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REVIEW ARTICLE

Multi-functional, Bioresorbable Stent Technology for Real-time Diagnosis

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ABSTRACT: Heart failure is one of the most significant public health concerns, with a mortality rate greater than most cancers. Due to this, cardiovascular disease has attracted intensive attention in the fields of medicine and engineering. Atherosclerosis is the underlying pathology responsible for these deaths. As people get older, it becomes a more common disease. High blood pressure and genetic factors are mainly related to this, which could be exacerbated by obesity and diabetes from an unhealthy lifestyle. For clinical improvement in the future, we could respond immediately to medical issues to prevent the recurrence of the disease. In this review, we investigate the current bioresorbable stent technology and the future of micro-fluidic sensing/wireless devices to overcome issues in current diagnosis. With advances in nanofabrication, new bioresorbable sensing/wireless components could be integrated into the stent without failure under expansion. The future shape of a bioresorbable electronic stent in the context of the emerging "Internet of Things" and how this will significantly influence future diagnosis technology for future generations are also discussed.

KEYWORDS: Multi-functional; Bioresorbable; Electronic Stent; Cardiovascular disease diagnosis; Wireless.

Introduction

The blood flow in an artery can be reduced or even reversed by a buildup of plaque inside the coronary arteries, which prevents heart muscles from receiving sufficient blood supply. If the blood supply to the arms and legs is cut off, severe agony and tissue death may result. A damaged cardiac muscle may be unable to pump effectively, resulting in heart failure. A stent is a device that helps to widen a section of an artery to enhance blood flow; they are crucial pieces of technology used to improve blood flow and revitalize the heart. Among many cardiac diseases, the most common cardiovascular disease is coronary artery disease. It commonly occurs with atherosclerosis. Atherosclerosis is a type of thickening or hardening of the arteries caused by the accumulation of plaque inside the wall of the coronary arteries. Cholesterol, fatty compounds, waste materials, calcium, and the clot-inducing substance fibrin make up plaques. Over time, plaques continue to collect and form in your arteries, causing them to narrow and harden. This makes vessels lose elasticity and limits blood flow to the heart muscle. Most hospitals use implantable medical devices (IMD) called stents to treat atherosclerosis.

Stents are tubular, implantable vascular scaffold devices that have a circular cross-section (Figure 1). They retain their shape when deployed in a vessel but are also designed to be elastic. Stents are used to reopen blocked vessels in various deployment locations from the biliary duct to the coronary arteries. The doctor uses the percutaneous coronary intervention to insert the stent into the target artery. PCI is a process that involves the usage of a stent to treat cardiovascular disease.[1] This technique involves a four-step process, which uses balloon angioplasty to open up clogged arteries. First, a series of catheters and guiding wires are inserted through the patient's skin. To be precise, they are most commonly inserted from the wrist's brachial artery. Next, the catheter is carried up the arterial vasculature to the location of occlusive disease inside the heart's coronary arteries. Then, a balloon inside the stent is inflated; subsequently, the stent expands with the balloon and is deployed through the catheters. The plaque material, which consists of fat deposits and cellular components like smooth muscle cells or inflammatory cells, is pushed back by the expansion of the balloon. Finally, the balloon is deflated, but the stent keeps its expanded shape to prevent plaque from recoiling. As a result, the proper flow of lumen in the location is restored.

Patients treated with PCI have shown improved coronary heart disease symptoms and enjoyed the procedure's benefits: reduced costs, less invasive than coronary artery bypass graft (CABG) surgery, and faster in-hospital recovery. However, one obstacle to this procedure was in-stent restenosis (ISR), a process where the overgrowth of scar tissue cells occurs nearby or inside the stents, obstructing the flow of blood again. 17%-41% of first-generation stents developed ISR. Second-generation stents were coated with drugs that prevent cell proliferation from addressing this issue. A drug-eluting stent (DES) slowly releases a drug from the stent to block cell proliferation.[2]

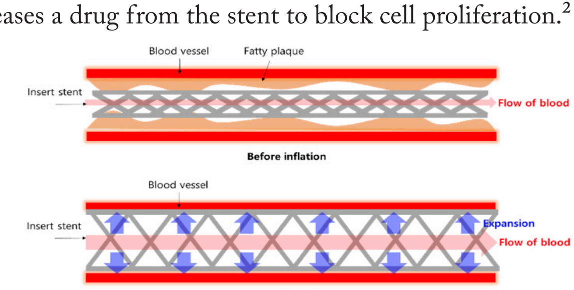

Figure 1: Schematic showing stent in an artery.

