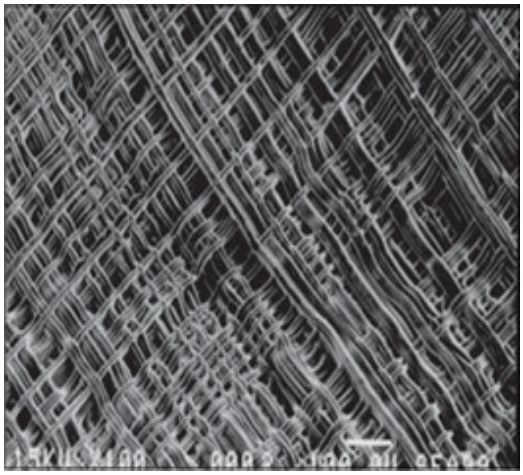

Figure 5 - Luminary surface of the Corvita™ prosthesis with interfibrous spaces with free communication pathways

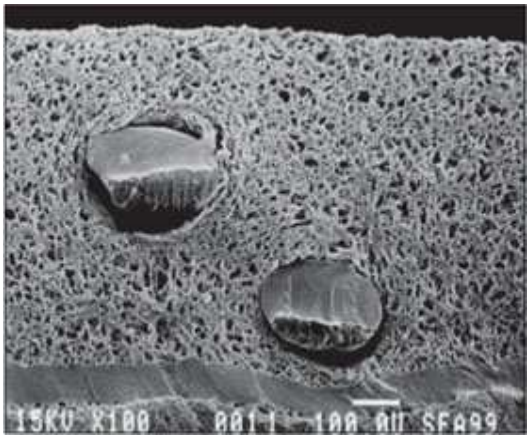

Figure 6 - Cross-section of Thoratec prosthesis with completely impermeable walls

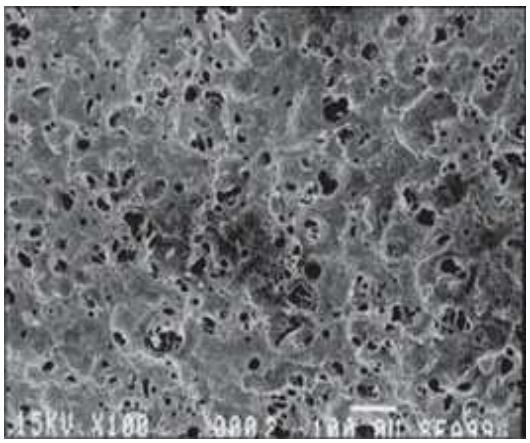

Figure 7 (A) - Pulse-Tec prosthesis with multiple holes on the surface

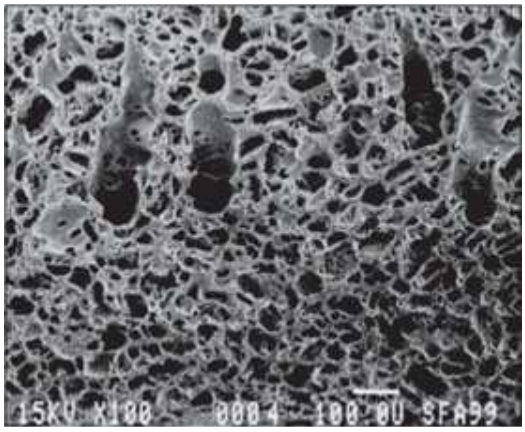

Figure 7 (B) - With a highly porous structure

Mitrathane™, a polyether urethane urea analogous to Biomer™, displays a cross-

sectional architecture comprising three distinct layers, yielding an outer layer with larger pores and an inner layer with significantly smaller pores. This design facilitates high longitudinal tensile strains and superior suture strength in comparison to expanded PTFE prostheses, with favorable radial compatibility for small-diameter human arterial tissue (Figure 8).

The Vascugraft® prosthesis is characterized by open pores extending through its wall thickness; its longitudinal and radial elasticity surpasses that of reinforced Gore-Tex® grafts. Significant attributes of the Vascugraft® include burst strength and suture retention strength that exceed minimum requirements for small-caliber arterial substitutes.

