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Research Article

NEXT GENERATION, DRUG ELUTING AND BIORESORBABLE STENT FOR CARDIOVASCULAR DISEASE

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Abstract

The leading cause of death in the globe is cardiovascular disease. Two thirds of these deaths are caused by the underlying pathology of atherosclerosis. Atherosclerosis, which is very critical vascular disease, is caused by the agglomeration of plaque in the arteries, blocking the blood flow in vessel. This phenomenon appears as our abnormalities of health, ranging from high blood pressure levels, high cholesterol levels to ischemia in severe case. Due to this, cardiovascular disease has attracted intensive attention in fields of medical and bio-medical engineering. An inflatable metal stent is frequently used in hospitals to repair blocked atherosclerotic arteries. However, it is still challenging in terms of two critical barriers: i) Complex surgical process for removing stent and ii) "in-stent restenosis," a wound reaction in which the vessel's lumen narrows again by excessive proliferation of vascular smooth muscle cells, is what causes stented veins to frequently silently re-block. To overcome these two main challenges, novel kinds of stent technology have been researched in terms of drug eluting technology and bioresorbable stent. Here we discuss the present state of stent technology and the potential of multi-functional stent for preventing of cardiovascular disease.

Keywords: Stent, Bioresorbable, Drug eluting, Atheroclerosis, In-stent resentosis

INTRODUCTION

The cardiovascular system, which is the biological path for providing nutrients and oxygen to all of our body, is essential part of our life. It is made up of the heart, a muscle pump, and a closed network of blood channels known as arteries, veins, and capillaries. The circulatory system's blood is pumped by the heart in what the name suggests is a closed circle or circuit of vessels as it repeatedly travels through the various "circulations" of the body. Among these systems, the cardiovascular system is main part of our circulation system as it is directly related to heart functions, ranging from expansion/contraction of atrium or ventricles to activities of conduction system of heart. Cardiovascular disease starts from formation of plaques inside of vessel's lumen. A buildup of plaque inside the coronary arteries can cause the blood flow in an artery to be slowed or even reversed, which inhibits the heart muscles from getting enough oxygen or nutrients to operate, causing ischemia or necrosis of myocardium. Severe anguish and tissue death could be caused by blocking the blood supply to the arms and legs. In severe case, heart failure could come from an impaired cardiac muscle's inability to pump properly. A stent is a medical device that widens a narrowed area of an artery to promote blood flow; they are essential pieces of medical technology used to increase blood flow and revive the heart. The most prevalent cardiovascular disease among the various heart conditions is coronary artery disease. It frequently happens along with atherosclerosis. The buildup of plaque inside the coronary artery wall results in atherosclerosis, a sort of thickening or hardening of the arteries. Plaques are composed of cholesterol, fatty acids, waste products, calcium, and the clotting agent fibrin. Your arteries gradually become narrower and harder as a result of plaque buildup and formation (Figure 1).

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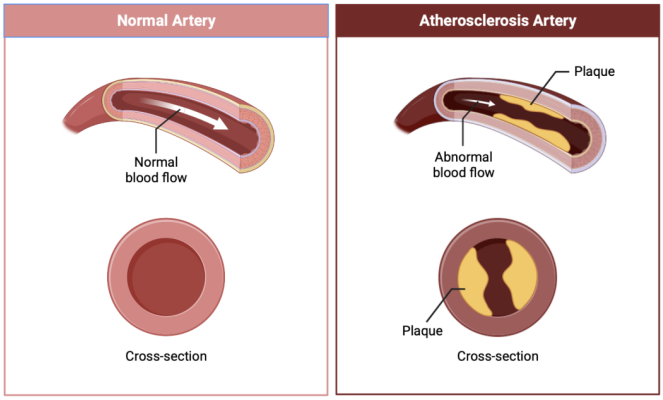

Figure 1. Schematics showing that before and after formation of atherosclerosis in artery