Discussion

Why is a multi-functional bioresorbable stent required?:

With the advancement of micro and nanofabrication techniques and wireless technology, bio-implantable technology for medical diagnosis has been improved.[3] Specifically, developing miniaturized microelectronics devices to continuously monitor the internal phenomena in real-time *in vivo*, such as blood flow velocity and pressure for cardiovascular implants,[4] and real-time measurement of pressure for intraocular and brain implants enhance the quality of diagnosis. Stents, which are typically tubular, with a circular cross-section, implantable vascular devices also have been developed with this multi-functional system to improve its functionality. When it is deployed in the vessel, restenosis occurs when an artery that was opened with a stent or angioplasty becomes narrowed vessel again. Currently, early diagnosis of restenosis is almost impossible to detect, and it is shown with significant chest pain or a second cardiac event in the worst case. Luckily, patients who find their restenosis still rely on lifelong medication. We should make medical treatments to predict possible issues in advance to prevent the worst cases. Remote detection of medical problems would significantly impact patient welfare and costs and decrease the risk of adverse events occurring outside the hospital environment unexpectedly. A promising solution is a stent with integrated sensors/wireless systems that can detect the growth or accumulation of cells (endothelial cells) and measure changes in flow and pressure across the local site of the blood vessel. A vital technology to achieve this integrated system within a limited space is micro/nanofabrication technology. As such, stents integrated with sensors/wireless systems will offer an advanced solution to unexpected restenosis detection (Figure 2).[5]

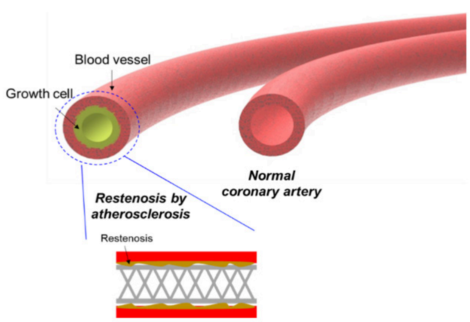

Figure 2: Schematic illustration of Restenosis.

Transient materials for stent application:

Using bioresorbable materials for stents in interventional cardiology is a novel approach to treating coronary artery disease.[6] The transient technology was introduced to the stent to overcome the limitations of current metallic stents, including late in-stent restenosis and permanent location in the vessel. The purpose of a bioresorbable stent is to provide mechanical support to the vessel for a long time before degradation and absorption in the body, enabling vessel healing and restoration of vasomotion. To develop practical bioresorbable stents, there have been many issues regarding the stability of materials in the fluidic environment of the body. In this section of the review, we investigate the current technologies of a bioresorbable stent, including the chemical and mechanical aspects of available materials and many approaches to improve it.

Transient metallic materials for stent application:

Many researchers have developed bioresorbable metallic materials to tune the mechanical, electrical, and degradation properties for bioelectronic applications. Mg (Magnesium), Mg-alloy, Mo, Zn (Zinc), and their oxide form have been considered promising metallic materials for bioresorbable electronics due to their biocompatibility.[7] Among them, the Mg-alloy metallic materials have been used commonly for bioresorbable stent applications.

Due to its mechanical properties and low degradation rate, pure magnesium is not suitable as a structural material for stents. For example, pure magnesium has a high modulus (41-45 GPa) and a low elasticity, so using it to make stents would cause it to be prone to damage under stress. As a result, magnesium alloys are appealing due to their excellent mechanical properties in terms of radial stiffness, biocompatibility, low cost, and low density. As the elastic modulus is proportional to radial stiffness, stents manufactured of magnesium-based materials have 50–240% thinner struts than cobalt-chromium and polymer stents, respectively, to maintain the required level of performance. Pure Mg, aluminum-containing alloys (AZ91, AZ31, LAE422, AM60, etc.), rare-earth elements containing alloys (AE21, WE43, etc.), and aluminum-free alloys (WE43, MgCa, MgZn) are the four main classes of Mg-based bioresorbable materials. These alloying elements optimize grain size, enhance corrosion resistance, and provide intermetallic states. The addition of rare-earth metals enhances castability and pressure resistance but exhibits low strength at room temperature.[8]