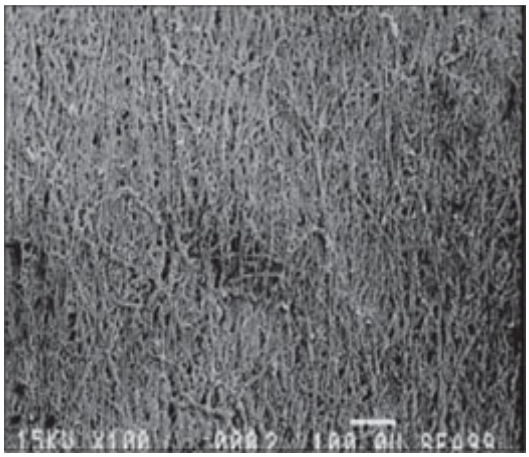

Figure 8 (A) - Mitrathane™ prosthesis with large pores on the surface

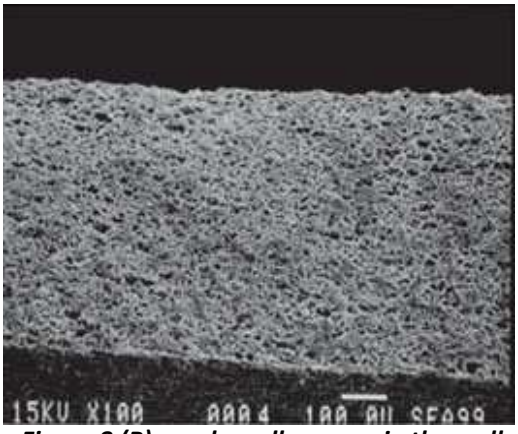

Figure 8 (B) - and smaller pores in the wall

Notably, the unique surface properties of Vascugraft® stem from the incorporation of carbonate groups, enhancing surface oxygen content. These characteristics contribute to an optimal morphology and satisfactory mechanical properties, facilitating successful long-term performance as arterial substitutes in vivo (Figure 9).

Despite the anticipated advantages of PU prostheses, including the development of a thin layer of endothelial cells on their inner surfaces, clinical outcomes have not aligned with experimental findings. Nevertheless, these prostheses exhibit commendable graft-host healing properties and resilience at suture sites.

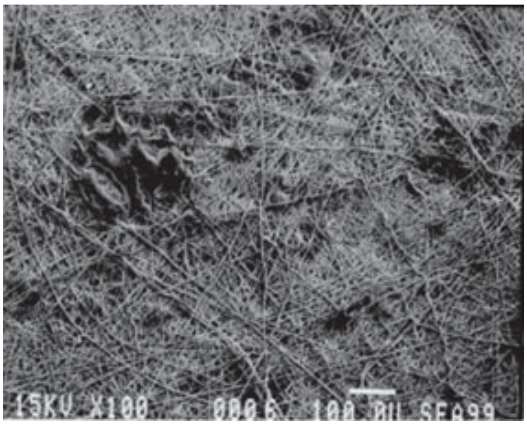

Figure 9 (A) - Vascugraft® prosthesis with open pores

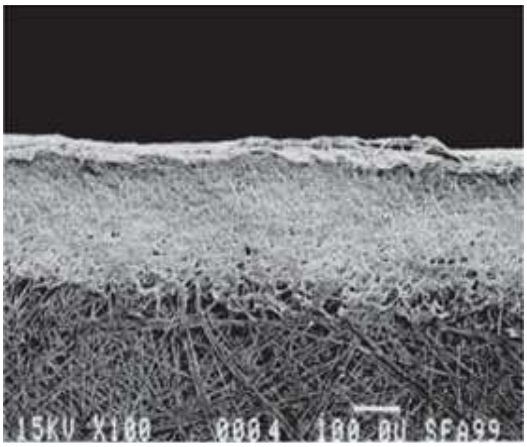

Figure 9 (B) - In wall thickness

Vascugraft® prostheses, when placed in direct contact with the endothelial layer of embryonic chicken aorta, effectively

facilitated the formation of a monolayer of cells on their surfaces. Polycarbonate-urethane vascular grafts promoted endothelialization of the lumen, leading to diminished proliferation and a thinner neointima compared to expanded PTFE (ePTFE) grafts.

