Polyurethanes and Their Applications in Cardiovascular Surgery: A Review

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Abstract:

Polyurethanes are a diverse family of polymers that hold a significant position in the medical industry. Their applications are extensive; however, it is important to recognize that polyurethanes are particularly well-suited for manufacturing devices tailored to specific applications. Accordingly, this overview highlights selected applications, focusing on specific processes, debated findings, and potential avenues for future development, though it is not exhaustive.

Cardiac surgeons' equipment demonstrates that polyurethanes play no significant role in intra-aortic balloons, blood bags for ventricular assist devices (VADs), catheters, and pacemaker leads, which are considered the most important components. Testing of polyurethanes as blood vessel substitutes remains incomplete due to their lack of long-term resistance to degradation. Breast implants covered with polyurethane foam continue to be a subject of scientific debate. Although the use of polyurethane is limited, these materials have interesting properties. Additionally, cardiac dressings and tissue engineering scaffolds offer promising avenues for new developments.

Keywords: Polyurethanes, Cardiovascular Surgical Procedures, Surgical Equipment, Tissue Engineering, Polymers

Introduction

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

PU elastomers typically exhibit a two-phase architecture, consisting of hard domains dispersed within a soft segment matrix. The hard domains are predominantly formed from diisocyanates and chain extenders, whereas the soft segments are composed of polyol sequences.

Consequently, polyurethanes are often classified as segmented block copolymers. This particular molecular architecture, combined with the intrinsic properties of the materials used in PU synthesis, imparts unique characteristics that distinguish these

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Received: 04/05/2025
Accepted: 09/08/2025

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polymers from others within the polymer family.[1,2]

Despite some claims in the existing literature, polyurethanes have gained traction in biomedical applications primarily due to their exceptional mechanical properties rather than their biological responses. While numerous studies support the assertion that polyurethanes exhibit "biocompatibility" and "blood compatibility," several publications indicate that these materials can degrade within the human body and demonstrate inferior blood compatibility compared to alternative materials used in vascular surgery. Nonetheless, the distinctive mechanical properties of polyurethanes make them highly advantageous for specific applications, particularly in situations where tissue resilience is critical.

Polyurethanes represent a diverse family of polymers that play a critical role in medical treatments. They offer significant advantages due to the ability to tailor their characteristics through synthesis. However, it is important to avoid unwarranted generalizations about this polymer family. For example, the blood response to PU surfaces can vary considerably among different formulations. Therefore, careful selection of a specific PU for each application is essential.[3]

It is clear that the development of newly designed polyurethanes is required for many applications, rather than relying solely on commercially available types. Historically, numerous successful applications of synthetic materials have emerged outside the biomedical field; however, preliminary tests in biomedical contexts often lack a robust scientific foundation and depend primarily on empirical evaluations. Today, advancing PU development requires a collaborative approach based on well-defined biomedical engineering criteria and a deeper understanding of material interactions.

Such collaboration facilitates the targeted synthesis of polymers, enabling the production of prototype medical devices tailored to specific requirements. Additionally, establishing robust correlations between implant outcomes and polymer properties is essential 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 expected to play a pivotal role in advancing numerous future biomedical engineering devices (Figure 1).

Polyurethane

PU materials first appeared in the medical field in the late 1950s. In 1958, Pangmann introduced a composite breast prosthesis encapsulated in PU foam. However, this PU polyester foam was susceptible to hydrolysis, posing challenges for implantation in the human body.

In the same year, Mandrino and Salvatori employed a rigid PU foam known as Ostamer for bone stabilization. By 1961, Dreier and colleagues proposed using a PU polyester, termed PU VC, for components in heart valves and aortic grafts. In the mid-1960s, Cordis Corporation commercialized PU polyester diagnostic catheters,[4-6] which garnered significant scientific interest in the search for an ideal biomaterial. Unfortunately, early cardiovascular applications of these PU esters produced unsatisfactory outcomes, as studies revealed their hydrolytic instability, leading to a widespread perception of polyurethanes as unsuitable for implantation.

This unfortunate conclusion mistakenly condemned the entire category of materials commonly known as polyurethanes, based on the shortcomings of a particular subclass, despite their significant industrial importance.

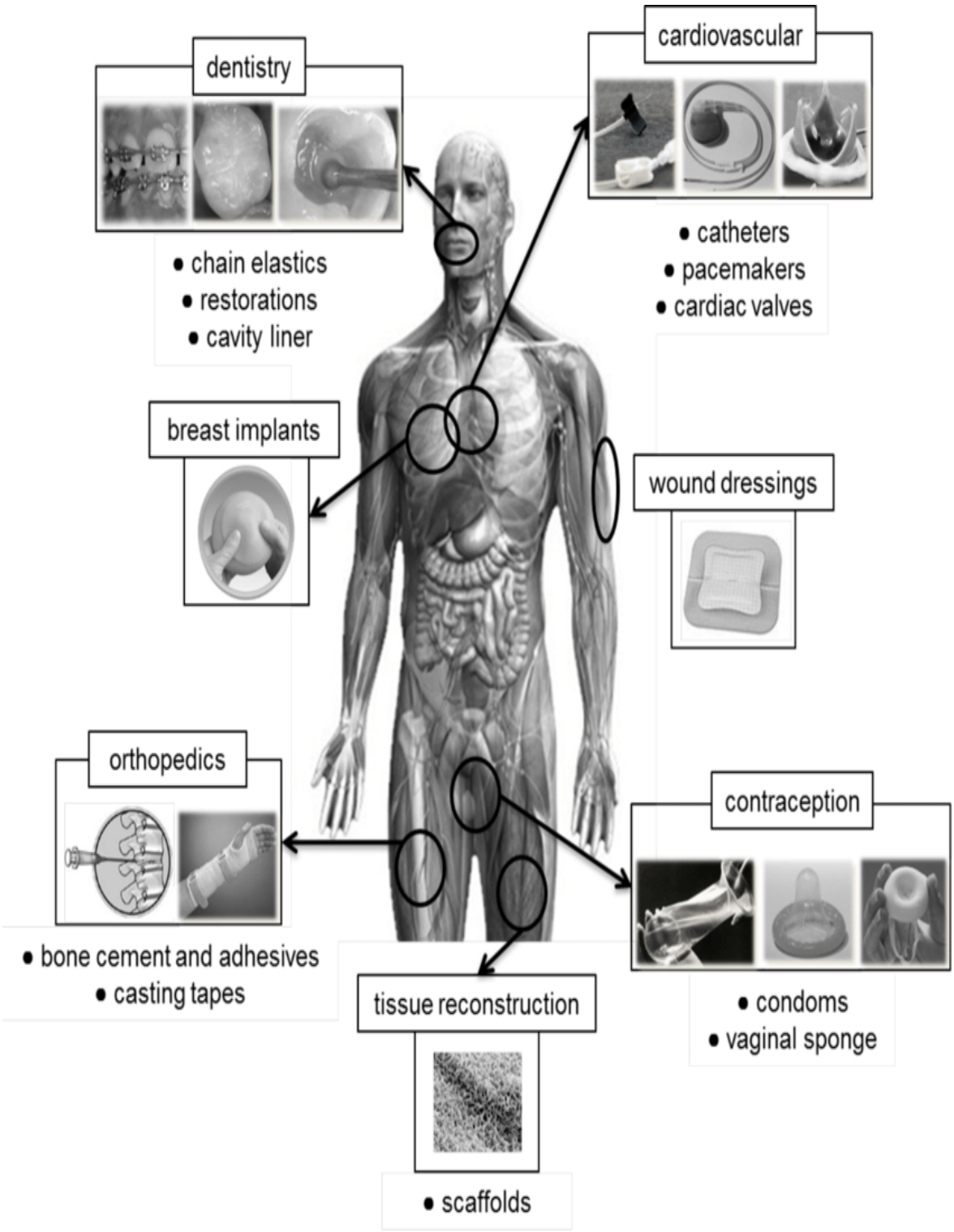

Figure 1 - Applications of polyurethane in medical engineering

This generalization arose from a limited understanding of the materials at the time, which inaccurately classified all polyurethanes as inherently degradable. Today, this characterization is widely recognized as an oversimplification, especially given the success of hydrolytically stable PU ethers, which have renewed interest in polyurethanes as potential biomaterials. Reflecting on the industry's history, one might wonder why early manufacturers did not anticipate the hydrolysis of polyurethanes.