This reduces the flexibility of the arteries and restricts blood flow to the heart muscle. Stents are implantable medical devices (IMD) that are commonly used in hospitals to treat atherosclerosis (1). Stents are circular-sectioned, tubular, implanted vascular scaffolding devices. They are made to be elastic but also maintain their shape when used in a vessel. Stents are deployed in a variety of places, including the biliary duct and coronary arteries, to unblock clogged vessels. The percutaneous coronary intervention (PCI) procedure is used by the doctor to place the stent in the target artery. PCI is a procedure used to treat cardiovascular disease that uses a stent. This method uses balloon angioplasty to clear blocked arteries over the course of four steps. Initially, a number of catheters and guiding wires are implanted through the patient's skin. To be specific, the devices are inserted via brachial artery in the wrist. The catheter is then advanced up the arterial vasculature to the site of occlusive illness within the coronary arteries of the heart. Following the inflation of a balloon inside the stent, the stent expands along with the balloon and is inserted through the catheters. The balloon's inflation forces the plaque material, which is made up of biological elements like smooth muscle cells or inflammatory cells as well as fat deposits, back.

The balloon is finally deflated, but the inflated form of the stent prevents plaque from recoiling. As a result, the lumen flow in the area returns to normal. Patients who received PCI treatment experienced fewer severe symptoms of coronary heart disease and benefited from the procedure's lower costs, less invasive nature compared to coronary artery bypass graft (CABG) surgery, and quicker in-hospital recovery. In-stent restenosis (ISR), a phenomenon where an overgrowth of scar tissue cells occurs near or inside the stents (Figure 2), presented a challenge to this treatment by once more restricting blood flow. ISR appeared in 17%-41% of first-generation stents (2).

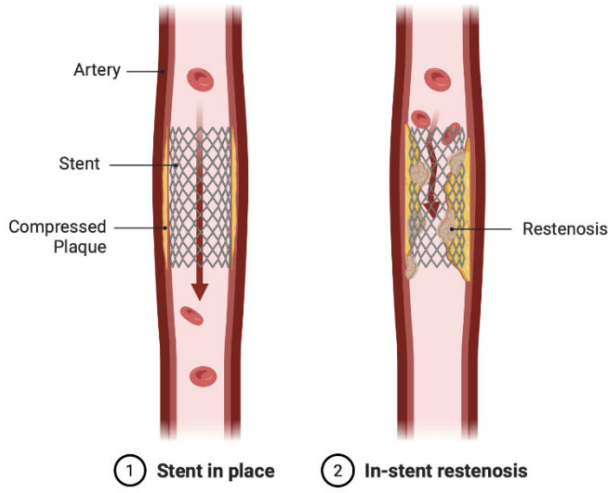

Figure 2. Schematics illustrating process of in-stent restenosis

Second-generation stents were coated with anti-proliferative medication to solve this problem. To stop cell proliferation, a drug-eluting stent (DES) gradually releases a medication from the stent. At last, future generation of stent will be bioresorbable, and drug eluting stent, which provides the solution to current limitation regarding in-stent restenosis and burden of additional surgical process. In this work, we would review the various approaches for developing new kinds of biomedical stent including drug-eluting, bioresorbable property and multi-functional system.