To enhance coagulation resistance, researchers have explored incorporating endothelial growth factors, gelatin, fibronectin, and ADPase into these prostheses, with some studies pre-coating PU grafts with endothelial cells. Additionally, Galti and colleagues combined a biodegradable PU vascular prosthesis with a liquid-rich material, revealing that structures enriched with unsaturated fatty acids prevented coagulation in the biodegradable PU vascular prosthesis.

PU vascular prostheses have displayed potential for improved coagulation resistance and reduced anastomotic hyperplasia when compared to alternatives such as Dacron® and ePTFE; however, they remain susceptible to biodegradation and mechanical failure. Wilson and colleagues developed a composite prosthesis featuring a porous elastomeric membrane composed of polyurethane in contact with blood, supported by a Dacron® mesh in the inner layer, thereby ensuring long-term dimensional stability.

The Vascugraft® prosthesis has been regarded as one of the most stable devices for thoracoabdominal bypass in canine models over one-year periods, although it exhibited in vivo damage to PU microfibers, diminished mechanical properties, and increased microphase separation. Carboxyl groups present within the Vascugraft® PU structure underwent collagenase or pancreatin-catalyzed hydrolysis under experimental conditions, leading to elevated surface hydrophilicity, moisture content, and fiber swelling. This hydrolysis reaction, driven by enzymatic cleavage of molecular chains, was accompanied by increased molecular weight and enhanced phase separation of the material, further aiding alignment of the organized phase along the axial direction of the fibers.

Following disappointing clinical outcomes, the manufacturer decided to discontinue the marketing of Vascugraft®. Currently, polyurethane devices available on the market possess limited applications, primarily restricted to arteriovenous (AV) accesses or vascular bundles.[44,45]

Nevertheless, PU vascular prostheses remain appealing due to their tunable properties, including wall porosity, elasticity, and mechanical characteristics. Initial blood contact has been satisfactory, resulting in various structures, including microporous (with or without interconnectivity between pores), fibrillated, and smooth designs, with or without polyester reinforcement. Excellent control over these variations has been achieved, prompting numerous studies to propose PU for coronary artery bypass grafts. However, experimental animal studies often yield disappointing outcomes concerning graft coagulation rates, particularly in small diameters, which tend to underperform without pharmacological intervention. Performance in medium-diameter arteries has generally been comparable to ePTFE grafts; however, PU grafts have exhibited a propensity for expedited degradation post-implantation.[46] In light of these findings, the future of polyurethane-based blood conduits appears uncertain unless newly developed, biostable polyurethanes can achieve improved patency rates through additional surface modifications. It is important to exercise caution, as much of the research on blood compatibility relies on tests such as total blood coagulation time, which may not accurately predict long-term implant performance. Ensuring the durability of small-diameter vascular grafts necessitates substantial advancements in design and functionality, underscoring the urgent need for continual improvements over existing materials to meet the demands for sustained performance in clinical applications.

6.4. Leads for Pacemakers

The implantation of the first pacemaker in 1959 utilizing an intravenous catheter marked the inception of a technological evolution in devices designed to address

various rhythm disorders. Modern pacemakers typically comprise a power source, an electronic field, pacing mechanisms, and electrodes, with the lead system playing a critical role in transmitting electrical stimuli to the heart while simultaneously sensing the heart's electrical activity through a pulse generator. Initially, conductive wires within the lead systems evolved from helical ribbons to simple single-strand coils and ultimately to more complex multi-strand coils. Since 1977, the alloy MP35N (comprising 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum) has predominantly been employed for conductive wires. Insulation is essential within the lead system to safeguard surrounding biological tissues from electrical activity.

Early leads were designed for indefinite lifespans, as they did not contain consumable components. However, with the introduction of lithium batteries, which offer extended longevity, failures in leads became increasingly apparent. These failures are frequently attributed to degradation or loss of insulating properties, conductor failures, or electrode defects. While silicone rubber remains the primary material utilized for insulation, alternatives including polyethylene, Teflon®, and various polyurethane formulations have also been utilized.[47]

Polyurethane leads were first introduced in 1978, with A80-2363 Pellethane™ employed as insulation in the inaugural human cardiac applications.