Notably, in 1954, textile chemists at DuPont developed Lycra as a superior alternative to natural rubber for elastic yarns; it was 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 had been specifically designed for medical applications. The following year, Ethicon introduced Biomer, a DuPont-licensed variant of Lycra. Both Avocatan and Biomer were synthesized from solutions and were not suitable for fabrication methods such as dipping, spraying, or casting. Nevertheless, these polymers were extensively studied as pioneering biomedical polyurethanes.[7] Avocatan was clinically used in the first intra-aortic balloon pump in 1971, and this product remains 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 had hindered the progress of applications such as heart balloon pumps and ventricular assist devices (VADs) 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 PU used in an implant, specifically as a catheter for the Avocatan heart balloon pump, although it was still classified as a testing material. As the integration of PU into medical devices expanded, research addressing toxicity and stability within the body gained momentum. The hydrolysis issues observed with PU 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 PU formulations. Subsequent investigations identified the susceptibility of polyether urethanes to oxidation, alongside significant concerns regarding the potential carcinogenicity of PU 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 PU Biomaterials: A Historical Perspective

In 1978, a seminal publication by Baxter and Travounol revealed that certain sterilized blood bags, identified as Texin, contained methylene dianiline. This discovery raised significant concerns within the medical community, which intensified in 1988 when Blais from the Canadian Ministry of Health highlighted issues related to gel-filled silicone breast prostheses coated with PU foam, known as the Mim prosthesis. The concerns raised by Blais were substantiated by research conducted by Batich and Williams, as well as Goudon and colleagues, prompting renewed focus on the stability and potential toxicity of these materials.[9] Although the potential carcinogenicity of

polyurethanes remains a subject of debate, no documented cases have been reported to date. In the early 1990s, manufacturers began reassessing their production and sales policies regarding medical polyurethanes, largely in response to liability concerns associated with Teflon, polyurethane, and silicone used in breast implants. In 1991, DuPont and Coritech discontinued production of Ethicon and divested Biomer. That same year, Pelthane, now owned by Dow, was restricted to implantation periods of less than 29 days.[10]

Anticipating these developments, Toratech Laboratories had already begun producing 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 the original materials, thereby facilitating transitions for manufacturers of existing devices without necessitating comprehensive redesigns. A noteworthy example is the PU 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 VADs and artificial hearts,[11] leading to numerous clinical implants utilizing these newer polymers instead of 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 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 investigated alternative soft segments to enhance performance and durability, focusing on methods to eliminate or minimize ether and ester linkages. One notable approach involves blending stable, hydrophobic polydimethylsiloxane (PDMS) with soft polyester or polycarbonate segments in PU formulations. In 1988, Pinchuk and colleagues reported on PDMS covalently bonded to polyurethanes and proposed an end-group modification strategy based on their experience with Avocatan 51. More recently, Gantillack and Mejz developed a new series of polyurethanes exhibiting high biocompatibility and enhanced properties attributed to increased siloxane content in both hard and soft segments. Additionally, Zicher introduced aliphatic PU polycarbonates, branded as "biodegradable polyurethanes" (Crownflex), which demonstrated increased biodegradability compared to earlier aromatic variants. 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 biologically derived polyether-based polyurethanes, especially when oxidation is the primary degradation pathway. When copolymerized with silicone polyols, polycarbonate polyurethanes combine the hydrolytic stability of PTMO-based polyurethanes with the oxidative resistance of the soft polycarbonate segments. The Polymer Technology Group has secured patents for these innovative formulations. Furthermore, Mejz and Gantillack developed a range of macrodiols with fewer ether linkages than PTMO; polyurethanes derived from poly(hexamethylene oxide),

poly(octamethylene oxide), and poly(decamethylene oxide) exhibit significantly improved stability. Kuri and colleagues at Medtronic introduced biocompatible polyurethanes using dimer acid soft segments, although these have yet to achieve commercial viability. Currently, several research groups are actively pursuing various innovative modifications to enhance biological stability in vivo. Despite these advancements, PTMO-based thermoplastic polyurethanes and polycarbonate soft segments remain the principal classes of polyurethanes employed for chronic implantation due to their extensive documentation and historical performance regarding adverse events, ensuring their continued prominence 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. While fibroblasts and endothelial cells are typically preferred for cytotoxicity testing, other cell types, such as neutrophils, lymphocytes, monocytes, and epithelial cells, may be used depending on specific applications involving the skin, blood, tympanic membranes, and 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 implantation sites include the cardiovascular system (such as grafts and synthetic vessels), stents, sinkhole valves, catheters, tympanic membranes, intraocular lenses (IOLs), 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 applications 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 primarily focused on 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 PU 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 beginning of discussions on hydrophobicity in polyurethanes, defined as the polymer's

ability 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 but increased thrombosis levels in vivo. Numerous of studies have since explored the chemical, morphological, and structural changes in polyurethanes and their corresponding blood responses. Modern approaches, including synthesis and surface modifications, such as variations in chemical composition and coating techniques, have been employed to enhance blood compatibility.

2.1. Heparin

A significant advancement in enhancing the blood compatibility of polyurethanes is the covalent attachment of heparin, a well-known anticoagulant. Numerous studies have demonstrated that stabilizing heparin on polyurethanes through various reaction mechanisms can effectively prevent material-induced clotting.

Unlike other biomolecules such as albumin, which may depend on surface adsorption, heparin requires the formation of covalent bonds to maintain its efficacy. Heparin adsorbed onto PU surfaces tend to dissipate within hours due to its high solubility and low affinity for surfaces compared 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 heparin coverage and increasing the density of reactive stabilization sites. Narayanan and colleagues used a polyethylene imine spacer to attach heparin to PU 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 improve 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 triazole acrylate grafted onto oxygen plasma-modified polyurethane. These methods collectively contribute to a comprehensive suite of strategies aimed at enhancing the blood compatibility of PU materials.[19]

Recent work by Gravinger and Park, along with their research teams, has focused on innovative strategies to improve the blood compatibility of polyurethanes by applying heparin-PEO-PDMS coatings or block copolymers of PEO with Biomer™ heparin onto PU substrates. In these systems, the hydrophobic blocks effectively adhere to the substrates, while the hydrophilic heparin-PEO segments expand upon exposure to aqueous environments. Specifically, 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 resulting 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 significant.[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 heparin itself. Protein adsorption studies further revealed that surface-bound heparin inhibits the adsorption of both albumin and fibrinogen, exhibiting low affinity for thrombin.