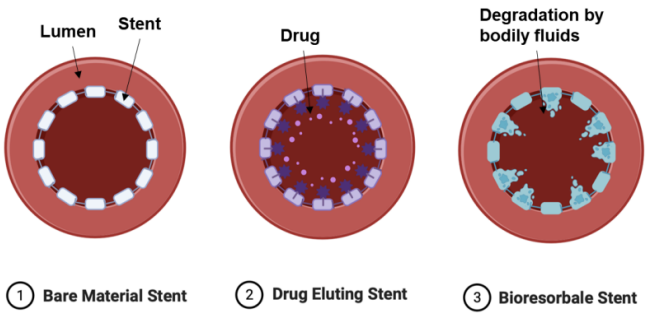

Figure 3. Various approaches for next generation stents

Various approach in stent development

Medical stent for vascular diseases has evolved considerably over the last 20 years. Firstly, the bare-metal stent, which is made of thin, uncoated metal wire formed into mesh-like tube. Mesh-like structure was adopted for releasing the stress to artery walls, minimizing the undesired damage. These long-lasting metallic frameworks are constructed of stainless steel, nickel-titanium alloys (nitinol), and cobalt-chromium (CoCr) alloys for balloon-expandable stents (3). Despite being seen as a turning point in the field of surgery, the revolution had its own drawbacks, including a higher risk of thrombosis and restenosis. It is quite likely that intravascular injuries will occur during stenting procedures and result in in-stent restenosis (ISR). ISR is the primary factor in arterial blockage over time, and stent failure results from the loss of artery patency. As early reports provided the results (4) that about 15–20% of all implanted stents patients required re-intervention within 6–12 months after the insertion of medical stent due to ISR. The introduction of drug-eluting stent has been a particularly significant development. Clinical outcomes achieved with these devices, notably the reduced incidence of ISR compared to bare-metal stents, have helped drive a growth in the use of percutaneous coronary. A drug-eluting stent that is inserted into clogged, diseased peripheral or coronary arteries and slowly releases a drug to stop cell proliferation. This avoids fibrosis, which could otherwise block the stented artery along with blood clots (thrombi). However, drug-eluting stent has also several disadvantages, including a predisposition to late stent thrombosis, prevention of late vessel adaptive or expansive remodeling, hindrance of surgical revascularization (5). To overcome these limitations, bioresorbable materials are introduced in fabrication of medical stent for providing natural absorption properties to stent, which prevent additional surgical process. Previous research has shown that the most critical period of vessel healing is almost completed by approximately three to nine months. In other words, the bioresorbable stent is temporary used for fully supporting the vessel during this critical period, and then resorbs from the body when it is no longer needed. There are many candidates for this future type of stent as we would address in next section.

Bioresorbable materials for future stent application

Bioresorbable electronic stent is promising technology that enables biocompable, non-invasive medical application. To realize the bioresorbable medical stent, various transient materials could be used as scaffold, and sensors. We would address the two types of bioresprbable materials; i) metallic bioresorbable material, and ii) polymeric bioresorbable material. Firstly, metallic materials have high mechanical strength compared with polymeric materials, providing robust mechanical support in lumen. Specifically, Mg and Ca (Alkali metal), Mo, Zn (Transition metal) and Fe and its alloys are widely used as bioabsorbable conductor (6). Principle of corrosion is same as the degradation of bioresorbable metallic stents through an electrochemical reaction that produces oxides, hydroxides, hydrogen gas, and possibly other compounds as shown in chemical reaction below.

$$M\ (metal) + H_2O \rightarrow M(OH)_2 + H_2$$

When the metal is exposed to moisture, the metal cation is converted to hydroxide compounds, which is soluble to water. Since each metal has different properties, the material is selected considering the operating time of the conductor in the body and the physiologically allowed local concentration threshold. Among bioresorbable metals, Mg is suitable for usage in the body and can apply various techniques of micro fabrication. For examples, it is utilized to make diverse parts of bioresorbable devices: electrodes, resistors, and capacitors. Alkali metals are usually covered with encapsulation layer as they are easily degraded rapidly in the biological environment. On the contrary, transition metals show much slower

dissolution rates than alkali metals, so they can be retained in the body for a period of time without encapsulation. However, if a large amount of metal is broken down at once, it may trigger a negative immune response. For this reason, local concentration threshold should be considered and maintained proper ranges in our body. One of strategies for controlling the decomposition rate is making metal composite, termed “alloy”. For example, Mg alloys, which decompose more slowly than pure Mg, are favored in implantable devices, which must operate over long periods. Expandability, plasticity, rigidity, and resistance to the elastic recoil of blood vessels are prior properties in mechanical aspects for stent. The stent should be stable for 4 to 6 months after implantation. These mechanical properties can be manipulated through alloying Mg : Cd, Tl, Li enhance the ductility with negligible influence on the strength; Sn, Pb, Bi, Sb enhance the strength with some decrease of the ductility; Al, Zn, Ca, Ag, Ce, Ni, Cu, thus enhance the strength and the ductility simultaneously but especially predominantly increasing the strength; and Th, Zn, Ag, Ce, Ca, Al, Ni, Cu enhance the strength and the ductility simultaneously but especially predominantly increasing the ductility (7). The mechanical properties of metallic materials are determined by their elastic modulus, tensile strength, compressive strength, and compressive and tensile yield strength. The thinner stents with more flexible devices and fewer vascular trauma are made possible by the high strength and high ductility materials. High elastic modulus to prevent acute stent recoil after balloon deflation; low yield strength (200–300 MPa) to the expansion of the stent during deployment; High tensile strength to increase stent radial strength to improve flexibility (> 300 MPa); and high ductility to sustain deformation during expansion without cracking (20–30% fracture elongation) are considered for bioresorbable stent fabrication.