For effective functionality, stent materials need appropriate mechanical features in expandability, plasticity, rigidity, and resistance to the elastic recoil of blood arteries, depending on the type of stent (balloon-expandable or self-expandable). In addition, the stent should also remain mechanically stable after at least 4-6 months after implantation. The mechanical properties of magnesium alloys are refined through their processing history of hot rolling, hot extrusion, and equal-channel angular pressing. This increases the strength of magnesium alloys while sometimes decreasing their ductility in some cases. Additionally, alloying has the potential to enhance the mechanical properties of Mg-based bioresorbable, including ductility and strength.

The degradation of metallic bioresorbable stents occurs through the corrosion of metals; an electrochemical reaction caused that produces oxides, hydroxides, hydrogen gas, and possibly other compounds (chemical equation 1).

$Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2$ (chemical eq. 1)

High-purity magnesium exhibits the lowest corrosion when exposed to air at room temperature. Pure magnesium has limitations as it corrodes quickly in a physiological environment (pH 7.4-7.6), generating hydrogen gas at rates unmanageable by the host tissue. In addition, corrosion speed is high in chloride-containing liquids or acid solutions. NaCl and minor amounts of other inorganic molecules, including Ca^{2+} and HCO_3^- are present in the human body. The

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presence of chloride ions accelerates corrosion, whereas phosphates and carbonates may foster the formation of corrosion product layers that protect or partially protect Mg from corrosion. Currently, the two most popular methods for enhancing Mg alloy biodegradation resistance are alloying and surface treatment or coatings.[9]

Synthetic polymeric materials for stent application:

The degradation of synthetic biodegradable polymeric materials in our body occurs mainly through two mechanisms: hydrolysis and oxidation. Polymers, including polyesters, polycaprolactone (PCL) polycarbonates, polyvinyl alcohol (PVA), and polylactic acid (PLA), degrade mainly via hydrolysis.[10] In hydrolysis-based degradation, water causes the cleavage of ester bonds in the polymer chain, separating polymers into a few oligomers or monomers that can be clearly absorbed in the bodily fluid. For example, the products from the degradation of PLA and PCL are small molecules, including lactic acid and 6-hydroxyhexanoic acid. These small molecules could be eventually eliminated from the body to the outside, like carbon dioxide and water. Unlike natural biodegradable polymers, synthetic polymers with a specific degradation rate can be produced, allowing us to control the degradation time in the artery. The degradation rate of biodegradable polymers can be tuned by many strategies, including change of composition, molecular weight, the crystallinity of polymers, blending, copolymerization, and surface modification (Figure 3).[11] Typically, blending and copolymerization are used to increase the degradation rate of a slowly degrading polymer. To reduce the degradation rate, increasing the crystallinity and molecular weight of the polymer can be the solution. The polymeric stent's mechanical softness and low modulus are considered critical advantages. Generally, polymeric materials consist of cross-linked polymeric chains which have freedom of movement in the matrix, enabling the relaxation of external stress. So a stent fabricated by polymeric material is mechanically robust under radial stress induced by expansion in an artery. In the future, we need to fulfill the requirements in biomedical engineering, including biodegradation rate, mechanical robustness, and biocompatibility.

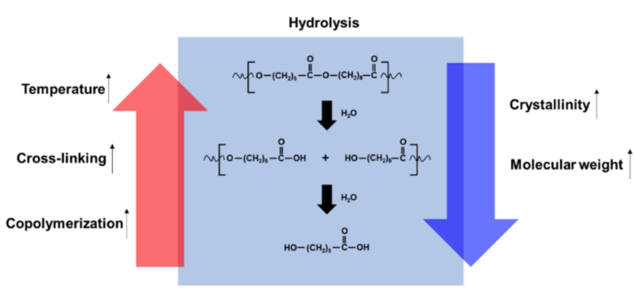

Figure 3: Strategies for tuning biodegradable polymers.