By 1980, Medtronic had introduced over five models of cardiac leads for medical use, the majority of which utilized Pellethane™ 2363 resins for insulation. Each manufacturer has developed proprietary insulating polymers with distinct characteristics. In extruded or molded forms, polyurethanes may crystallize, leading to the separation of hard (isocyanate) and soft (polyether) segments—this phenomenon is contingent upon the ratio of hard to soft segments, as well as various other processing parameters.[48]

Although polyurethanes generally exhibit lower tensile strength, hydrolytic stability, and fatigue life in comparison to silicone rubber, they provide a significantly better coefficient of friction in blood contact. This advantage renders PU leads more manageable when positioned in smaller veins. Segmented ether-based polyurethanes have demonstrated resistance to coagulation comparable to silicone rubber; however, some studies indicate lower coagulation performance relative to silicone. These materials are frequently suitable for use in implantable devices that come into contact with blood, owing to their favorable cross-sectional properties.

Nonetheless, certain manufactured leads have revealed defects associated with manufacturing stresses, contributing to increased sensitivity to changes and complications during removal. Research conducted by Pirzada and colleagues indicated that failure rates remain a concern, as electrodes may not be retrieved following insulation failures. Consequently, these materials frequently remain within patients, presenting challenges during removal.

The insulation failure in PU leads can be attributed to three primary mechanisms: environmental stress cracking (ESC), metal ion oxidation (MIO), and crush damage—the latter frequently occurring during subclavian entry when the lead is compressed between the clavicle and the first rib.

While some researchers, including Antonelli and colleagues, have found that perforation of the subclavian vein impairs the performance of PU insulated leads, most studies have not demonstrated statistically significant differences in time to failure between leads implanted via subclavian versus cephalic approaches. Nevertheless, MIO and ESC are regarded as the most plausible explanations for insulation failures.

At present, polyurethanes, along with polyethylene and silicone rubber, are widely acknowledged for their insulation properties in pacemaker leads. Polyurethanes provide good blood compatibility, low friction coefficients, high durability under flexural stress, and commendable mechanical

strength. However, concerns regarding the biostability of polyurethane insulation materials have arisen due to the detection of fissures and stress cracks. As discussed in Chapter 5, the underlying causes of these vulnerabilities remain inadequately understood at the molecular and biochemical levels. Despite the significant issue posed by oxidative degradation, research into the development of long-term stable polyurethanes continues. Presently, competition between polyurethanes and silicone rubber for this application remains intense.[49]

6.5. Surgical Closure of Atrial Septal Defects

The surgical closure of atrial septal defects has remained a reliable procedure for over four decades, characterized by a mortality rate of less than 1% and minimal complications. However, the intricacies of cardiopulmonary bypass necessitate sternotomy or thoracotomy, leading to unavoidable hospitalization and an extended recovery period. This has catalyzed the development of minimally invasive techniques and devices for the closure of medium-sized atrial septal defects via catheterization.

More than two decades after the introduction of the two-piece "diabolic button" in 1954, King and Mills advanced the field by developing a double umbrella device featuring a central locking mechanism. Subsequently, Rashkind introduced a single-disc polyurethane prosthesis incorporating six radial legs, three of which maintained tips at right angles. Despite clinical trials involving this design producing six unfavorable outcomes among 19 patients, it laid the groundwork for further innovation in the field. Lock and colleagues introduced the Lock-USCI Clam, designed with two polyester squares facing each other, connected by four radial ligands to minimize leakage.

This concept was further refined with the incorporation of nitinol, a shape-memory alloy, resulting in the commercialized device known as Cardioseal®. Sidris and colleagues reported successful closures of atrial defects using this device, which comprises a left atrial disk (the occluder) and a right atrial stem (the occluder on the opposite side). Notably, this occluder is constructed from a square piece of polyurethane foam, although its specific properties remain inadequately defined.[50]

Building on these advancements, Babic and colleagues developed the Atrial Septal Defect Occlusion System (ASDOS), which consists of two self-expanding umbrellas crafted from a nitinol wire frame and a thin polyurethane membrane (Figure 10).