Conversely, proteins such as fibronectin and antithrombin III continue to bind 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 solely dependent 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 molecules can reduce 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 also promote 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 of the biological pathways governing hemostasis.

It is essential to recognize that immobilized heparin may degrade under in vivo conditions, leading to a gradual decline in coating effectiveness over time, an issue relevant to all molecules affected by hemostatic, immunogenic, or metabolic factors. An intriguing alternative involves synthetic polymers that mimic natural biomolecules. For instance, Ito and colleagues explored the use of poly sodium vinyl sulfonate, a synthetic compound that activates antithrombin III. This polymer was stabilized through atmospheric plasma modification and graft polymerization onto polyurethane, resulting in reduced 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 reduce thrombin formation and activity, as well as fibrinolysis and the activation of platelets, complement, and neutrophils in 20 adult patients undergoing cardiopulmonary bypass. Various blood tests were conducted, and postoperative sampling of the tubing was performed. While the heparin-coated circuits demonstrated reduced platelet adhesion, they did not provide significant advantages in other clinical evaluations. The study concluded that heparin-coated circuits, when used alongside standard systemic heparin dosages, decreased platelet adhesion and improved platelet function but did not produce a significant anticoagulant effect during cardiovascular bypass procedures. These findings have been further supported by subsequent research.

Moreover, Winterton and colleagues raised an important consideration regarding the application of heparin coatings in medical devices, such as IOLs. If immobilized heparin indeed reduces clot formation through specific biological mechanisms, it raises 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. Therefore, a coating with minimal bulk may offer a more effective approach to preventing cell recolonization. This consideration highlights the challenges inherent in designing medical coatings that succeed in one specific context but encounter difficulties in other medical engineering applications. Ultimately, numerous instances indicate that a coating, without a comprehensive understanding of its biological functions and the molecular interactions between the coating and associated proteins across diverse medical applications, may produce unexpected outcomes.

3. Biodegradability of Polyurethanes

Another critical challenge in investigating polyurethanes for medical applications involves the preparation of recovered samples for analysis. It is essential to thoroughly remove inhibiting tissues, cellular material, absorbed blood clots, and residual protein layers from medical devices to accurately assess changes in both the surface and bulk properties of polyurethanes. However, medical devices are often fixed using formaldehyde or glutaraldehyde, which leads to extensive networking and the formation of strong chemical bonds with the device structure. This fixation process complicates the thorough removal of implants, and cleaning methods can introduce artifacts that distort material analyses. For example, if residual tissues, lipids, or protein attachments remain, it becomes impossible to rigorously evaluate biodegradation-induced changes through detailed examination of surface chemistry or mechanical properties. In such situations, only macroscopic observations, such as dimensional changes, discoloration, cracks, and fissures, can be performed, thereby limiting the understanding of the materials' biocompatibility and performance 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 remove sufficient fixed tissue, thereby hindering sensitive surface analyses of PU materials. Alternative techniques involving acidic or basic conditions have also been examined; nevertheless, some methods may be excessively harsh, potentially causing 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 the boiling point led to substantial alterations in the microporous morphology and microfibrosis of PU 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 Insulation Materials

In 1986, Pirzada and colleagues published the first long-term study of polyurethane-coated unipolar electrodes in patients, reporting no observable surface cracking that led to insulation failure, except at sutured sites. However, this investigation focused exclusively on macroscopic properties and did not include deeper chemical analyses.

Subsequent research by Chawla and colleagues examined PU cardiac pacemaker leads, which exhibited significant electrical disturbances upon removal from the body. They employed techniques such as optical microscopy, scanning electron microscopy (SEM), and Fourier-transform infrared (FT-IR) spectroscopy. Their findings revealed extensive damage to the PU insulation, characterized primarily by widespread cracking. Many retrieved leads displayed dull, rough, and uneven surfaces. SEM examination of the lead insulation at 30x and 300x magnifications revealed patterns of transverse erosion and areas of reduced 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, in 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 reduced intensity compared to a reference PU 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).

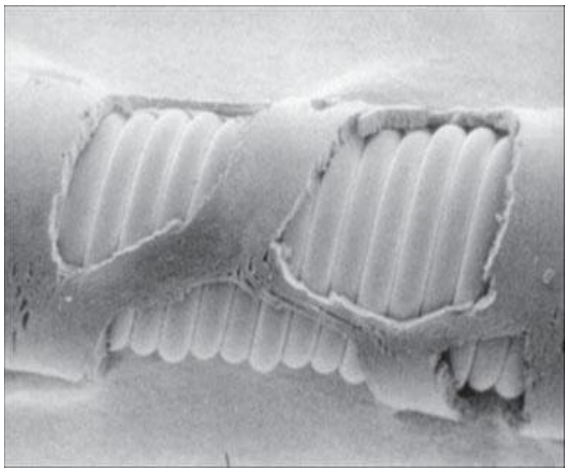

Figure 2 - A cardiac pacemaker lead removed from the body 14 months after implantation. Residual stress in the insulation caused cracks perpendicular to the device's longitudinal axis.

Moreover, Stokes and colleagues observed that the visual appearance of degraded polymers varied, ranging from colorless to amber and even to darkened shades resembling soft, resin-like materials. The degraded segments were typically small, affecting only a few millimeters along the 58-centimeter length of the device. A significant 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 the conductive coils, contributing to the biodegradation of the polyurethane.

Notably, the concentration of transition metals within the PU 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, with the degree of damage to Pellethane™ 2363-80A 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 the points of contact with cobalt rods, with cracks observed throughout the material's thickness in three samples.[26]

3.1.2. Heart Valves

In animal studies, PU heart valves have predominantly encountered challenges such as calcification, coagulation, and mechanical failure. McKay and colleagues found that the initial generation of PU valves performed poorly in durability tests, failing to withstand more than 100 million cycles, approximately equivalent to 2.5 years of physiological use. In contrast, advancements in valve technology have led to the development of PU valves constructed from C156Lycra®, which successfully endured over 400 million cycles, corresponding to nearly 10 years of in vivo operation. Remarkably, certain polyethyleneurethanes (PEUU) valves surpassed 800 million cycles without failure, indicating over 20 years of potential clinical viability. In comparison, 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 PU 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 PU leaflets, whereas 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 periods necessitate thorough investigation of their biostability to ensure device success. For example, the biostability of a hydrophilic microporous vascular prosthetic fabricated from Mitrathane®, a PU based on PTMO, MDI, and ED, was assessed. Pinter and colleagues reported that after six months, the longest implantation period studied, all vascular grafts were 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 remained stable when immersed in water at 37 °C 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 result from cycles of swelling and deswelling.[29]

3.1.4. Calcification and 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 laboratory-made mechanical blood pumps and polymeric heart valves, including those containing PU components.

While calcification is a normal physiological process involved in the formation of bone, dentin, and enamel, calcium deposits in soft tissues are uncommon. Nevertheless, such deposits can occur 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 include 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 over smooth surfaces, such as polymeric tri-leaflet heart valves, most deposits are associated with 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 without 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 process.