Bioresorbable polymer is another class of transient materials for medical stent. Unlike metallic matrials, it has mechanical softness, which is preferred to minimize the mechanical stress on endothelial. Moreover, changing of molecular structure could provide mechanical toughness and softness simultaneously. Although many advantages exist, it is still challenging to use polymeric materials as medical stent due to mechanical fracture during insertion of stent. To overcome this issue, many researchers have focused on bioresorbable polymeric materials. Bioresorbable insulating materials are made of both natural and artificial polymers, or inorganic materials, which exhibit bioresorbability, such as metal oxides and metal nitrides. They have two usages: the dielectric layer or an encapsulant in bioresorbable electronics. Synthetic polymers are preferred rather than natural polymers because their dissolution rates can be manipulated by adding different molecules and adjusting the molecular ratio, and bioabsorbability has been demonstrated. However, research on optimizing the degradation rate, mechanical properties, low water and oxygen permeabilities, and biocompatibility of polymeric materials is still needed. Poly lactic acid (PLA) and poly lactic glycolic acid (PLGA) are synthesized bioresorbable polymers, which is commonly considered for medical stent (8). Different from metals, the principle of decomposition is based on hydrolysis, which occurs via chemical reaction between ester and water.

Multi-functional stent for real-time monitoring

To detect the unexpected problems in artery, for examples, detachment of stent from endothelial, blood leakage out of stent, and decrease flow rate of blood inside of stent due to in-stent restenosis, stent requires additional functions for real-time monitoring of checking the status of stent. There have been many progresses to fabricate multi-functional stent integrated with various sensors (9). In-stent restenosis obstructs the normal blood flow inside arteries and will consequently result in drastic change of local blood pressure, and blood flow characteristics. Impedance sensor, of which impedance is sensitively changed when it contacts with cells. By integrating with this impedance sensor on stent, in-stent restenosis caused by differentiation of cells could be detected directly and it enables early medical treatments. Pressure sensor is one of promising candidates to detect the blood leakage out of flow path formed by stent. When abnormal blood flow occurs, which induces unexpected pressure to surface of stent, the pressure sensor detects the change of pressure. Moreover, wireless components (Bluetooth antenna and coil-type antenna) are essential parts of multifunctional stent to transmit the power and the real-time data detected from sensors as mentioned above. Coil-type wireless antenna provides the optimized power, which is required to operate sensors. As supportive device to antenna, memory devices are regarded as promising technology, which could store all data inside of devices. By using this, doctor could check all events occurred inside of the arteries later.

Conclusion (300 words)

Despite advances in cardiovascular stents in terms of minimization of surgical process and clinical outcomes, there are many challenges to overcome the current burden of patients, ranging from invasiveness, clinical monitoring to accurate therapeutic methods. There have been numerous research reports as the preferred therapeutic option for stent design to overcome the limitations. Various strategies for next generation medical stent is divided in three main directions: i) biocompatible and biodegradable materials to prevent further thrombosis, and in stent restenosis, ii) soft design or materials for minimizing the stress to endothelial and iii) integration of additional functions to stent that enables monitoring of internal environments. We reviewed these three main issues for presenting future direction of medical stent. The BRS technology is still in its infancy, thus further research and development are required to improve it and find a secure market. Without a doubt, BRS in the future is more likely to have an impact on a number of recent developments in interventional cardiology. About BRS, it is evident that the subsequent generation must have a secure implantation and greater mechanical stability. According to our knowledge, recent studies have a difficulty to providing a commercially available bioresorbable stent without thrombosis incidence. According to the available findings, there don't appear to be any compelling clinical arguments in favor of switching from the currently used stents to one of the novel stent designs. However, published data have not yet confirmed any outperformance of what was anticipated from the current drug-eluting stent, which means that bioresorbable devices need to demonstrate a clear therapeutic advantage over drug-eluting stent. More importantly, many of the previously proposed and developed designs are currently being tested in vivo due to insufficient clinical findings. Integrating of drug-eluting stent system with scaffold of stent fabricated by bioresorbable materials would pave the way for advanced type of medical stent. In addition to this novel material design, nano-device fabrication of sensors or other electrical and medical

components might be integrated on stent to monitor the patient's and respond immediately to emergencies.

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