Each umbrella is designed with four arms that ensure a rounded shape upon deployment, resulting in a disc-like configuration reminiscent of a flower when viewed from the frontal aspect. Clinical results pertaining to the ASDOS have been promising, with complete endothelialization of the smooth polyurethane membrane observed three months post-implantation in porcine models. In addition to robust clinical follow-ups, further investigation into the long-term performance of such devices is imperative. Animal testing and analysis of implanted devices during reoperations or autopsy must remain a priority, alongside a comprehensive comparison with newer devices, such as the Amplatzer®.

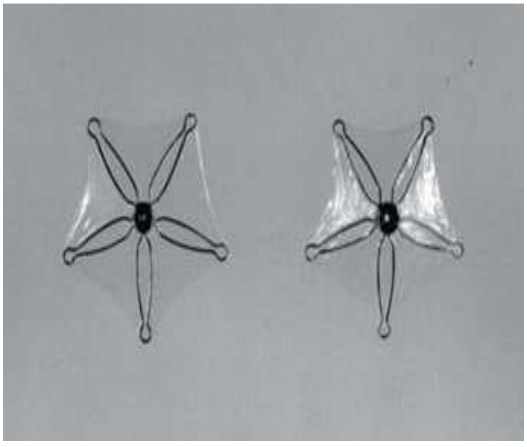

Figure 10 - Arterial Septal Defect Occlusion System (ASDOS) for closure of arteriovenous systolic defects. It consists of two self-expanding cannulas made of a nitinol wire frame with a thin polyurethane membrane.

The Amplatzer® features a mesh-like configuration composed of nitinol wire, designed to form two opposing discs with a waist in between.[51]

Despite a limited market size, the demand for non-surgical treatments for intracardiac septal defects persists as a notable challenge. Polyurethane devices reinforced with nitinol represent a compelling option; however, they must contend with polyester umbrellas and nitinol shells. Current clinical outcomes have yet to establish a definitive superiority among these alternatives, necessitating further evaluation.

Non-porous polyurethane exhibits commendable attributes regarding softness, biological response, and durability, rendering it preferable to its porous counterpart. Nevertheless, inadequate comparative studies encompassing the healing properties of both types currently hinder advancements in polyurethane applications within this domain.

In conclusion, while no significant advancements in polyurethane technology are anticipated in the immediate future, the limited market presence and considerable competition may constrain the proliferation of these devices. Nonetheless, ongoing innovations in the application of polyurethanes across various fields may create new opportunities for future exploration.

6.6. Ventricles for Ventricular Assist Devices and Fully Implantable Artificial Hearts

The development of ventricular assist devices (VADs) and fully implantable artificial hearts has confronted substantial challenges, primarily attributable to the absence of suitable polymers for blood-contacting surfaces and issues related to mechanical performance. Given that no external materials can authentically replicate the natural endothelial lining, researchers have explored diverse strategies, including the creation of a pseudo-intima and the reduction of protein or cellular interactions at the material interface.

Presently, smooth polyurethane (PU) surfaces are integrated into numerous VADs and artificial heart applications due to their capability to resist blood coagulation at the interface (Figure 11). However, identifying the most appropriate polyurethane for long-term use persists as a critical challenge. Biomer™ has been utilized in the ventricles of several VADs and artificial hearts, despite its insufficient blood compatibility. Nevertheless, it demonstrates excellent abrasion resistance and bending flexibility. Other polyurethanes commonly employed in this realm include Avcothane™-51, Elasthane®, and Pellethane™.[52]

Figure 11 - Ventricular assist device chamber made of polyurethane: despite poor blood compatibility, it exhibits excellent abrasion and flexural properties