A critical factor in evaluating calcium mineralization associated with biomaterials is the age and species of the animal used in such studies. The dynamics of calcium turnover in young, growing animals differ significantly from those in adult specimens, potentially resulting in accelerated

mineralization within medical devices. Additionally, mechanical loading conditions and the frequency of loading cycles vary with the animal's age. Furthermore, the implantation site has a considerable influence on the rate of calcium mineralization. For instance, Bornak et al. observed that samples of PEUU exhibited lower levels of mineralization in a subcutaneous implant model tested in prairie dogs compared to those implanted at the pericardial site in bovine subjects.[30]

As previously discussed, calcium mineralization associated with biomaterials involves complex interactions influenced by intricate metabolic processes. Consequently, it remains unclear whether calcium mineralization is a direct result of PU degradation, a side effect of this degradation, or an entirely separate molecular phenomenon. Nonetheless, it is important to note that device defects can also contribute to calcium mineralization.

3.1.5. Electric Stresses

Given the widespread use of PU materials as insulation for pacemaker leads, it is essential to recognize the potential impact of electrical discharge on the dielectric properties of the insulation sheath. When an insulating material consists of two or more distinct phases or contains dispersed macroscopic regions, space charges can accumulate at these interfaces due to differences in conductivity and dielectric permittivity. This accumulation of space charge leads to field distortion and may result in dielectric losses. Interfacial polarization can result 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, arising 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 occur when materials are subjected to electrical 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 electric 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 electrical stress in the presence of moisture, even without 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 environment that facilitates treeing. Although initial degradation may exacerbate treeing conditions, research on this aspect within PU applications, particularly in combination with metallic conductive materials, remains limited. Further investigation is warranted to address this significant concern.[31]

4. PU Configurations in Medical Applications

PU materials are essential in a wide range of medical applications, requiring each configuration exhibits a comprehensive set of mechanical properties tailored to its specific physical and chemical environment.

4.1. Tubing

Biomedical PU tubes can be fabricated using three primary methods: extrusion, solvent casting, and fiber methods. In the extrusion process, precise temperature control is crucial, as excessive heat may lead to polymer degradation. Although extrusion is generally the preferred method for tube fabrication, solvent casting is 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 negatively affect the performance of the final product. This can be achieved through various methods, such as gas flow, low-heat drying, or vacuum drying. After drying, the products should be washed with water to ensure the removal of any remaining solvent residues. However, caution is necessary during washing, as water exposure may cause undesirable side reactions, underscoring the importance of careful solvent selection.

To produce thicker sections, multiple iterations of this process may be performed. Conversely, porous tubes can be fabricated using fiber methods, in which strands obtained through spinning are woven or assembled into cylindrical forms. This fibrous winding can also be applied directly by adjusting the rotational pattern on a screw mandrel, offering 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

PU coatings are employed to modify the surface properties of various biological materials. These coatings are versatile, providing benefits such as flexibility, toughness, excellent electrical insulation, and strong adhesion. While traditional solvent-based and spraying methods remain the most commonly utilized techniques, plasma spraying is increasingly gaining attention 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. For both scientific and economic reasons, a high polymer concentration is preferred to minimize solvent usage; however, this must be balanced against the mixture's viscosity and the desired properties of the coating after solvent removal. Cleanliness is paramount in preparing the coating surface; it must be free of contaminants, and moisture levels can often be reduced 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

PU foams are primarily produced by the reaction of water with isocyanates, which generates 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 through heat and mass transfer. In addition to the essential components, polyisocyanate, polyol, water, and catalysts, foam production often requires additives such as nucleating agents, secondary blowing agents, and surfactants. The effects of these additives on biological responses remain largely unclear and warrant thorough evaluation.[34]

4.4. Fibers, Sheets, and Films

PU fibers are predominantly manufactured through extrusion and fiber spinning methods, which utilize isocyanates and chain extenders. In certain cases, the solvent reaction method described by Lamba et al. may be used to produce fibers with irregular cross-sections. After fiber production, various components can be woven together using textile machinery. For comprehensive insights into PU fiber applications, formulations, and production processes, the existing literature provides extensive documentation. The primary methods for producing PU sheets are extrusion and casting, both of which can be performed 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 mainly in how the reactive components are deposited. 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 traveling a specified distance, the materials are 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 thick); rather, they are predominantly composed of rigid urethane and serve applications such as packaging or surface modification to regulate vapor permeability. Gas permeability characteristics also vary with increased network connectivity and depend on the specific type of PU used (e.g., polyether, castor oil-based, or polyester). Films are typically produced using solution casting methods. To achieve films that are clear and free of bubbles, it is essential that the polymer is fully dissolved to yield a transparent solution. In the dipping process, achieving consistent thickness requires 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 critical requirement for all medical polymers, ensuring their integrity while effectively eliminating microbial life. This process involves three principal methods: heat, gas, and radiation. The effectiveness of sterilization depends mainly on the chosen method rather than the material itself. If a specific material does not tolerate the parameters of a selected sterilization process, alternative methods should be considered. Adjusting sterilization parameters directly impact the efficiency of the process.

Two methods can be used to assess this effectiveness. The first involves immersing the equipment in a liquid microbiological culture; if 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 sterilization validation procedures to graphically represent the assurance level, typically ranging from 6 to 10.[36]

6. Cardiovascular Applications of Polyurethanes

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

· Transient cardiovascular devices are commonly utilized in emergency situations, typically for periods ranging from several days to a few weeks. This category includes intra-aortic balloon pumps, temporary left ventricular assist devices (LVADs), and biventricular assist devices, all intended for removal once the heart has sufficiently recovered.

· Intermediate cardiovascular devices are utilized for patients awaiting heart transplants when suitable donor organs are not immediately available. Common examples include VADs 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, thus eliminating 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 concerns regarding long-term stability, blood compatibility, and material properties.

The success of cardiovascular devices depends on appropriate polymer selection, a thorough understanding of processing methodologies, proper user training, and rigorous clinical evaluation.[37]

Polyurethanes are often favored for their potential blood compatibility. However, despite promising results in applications such as intra-aortic balloons, VADs, and artificial hearts, there have been instances of unreliable scientific extrapolations and overly optimistic expectations. These issues have prompted a re-evaluation of biocompatibility concepts. Throughout this discussion, the limitations of polyurethanes for long-term cardiovascular applications have become increasingly apparent. In particular, 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 possible 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 by temporarily unloading the heart's preload through assistive pumps, thereby allowing recovery from left ventricular failure.

The relationship between diastolic aortic blood pressure and coronary flow led to the development of the counterpulsation concept, initially introduced by Moluopoulos and colleagues using intra-aortic balloon devices. Following the work of Kantrowitz and his team in 1967, the intra-aortic balloon became an essential tool for supporting circulation in patients recovering from cardiopulmonary bypass. The intra-aortic balloon, used in conjunction with conventional heart-lung machines, enhances blood flow to patients in a pulsatile manner by inflating with a predetermined volume of gas during diastole and deflating during systole.[38]