What kinds of components could be integrated with the transient property?:

Implantable electronic devices allow physicians to extract meaningful data in real-time and activate corresponding tissue functions by electrical stimuli to interface with the human body. Unlike most conventional bio-implantable electronic devices that remain functional and intact in the body for an infinite time frame, biodegradable electronic devices feature a stable operation in a defined time before complete degradation within the body. The concept of the transient device has strong advantages for immediately controlling diagnostic or therapeutic functions, enabling the monitoring of short-term biological responses, such as for wound healing and infections, while avoiding adverse effects associated with long-term implantation of bio-implantable devices. Moreover, secondary surgical procedures are needed for device removal without this property. We need an advanced version of bio-implantable sensor/wireless electronic components to make such a system. There have been many signs of progress in bioresorbable electronic devices, which could be integrated with a stent for biomedical applications, including implantable pH and a pressure sensor for detecting a rheological property of blood flow in a vessel, impedance sensor to detect the cell growth near endothelium, wireless antenna for data and power transmission,[12] and memory to memorize data. Of those parts, the doctor might miss.[13] As we could find in previous reports, bioresorbable electronic components should be fabricated in a flexible thin film to be integrated into the stent. For example, researchers report materials, device architectures, integration strategies, and *in vivo* demonstrations in rats of implantable, multifunctional silicon sensors for the brain.

All of the constituent materials naturally resorb via hydrolysis and/or metabolic action eliminating the need for extraction.[14] All sensors are fabricated in the shape of thin film and can detect flow rate, temperature, and pH of the internal body, which are also vital components in bioresorbable electronics stents. Another research group showed the multi-functional stent integrated with an antenna for power/data transmission, flow/temperature sensors, memory storage devices, anti-inflammatory nanoparticles, and drug-loaded core/shell nanospheres activated by an external optical stimulus. The entire operation mode of the stent is as follows: the flow sensor measures blood flow, which is stored in the embedded memory module for pattern analysis and diagnosis. Catalytic reactive oxygen species scavenging and hyperthermia-based drug release can be used as advanced therapies.

Real-time monitoring stent:

As previously mentioned, the smart stent has been developed to minimize the surgical process. In conventional stent technology without multi-functions, detecting other diseases was challenging because the doctor must check the status of inserted stents via medical instruments, including Computed Tomography (CT), Magnetic Resonance Angiography (MRI), which could provide discontinuous data by capturing the image. For this reason, it is impossible to respond immediately in an emergency. For example, despite using stents to improve blood flow, the physiological process can produce restenosis, a phenomenon that causes tissue growth, again closing the vessels. In-stent restenosis obstructs blood flow inside the artery and will result in variations in local blood pressure, hemodynamics, and blood flow characteristics. The early signs of the in-stent restenosis can be detected with pressure/flow sensors and wireless platforms by properly monitoring these parameters (Figure 4).

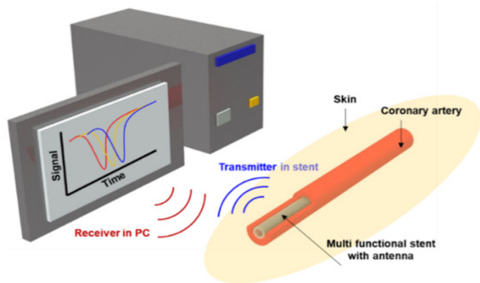

Figure 4: Real-time wireless monitoring stent.

Conclusion

In this review, we consider the promising technologies for the stent. First, we introduce the necessity of a multi-functional bioresorbable stent fabricated from a biocompatible and bioresorbable material. To investigate the candidates, we divided the bioresorbable materials into two categories: i) metallic and ii) polymeric materials. Metal is an essential component in a stent for supporting the shape of the stent and providing electrical functions. Most of the sensors integrated on bioresorbable stents have been fabricated with bioresorbable metals such as Mg, Zn, and Mo. Bioresorbable polymer is also the main component for the stent to provide mechanical flexibility to all components on the stent.

Moreover, in contrast with metal, it could be used as an encapsulation layer for preventing current leakage from the wireless/sensor components, resulting in malfunction. The lifetime of a bioresorbable stent dominantly depends on the bioresorbable polymeric materials. We review the available kinds of sensor/wireless devices which could be integrated into the stent and their valuable functions. Such devices have great potential for real-time and continuous monitoring of parameters such as the stress of endothelium and blood flow. In addition, the monitoring done with smart stents may help prevent some clinical complications of conventional stents, which include stent thrombosis (a life-threatening event where the artery is completely blocked due to the formation of a blood clot in the stent) and in-stent restenosis (a slow re-narrowing of the segment with the stent).

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