Since Bortus and Pierse first employed segmented polyether polyurethane in a ventricular assist pump in 1967, these polyether polyurethanes have seen extensive application in various artificial hearts and circulatory assist devices. Unfortunately, these materials are susceptible to degradation due to concerns regarding elastomeric stability. Consequently, the production of older polyether polyurethanes, such as Biomer™ and Pellethane™, has diminished or ceased entirely due to their inadequate long-term performance and the associated risks during implantation. Furthermore, these materials demonstrate nearly impermeable characteristics in

relation to water and water vapor. For instance, McGee and colleagues discovered that membranes composed of Biomer™ and Tecoflex® exhibited high water transfer rates of 0.020 and 0.022 grams per square centimeter over a 24-hour period, respectively. This indicates that moisture can permeate the walls of the polyurethane elastomer, potentially contaminating the motor chamber of devices during prolonged use. Such contamination negatively impacts the durability of these devices, ultimately resulting in failure. Therefore, older polyether polyurethanes do not satisfy the stringent requirements necessary for the next generation of fully implantable artificial hearts and VADs. Thus, the identification and selection of biostable and permeable materials for novel ventricular designs is essential.[53]

Recent advancements have resulted in the formulation of new commercial polyurethanes, including Corathane®, ChronoFlex®, and Carbothane®. These polymers incorporate a conjugated carbonate linkage (O-CO-O) in the soft segment, which exhibits superior stability compared to the ether linkages (C-O-C) found in older polyether polyurethanes when subjected to biological environments. Research conducted by Pinchuk demonstrated that Corathane® films displayed greater biological stability than Pellethane™ 2363-80A in a 400% Stokes strain test. Similarly, Reed and colleagues found that ChronoFlex® films were more robust than Biomer™ films under identical testing conditions. These findings underscore the significant biostability advantages presented by polycarbonate polyurethanes in comparison to their polyether counterparts. However, polycarbonate polyurethanes may still lack sufficient resistance to biodegradation for long-term applications.

The utilization of these materials in the construction of ventricles presents notable advantages over polyether polyurethanes. Additionally, further polyurethanes have been developed as potential alternatives. For example, Biolon™, a urethane polyether produced by 3M Health Care, has been selected by researchers at Pennsylvania State University. Concurrently, the Baylor Heart Institute has restricted the use of polyether polyurethane for pump materials, while a Japanese program has embraced partitioned polycaprolactone, Miractran E980. It is vital to acknowledge that none of the commercially available polycarbonate polyurethanes are entirely impermeable to water vapor. While this characteristic reduces the risk of fluid ingress into regions where impermeability is critical, the issue remains unresolved, signaling a need for further modifications to achieve fully non-permeable ventricles for application in artificial hearts and VADs.[54]

Anticipated future developments in biomaterials are likely to exhibit enhanced biocompatibility, biological function, and long-term durability. Given their historical success and potential, polyurethanes are projected to play a significant role in medical applications. As noted by Secher, polyurethane elastomers are vital to the overall quality and efficacy of global therapeutic systems. Polyurethanes have seen widespread implementation across various prosthetics, implants, and medical consumables, particularly in applications necessitating compatibility with soft or cardiovascular tissues. Moving forward, an exploration of the future of polyurethane polymers in major applications is warranted.

As the only family of elastomers that consistently demonstrates flexibility, acceptable durability, and good blood compatibility, polyurethanes present promising prospects within the medical field. Nonetheless, there remains a pressing need to address the challenges of long-term durability and water vapor permeability inherent in these materials. With Biomer™ no longer available in the market and Pellethane™ facing limitations, the quest for novel polymers that guarantee biological stability over extended periods while maintaining performance is critical. As delineated in Section 6, several of the new polyurethanes introduced should adhere to essential criteria. It may not be imperative to

develop a single polyurethane that meets all requirements simultaneously; rather, the necessity for impermeability to water vapor can be addressed through surface modifications or coatings.

Research in this area is crucial, especially as artificial hearts represent a promising solution to the significant shortage of donor hearts. It is our belief that polyurethane elastomers hold considerable potential for advancement in this field, and as access to innovative materials expands, support for research initiatives in this domain will be essential.