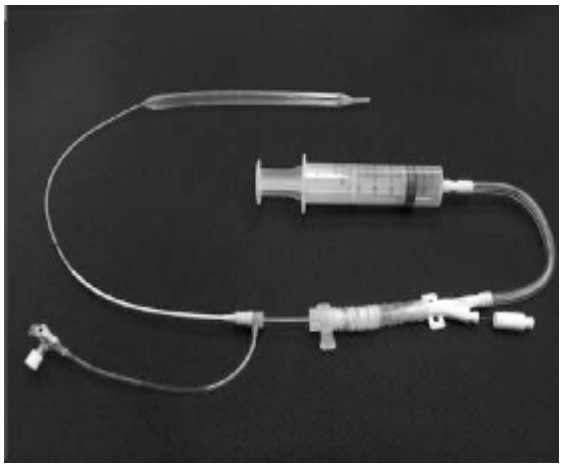

Figure 3 (A) - Intra-aortic balloon: general view

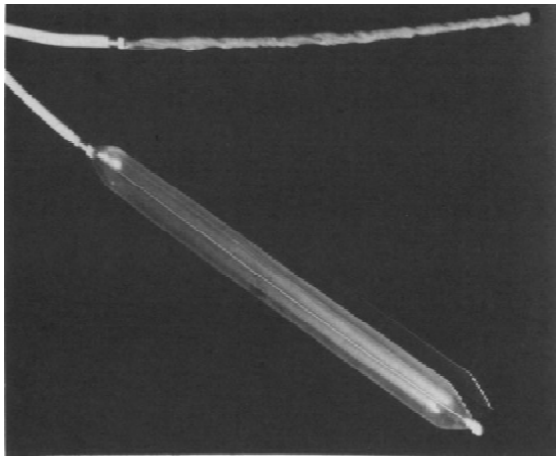

Figure 3 (B) - Intra-aortic balloon: details of the polyurethane balloon

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

Our evaluation encompassed 112 devices and revealed that microscopic analyses disclosed no significant changes in shape or

color, with no discernible wear or fractures detected. However, 61% of the PU 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 use include difficulties with catheter placement, incorrect positioning, balloon degradation, hemolysis, infections, and neurological or vascular injuries. Only a few of these complications are attributed to the PU 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. However, these benefits are not consistently observed in cases of severe heart failure. Research in canine models has indicated an increase 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 PU intra-aortic balloon catheters, causing the PU material to harden and rupture. It is essential to avoid contact with these substances during dressing changes or when 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, making it an indispensable tool for patients following open-heart surgery. PU balloons are considered satisfactory, reflecting the maturity of 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 lasting several weeks. While minor improvements may still be anticipated, no fundamental changes are considered necessary given the low defect rate. Emerging issues are likely associated with manufacturing defects or friction against calcified 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 PU began in 1958 with the introduction of a PU film sandwiched between solid Teflon anchoring rings and semi-circular sections for connections. Between 1960 and 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 resembling a parachute. This design features a simple structure with a thin circular PU membrane mounted on a fixed PU plate, incorporating numerous cavities or pores. These innovations reduce flow resistance while aiding 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 improved, with no stagnant points identified around the membrane, thereby facilitating effective anticoagulation.[40]

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

PU heart valve prostheses are fabricated from solvent-cast PU sheets, which are heated and shaped to achieve the desired leaflet geometries. Alternatively, dipping techniques are used, where stainless-steel molds are immersed in a PU solution to form the valve leaflets.

Results from studies utilizing the dipping technique indicated a more uniform distribution of average circumferential velocity and normal Reynolds stresses originating 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 investigated 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 considered satisfactory, leading the authors to recommend its use for temporary LVADs.[41]

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

Numerous challenges related to heart valves arise from their dynamic behavior and the resulting 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. These measurements revealed that maximum disturbance levels corresponded to the severity of stenosis. Furthermore, the morphology of velocity and disturbance waveforms was closely associated with the geometry of the stenosis and the specific valve position (aortic versus 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 have potential for valve replacement, others report 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 their primary application being restricted to VADs and artificial hearts.

Currently, the use of polyurethane-based heart valves is limited to short-term applications within VADs and artificial hearts serving as bridges to transplantation. Due to their susceptibility to rupture and calcification, these PU valves are not considered suitable for long-term implantation. However, for temporary use, they provide an economical solution with adequate hemodynamic performance. Given their current developmental stage, these valves should be restricted to extracorporeal devices, making implantation within the body inappropriate.[42]

6.3. Vascular Grafts

At the beginning of the 20th century, research demonstrated that both homologous and heterologous arteries and veins could effectively serve as arterial substitutes in canine models. Additionally, implanted autologous vein materials proved suitable for arterial replacement in human subjects. However, early advancements in graft technology primarily focused on non-biological tubular constructs. The introduction of Vinyon-N in 1952 marked a significant breakthrough in the development of porous tissue arterial prostheses, especially given the challenges associated with smooth-walled tubes. Over time, more durable materials such as PET and polytetrafluoroethylene (PTFE) were developed, exhibiting considerable longevity. Although PU blood conduits attracted interest due to their adaptable properties, results have been inconsistent. The use of bovine heterografts and human umbilical cord allografts, once common in vascular surgery, has since declined in popularity.[43]

PU grafts exhibit a wide range of physical properties that can be modified by varying the PU concentration, modifying the freezing temperature, and adjusting the freezing methods used. Since porosity is crucial for the long-term performance of small synthetic vascular prostheses, increased graft permeability has been associated with enhanced tissue integration. Implants with pore sizes between 10 and 45 microns promoted the internal growth of fibrohistiocytic tissue and capillaries, whereas those with pore sizes greater than 45 microns led to the development of organized fibrous tissue with minimal cystic response. Consequently, microporous vascular prostheses that maintained elasticity several months after implantation showed limited internal or fibrohistiocytic tissue growth.

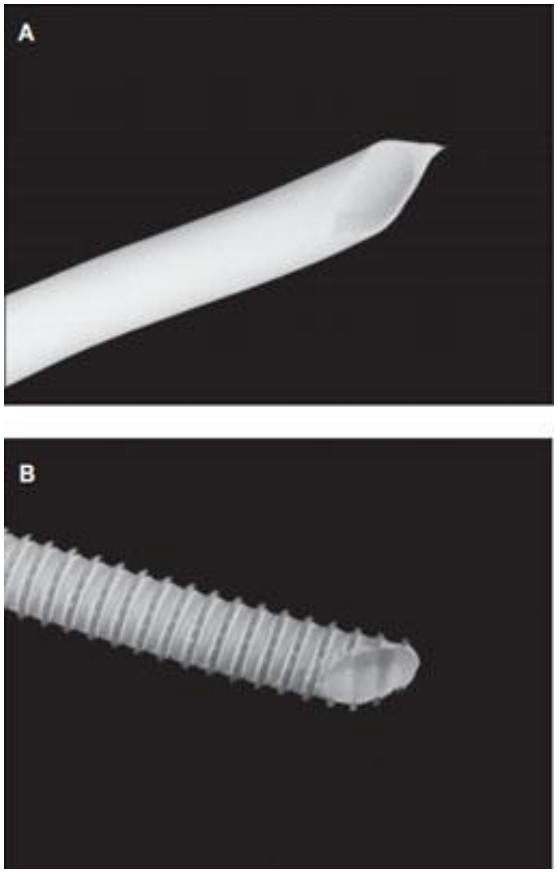

Figure 4 - Polyurethane grafts (A) without external support; (B) with external support

Several PU vascular prostheses have advanced to industrial production as substitutes for small-diameter arteries. Notable examples include Corvita®, Thoratec®, Pulse Tec®, Biomer™, Mitrathane™ (available in both hydrophilic and hydrophobic forms), and Vascugraft®. Each of these prostheses exhibits unique characteristics that merit attention.