7. Organ Resurrection in Tissue Engineering

The field of tissue engineering is experiencing substantial growth as it presents a promising pathway for the creation of replacement organs that are both efficient and associated with a reduced risk of rejection, in addition to the repair of damaged organs. Polyurethanes are increasingly recognized for their utility as scaffold materials. Biodegradable designs aimed at controlled tissue regeneration are anticipated to be beneficial, while biostable polyurethanes—characterized by their elastomeric properties that can be tailored across a wide range of applications—hold promise as durable structural support materials. Achieving improved biological integrity, specifically the minimization of foreign body responses such as capsule formation, is crucial for the success of these materials in applications within the realm of tissue engineering.[55]

7.1. Biodegradable Vascular Grafts

The demand for small-diameter blood conduits is increasingly acknowledged in medical applications. One promising approach involves the development of biodegradable scaffolds that facilitate the regeneration of natural blood vessels while gradually undergoing degradation over time. Researchers have produced composite scaffolds composed of polyurethane and polylactic acid, which have been evaluated for their potential to support neovascularization. Despite initial optimism, animal studies have not demonstrated the feasibility of generating new arteries using this method, raising concerns about the serious risks associated with human applications.

Emerging strategies include organogenesis utilizing collagen, as well as the application of autologous conduits. The investigation into homologous veins and arteries continues, but an intriguing research avenue lies in the potential application of xenografts and gene therapy for vascular devices.[56]

While the pronounced need for effective vascular solutions is evident, no proven concepts in tissue engineering aimed at vascular applications have yet been established. Although cell culture techniques have not yielded the anticipated outcomes, the exploration of various growth factors offers new prospects for future research, which may progress to clinical trial stages in the near future. The potential contributions of polyurethanes in this domain remain uncertain; however, their diverse properties could confer significant advantages in the development of innovative solutions.

7.2. Blood Filters

Blood filters are classified into two principal categories: surface filters and depth filters. Surface filters consist of a mesh that interacts with blood flow, capturing particles that exceed the size of the pores. In contrast, depth filters possess a complex structure that enables blood to engage with synthetic surfaces multiple times during filtration. Common materials used for surface filters include nylon and polyurethane, whereas polyester wool or polyurethane foam are typically employed in depth filtering applications.

However, polyurethane foams are regarded as unsuitable for blood bank filtration, dialysis, and extracorporeal filtration processes due to their rapid clogging with debris and potential for hemolysis.

Given the availability of more efficient and cost-effective materials for blood filtration, such as nylon, polypropylene, and

polyester, these alternatives are generally favored over polyurethane options. It is imperative to develop polyurethanes with significantly enhanced efficiency for such applications. While numerous researchers have regarded polyurethanes as blood-compatible in the contexts of vascular grafts, pacemaker insulation, ventricular assist devices (VADs), and artificial hearts, the suboptimal performance of these biomaterials as blood filters raises critical inquiries regarding their true compatibility with blood and the influence of specific material properties on this compatibility. Factors such as hemodynamic flow patterns can significantly affect clot formation within vascular grafts; nonetheless, the inadequate performance of polyurethanes as blood filters necessitates further investigation. Addressing these concerns is vital for the rational design and development of improved polyurethanes tailored for blood filtration applications.[57]

Conclusion

Polyurethanes significantly contribute to the advancement of medical devices, and a thorough review of their applications underscores the importance of this polymer family. While well-established uses for flat membrane polyurethanes exist, ongoing opportunities for development continue to emerge. With generally satisfactory biological responses, efficiency, and ease of production, polyurethanes are recognized as the material of choice in cardiac surgery for applications such as intra-aortic balloon catheters and ventricular devices. However, concerns regarding their long-term stability as blood conduits remain pertinent. Recent advancements in biodegradable polyurethanes indicate their potential to serve as scaffolds in wound dressings and to facilitate internal tissue regeneration, particularly in the context of nerve guide channels. To maximize the effectiveness of polyurethanes in medical engineering, chemists engaged in synthesizing these materials must collaborate closely with clinical practitioners to develop tailored solutions for specific applications. The extensive variation within the broad family of polyurethanes is of great significance; without it, the toolkit of modern medicine would be markedly incomplete. Certain applications, such as breast implants and vascular grafts, are constrained by suboptimal outcomes, while others, including intra-aortic balloons, ventricular devices, and pacemaker leads, present promising opportunities for growth within the medical field. Future advancements in tissue engineering are anticipated to emerge from the exploration of composite and biodegradable polyurethanes, contingent upon meticulous examination of their degradation rates. It is evident that the application of polyurethanes as external scaffolds in tissue engineering is still in a developmental stage.

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