The Corvita® prosthesis, fabricated from PU carbonate, features a flexible fibrous structure with interconnected open spaces; however, it necessitates careful coating to prevent blood loss during implantation. The Thoratec® prosthesis, composed of polyether-urethane-urea, does not require sealing or initial coagulation and promotes minimal tissue ingrowth (Figure 6). In contrast, the Pulse-Tec® prosthesis has the fewest openings on its exterior surface, offering resistance to collapsing forces while inhibiting tissue ingrowth (Figure 7).

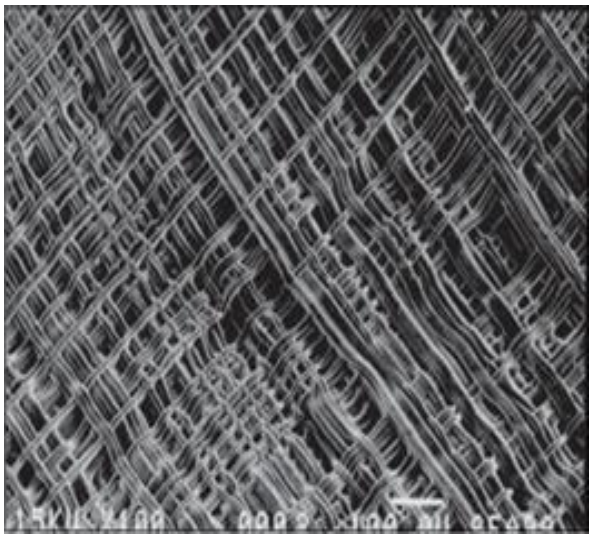

Figure 5 - Luminal surface of the Corvita™ prosthesis with interfibrous spaces showing open communication pathways

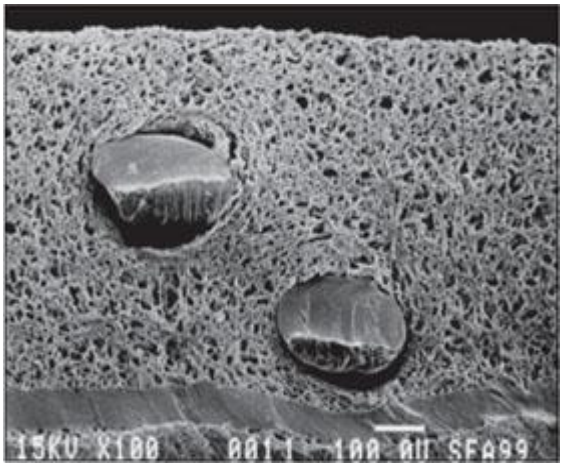

Figure 6 - Cross-section of the Thoratec prosthesis with completely impermeable walls

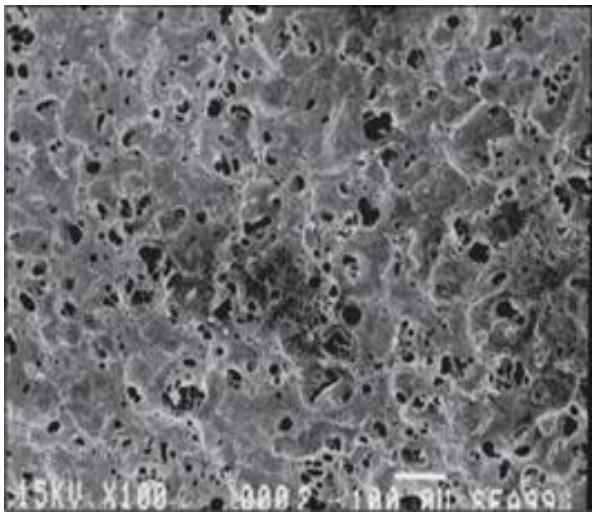

Figure 7 (A) - Pulse-Tec prosthesis featuring multiple holes on its surface

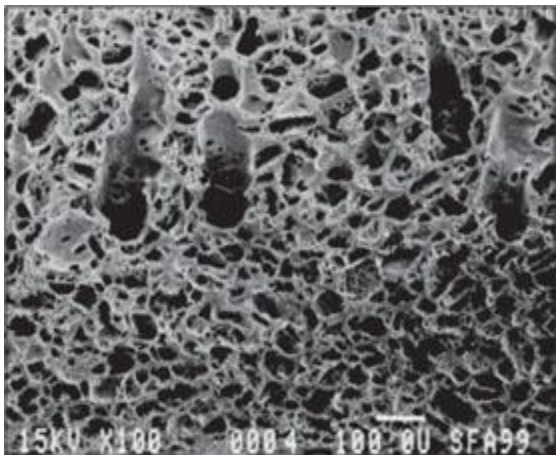

Figure 7 (B) - Featuring a highly porous structure

Mitrathane™, a polyether urethane urea similar to Biomer™, displays a cross-sectional structure composed of three distinct layers. The outer layer contains larger pores, while the inner layer has significantly smaller pores. This design enables high longitudinal tensile strain and superior suture strength compared to expanded PTFE prostheses, along with favorable radial compatibility for small-diameter human arterial tissue (Figure 8).

The Vascugraft® prosthesis features open pores extending through its entire wall thickness. Its longitudinal and radial elasticity surpasses that of reinforced Gore-Tex® grafts. Notably, the Vascugraft® exhibits burst strength and suture retention strength that exceed the minimum requirements for small-caliber arterial substitutes.

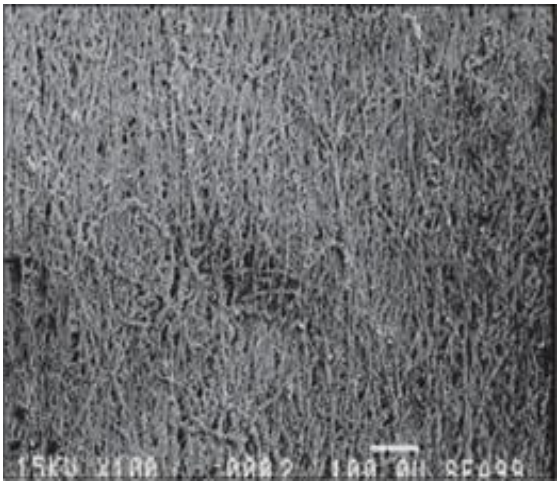

Figure 8 (A) - Mitrathane™ prosthesis featuring large pores on its surface

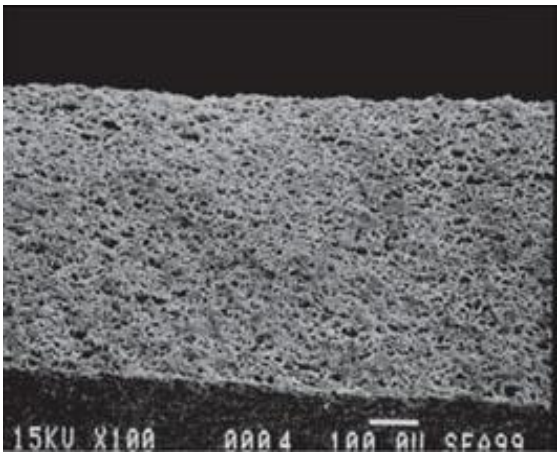

Figure 8 (B) - Shows smaller pores in the wall

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

Despite the anticipated advantages of PU prostheses, such as the development of a thin endothelial cell layer on their inner surfaces, clinical outcomes have not aligned with experimental findings. Nevertheless, these prostheses demonstrate excellent graft-host healing properties and strong resilience at suture sites.

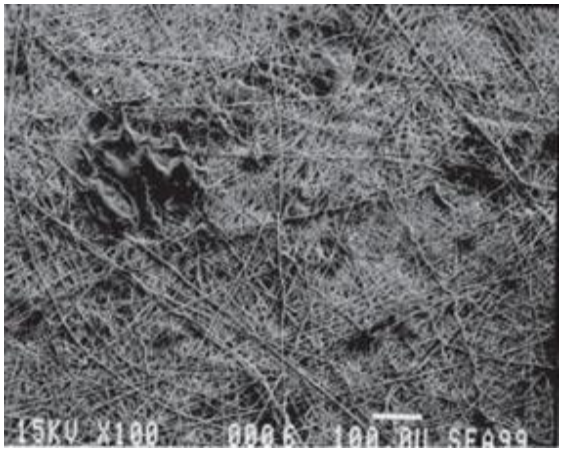

Figure 9 (A) - Vascugraft® prosthesis with open pores

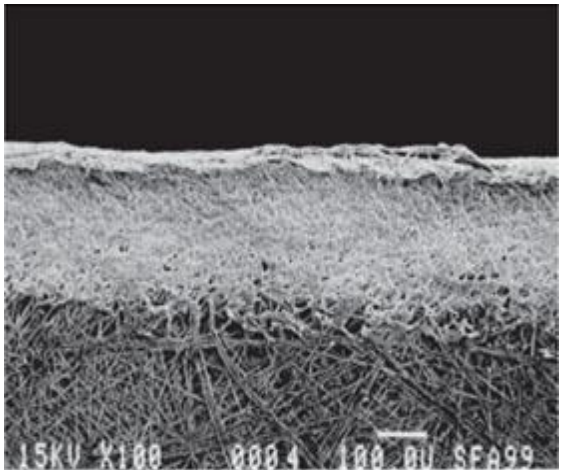

Figure 9 (B) - Wall thickness

Vascugraft® prostheses, when placed in direct contact with the endothelial layer of embryonic chicken aorta, effectively facilitated the formation of a cellular monolayer on their surfaces. Polycarbonate-urethane vascular grafts promoted endothelialization of the lumen, resulting in reduced cell proliferation and a thinner

neointima compared to expanded PTFE (ePTFE) grafts.

To enhance resistance to coagulation, researchers have explored incorporating endothelial growth factors, gelatin, fibronectin, and ADPase into these prostheses. Some studies have also involved 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 effectively prevented coagulation in the biodegradable PU vascular prosthesis.

PU vascular prostheses have displayed potential for enhanced resistance to coagulation and reduced anastomotic hyperplasia 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 made of PU in contact with the blood, supported by an inner layer of Dacron® mesh, thereby ensuring long-term dimensional stability.

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

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

Nevertheless, PU vascular prostheses remain attractive due to their tunable properties, including wall porosity, elasticity, and mechanical characteristics. Initial blood compatibility 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-diameter grafts, which tend to underperform without pharmacological intervention. Performance in medium-diameter arteries has generally been comparable to that of ePTFE grafts; however, PU grafts have exhibited a tendency toward accelerated 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 continuous 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 beginning of a technological evolution in devices designed to treat various rhythm disorders. Modern pacemakers typically consist of a power source, an electronic field, pacing mechanisms, and electrodes. The lead

system plays 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 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 used for conductive wires. Insulation within the lead system is essential to protect surrounding biological tissues from electrical activity.

Early leads were designed for indefinite lifespans because they did not contain consumable components. However, with the introduction of lithium batteries, which offer extended longevity, lead failures 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 PU formulations have also been utilized.[47]

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

By 1980, Medtronic had introduced over five models of cardiac leads for medical use, most of which utilized Pellethane™ 2363 resin for insulation. Each manufacturer 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 depends on the ratio of hard to soft segments, as well as various other processing parameters.[48]

Although PUs generally exhibit lower tensile strength, hydrolytic stability, and fatigue life compared to silicone rubber, they provide a significantly better coefficient of friction when in contact with blood. This advantage makes PU leads easier to manage when placed in smaller veins. Segmented ether-based polyurethanes have demonstrated resistance to coagulation comparable to that of 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 due 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 indicates that failure rates remain a concern, as electrodes may not be retrievable following insulation failures. Consequently, these materials frequently remain within patients, posing 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 the subclavian versus cephalic approaches. Nevertheless, MIO and ESC are considered the most plausible explanations for insulation failures.

Currently, 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 notable mechanical strength. However, concerns about the biostability of PU insulation materials have emerged 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 developing long-term stable polyurethanes continues. At present, 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, with a mortality rate of less than 1% and minimal complications. However, the complexities of cardiopulmonary bypass necessitate sternotomy or thoracotomy, leading to unavoidable hospitalization and prolonged recovery. Consequently, this has driven the development of minimally invasive techniques and devices for closing 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 PU prosthesis with six radial legs, three of which had tips oriented at right angles. Although clinical trials of this design resulted in six unfavorable outcomes among 19 patients, it laid the foundation for further innovation in the field. Lock and colleagues later introduced the Lock-USCI Clam, designed with two polyester squares facing each other and connected by four radial ligaments 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, the occluder is made from a square piece of PU 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 made from a nitinol wire frame and a thin PU 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 front. Clinical results related to the ASDOS have been promising, with complete endothelialization of the smooth PU membrane observed three months after implantation in porcine models. In addition to thorough clinical follow-ups, further investigations into the long-term performance of these devices are imperative. Animal testing and analysis of implanted devices during reoperations or autopsies must remain a priority, alongside comprehensive comparisons with newer devices, such as the Amplatzer®.

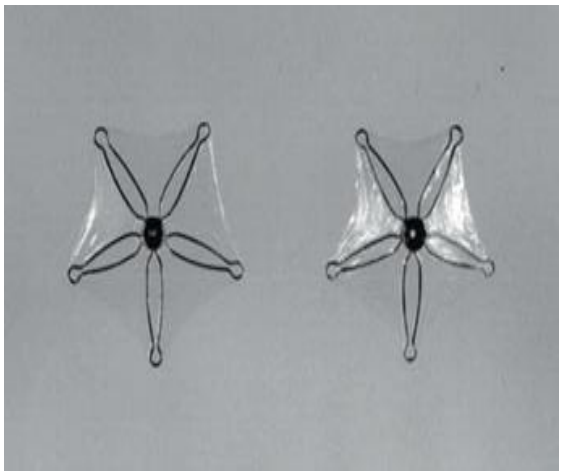

Figure 10 - Arterial Septal Defect Occlusion System (ASDOS) for the closure of arteriovenous systolic defects. It consists of two self-expanding cannulas made from a nitinol wire frame covered with a thin polyurethane membrane.

The Amplatzer® device features a mesh-like structure made of nitinol wire, designed to form two opposing discs connected by a central waist.[51]

Despite a limited market size, the demand for non-surgical treatments of intracardiac septal defects remains a significant challenge. PU devices reinforced with nitinol present a promising option; however, they must compete with polyester umbrellas and nitinol shells. Current clinical

outcomes have not yet demonstrated definitive superiority among these alternatives, highlighting the need for further evaluation.

Non-porous PU demonstrates excellent properties in terms of softness, biocompatibility, and durability, making it more desirable than its porous counterpart. However, the lack of comprehensive comparative studies on the healing properties of both types currently limits progress in PU applications in this field.

In conclusion, although no significant advancements in PU technology are expected in the near future, the limited market presence and considerable competition may restrict the widespread adoption of these devices. Nevertheless, ongoing innovations in the application of polyurethanes across various fields could create new opportunities for future development.

6.6. Ventricles for VADs and Fully Implantable Artificial Hearts

The development of VADs and fully implantable artificial hearts has confronted substantial challenges, primarily attributable to the lack of suitable polymers for blood-contacting surfaces and mechanical performance issues. Since no external material can truly replicate the natural endothelial lining, researchers have explored various strategies, including the creation of a pseudo-intima and the reduction of protein or cellular interactions at the material interface.

Currently, smooth PU surfaces are incorporated into numerous VADs and artificial heart applications due to their ability to resist blood coagulation at the interface (Figure 11). However, selecting the most appropriate PU for long-term use remains a significant challenge. Biomer™ has been utilized in the ventricles of several VADs and artificial hearts despite its limited blood compatibility. Nevertheless, it demonstrates excellent abrasion resistance and bending flexibility. Other polyurethanes commonly employed in this field include Avcothane™-51, Elasthane®, and Pellethane™.[52]

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

Since Bortus and Pierse first employed segmented polyether PU in a ventricular assist pump in 1967, these polyether polyurethanes have been extensively used in various artificial hearts and circulatory assist devices. However, concerns regarding elastomeric stability have revealed that these materials are susceptible to degradation. 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 exhibit near-impermeability 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 24 hours, respectively. This indicates that moisture can permeate the walls of the PU elastomer, potentially contaminating the motor chamber of devices during prolonged use. Such contamination adversely affects device durability, ultimately resulting in failure. Therefore, older polyether polyurethanes do not meet the stringent requirements necessary for the next

generation of fully implantable artificial hearts and VADs. Consequently, identifying and selecting biostable and permeable materials for novel ventricular designs is essential.[53]

Recent advancements have resulted in the development of new commercial polyurethanes, including Corathane®, ChronoFlex®, and Carbothane®. These polymers feature a conjugated carbonate linkage (O-CO-O) within the soft segment, which exhibits superior stability compared to the ether linkages (C-O-C) found in older polyether polyurethanes when exposed to biological environments. Research by Pinchuk demonstrated that Corathane® films exhibited 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 of polycarbonate polyurethanes over their polyether counterparts. However, polycarbonate polyurethanes may still lack sufficient resistance to biodegradation for long-term applications.

The use of these materials in ventricle construction offers significant advantages over polyether polyurethanes. Additionally, other 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. Meanwhile, the Baylor Heart Institute has restricted the use of polyether PU for pump materials, and a Japanese program has adopted partitioned polycaprolactone, Miractran E980. It is vital to acknowledge that none of the commercially available polycarbonate polyurethanes are entirely impermeable to water vapor. Although this characteristic reduces the risk of fluid ingress into regions where impermeability is critical, the issue remains unresolved, indicating a need for further modifications to achieve fully impermeable ventricles for application in artificial hearts and VADs.[54]

Anticipated future developments in biomaterials are expected to exhibit enhanced biocompatibility, improved biological functionality, and increased long-term durability. Given their historical success and potential, polyurethanes are projected to play a significant role in medical applications. As noted by Secher, PU elastomers are vital to the overall quality and effectiveness of global therapeutic systems. Polyurethanes have been widely implemented in various prosthetics, implants, and medical consumables, particularly in applications necessitating compatibility with soft or cardiovascular tissues. Moving forward, a comprehensive exploration of the future applications of PU polymers is warranted.

As the only family of elastomers that consistently demonstrates flexibility, acceptable durability, and good blood compatibility, polyurethanes hold promising potential in the medical field. However, significant challenges remain regarding their long-term durability and water vapor permeability. With Biomer™ no longer available in the market and Pellethane™ facing limitations, the search for novel polymers that ensure biological stability over extended periods while maintaining performance is critical. As outlined in Section 6, several newly developed polyurethanes should meet essential criteria. It may not be imperative to develop a single PU that meets all requirements simultaneously; instead, the issue of water vapor impermeability can be addressed through surface modifications or coatings.

Research in this area is crucial, particularly because artificial hearts offer a promising solution to the significant shortage of donor organs. We believe that PU elastomers hold considerable potential for advancement in this field. As access to innovative materials expands, continued support for research initiatives in this domain will be essential.

7. Organ Regeneration in Tissue Engineering

The field of tissue engineering is experiencing significant growth, offering a promising pathway for creating replacement organs that are both effective and associated with a reduced risk of rejection, as well as for repairing 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 elastomeric properties that can be tailored for a wide range of applications, show promise as durable structural support materials. Enhancing biological compatibility, particularly by minimizing foreign body responses such as capsule formation, is crucial for the success of these materials in tissue engineering applications.[55]

7.1. Biodegradable Vascular Grafts

The demand for small-diameter blood conduits is increasingly acknowledged in medical applications. One promising approach involves developing biodegradable scaffolds that promote the regeneration of natural blood vessels while gradually degrading over time. Researchers have fabricated composite scaffolds composed of PU 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 using collagen and the application of autologous conduits. Research into homologous veins and arteries continues; however, an intriguing area of investigation is the potential application of xenografts and gene therapy for vascular devices.[56]

The pronounced need for effective vascular solutions is evident; however, no proven concepts in tissue engineering specifically targeting vascular applications have yet been established. Although cell culture techniques have not produced the anticipated outcomes, the exploration of various growth factors offers new prospects for future research, potentially advancing to clinical trial stages in the near future. The potential contributions of polyurethanes in this field remain uncertain; however, their diverse properties may offer significant advantages in developing 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 larger than the pore size. In contrast, depth filters have a complex structure that enables blood to contact synthetic surfaces multiple times during filtration. Common materials used for surface filters include nylon and polyurethane, whereas polyester wool or PU foam are typically employed in depth filtering applications.

However, PU foams are considered unsuitable for blood bank filtration, dialysis, and extracorporeal filtration processes because they rapidly clog with debris and have the potential to cause hemolysis.

Given the availability of more efficient and cost-effective materials for blood filtration, such as nylon, polypropylene, and polyester, these alternatives are generally preferred over polyurethane. It is therefore imperative to develop polyurethanes with significantly enhanced efficiency for such applications. Although many researchers have considered polyurethanes to be blood-compatible in contexts such as vascular grafts, pacemaker insulation, VADs, and artificial hearts, their suboptimal performance as blood filters raises important questions about 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 specifically for blood filtration applications.[57]

Conclusion

Polyurethanes play a crucial role in advancing medical devices, and a comprehensive review of their applications underscores the importance of this polymer family. While well-established uses for flat membrane polyurethanes exist, new 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 about their long-term stability as blood conduits remain relevant. Recent advancements in biodegradable polyurethanes suggest their potential as scaffolds in wound dressings and to support internal tissue regeneration, particularly in nerve guide channels. To maximize the effectiveness of polyurethanes in medical engineering, chemists synthesizing these materials must collaborate closely with clinical practitioners to develop tailored solutions for specific applications. The extensive diversity within the PU family is highly significant; without it, the toolkit of modern medicine would be markedly incomplete. Certain applications, such as breast implants and vascular grafts, are limited 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 expected to arise from exploring composite and biodegradable polyurethanes, contingent upon careful evaluation of their degradation rates. It is evident that the application of polyurethanes as external scaffolds in tissue engineering remains in the developmental stage.

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