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Review Article

Recent Advances in the Treatment of Coronary Artery Disease

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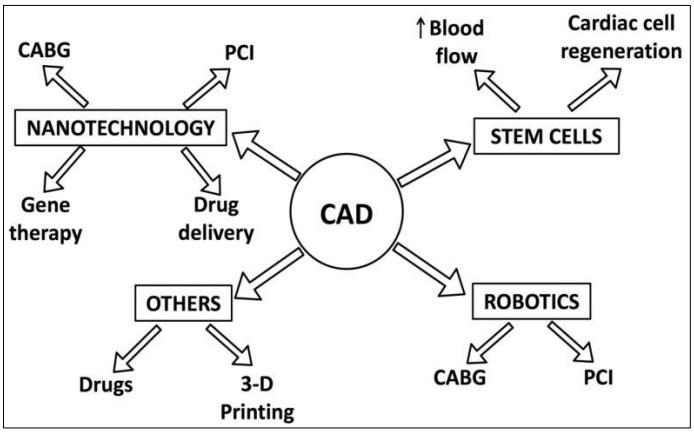
Abstract: In the last decade, significant advancements in CAD treatment have been made. The existing treatment is medical, surgical, or a combination of both depending on the extent, severity, and clinical presentation of CAD. The collaboration between different science disciplines such as biotechnology and tissue engineering has led to the development of novel therapeutic strategies such as stem cells, nanotechnology, robotic surgery, and other advancements (3-D printing and drugs). These treatment modalities show promising effects in managing CAD and associated conditions. Research on stem cells focuses on studying the potential for cardiac regeneration, while nanotechnology research investigates nano-drug delivery and percutaneous coronary interventions including stent modifications and coatings.

Keywords: CAD treatment, biotechnology, 3-D printing, drugs, cardiac regeneration.

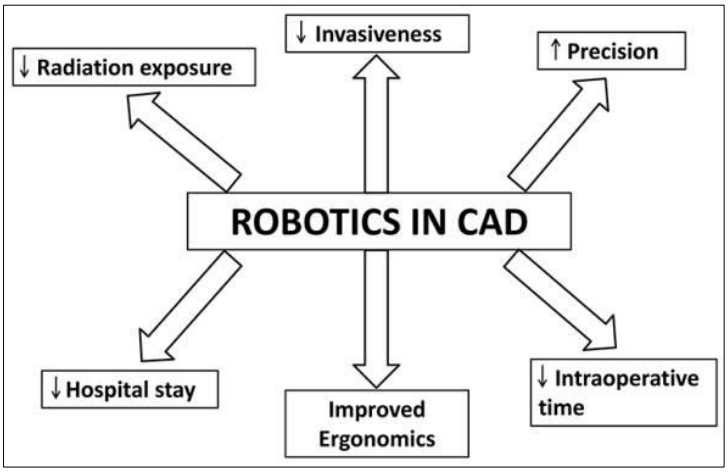
INTRODUCTION

The first coronary artery bypass operation (CABG) was performed on May 2, 1960. The first percutaneous coronary intervention (PCI) was performed almost 20 years later. Since then, the invasive treatment of coronary artery disease (CAD) has moved into the spotlight of cardiac medical care. There has been a greater focus in research aimed at all aspects of CAD in the last decade. Due to exhaustive efforts from clinicians and researchers worldwide, there has been significant progress made in developing novel strategies for patients suffering from CAD and its associated complications. These strategies have ranged from drugs to robotic surgery to nanotechnology. This article will summarize the literature on the recent advances in coronary artery disease research in respect to therapeutics and biomarkers. This article will cover topics under the following headings: robotic surgery, nanotechnology, stem cells, and other related advancements.



Robotics

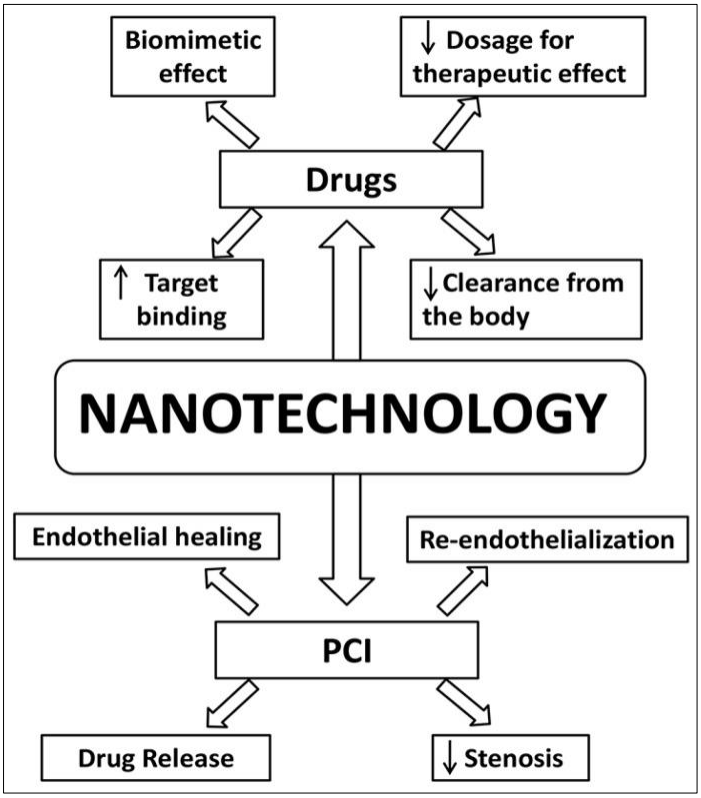
Robots have been in place in mass production industries for many years. However, their introduction to medicine was fairly recent and started in the fields of surgery and radiotherapy[1]. In cardiology, they have been in use for more than a decade for surgeries like mitral valve repair, coronary artery bypass graft, and septal defect closure. The technology is fast evolving with reports emerging about their potential applications in percutaneous coronary intervention and atrial fibrillation ablation [7]. Robotics provide the operator with advantages such as improved ergonomics, precision and sometimes shortening of intraoperative time [8]. There have been reports that robot-assisted surgery can shorten patient hospital stays and improve patient perception [8]. They performed coronary angioplasty and reported a 100% success rate (measured in terms of less than 30% residual stenosis along with the absence of major cardiac complications) in all of their patients (80 subjects) [10]. In a multicenter study published by Weisz *et al*., a percutaneous coronary intervention was performed for patients with coronary artery disease [11]. They used similar success criteria (measured in terms of less than 30% residual stenosis along with the absence of major cardiac complications) and reported a 97.6% rate of success (164 patients). They also reported a significant reduction (95%) in operator radiation exposure. Robotics has also been used to perform coronary artery bypass grafting in CAD patients [12]. The procedure, including the harvesting of the mammary arteries and anastomosis, can be performed endoscopically. The current state of robotic surgery is promising in the treatment of CAD. These systems are of excellent quality with high-end technology. Their proposed benefits in the form of improved precision, increased visibility, improved ergonomics, and reduced radiation exposure have been documented, which have translated into improved patient recovery times with reduced hospital stays.



Nanotechnology

Nanotechnology has been used in the synthesis of dimyristoyl phosphatidylcholine, which mimics the surface characteristics of HDL by mediating the removal of cholesterol from the peripheral tissues and transporting it to the liver. In an animal model study, mice fed with a cholesterol-rich diet showed significantly lower plaque volume and cholesterol content in the aorta when treated with dimyristoyl phosphatidylcholine liposomes [14]. Fumagillin is an anti-angiogenic drug that has been shown to inhibit angiogenesis thereby promoting plaque regression in coronary arteries. One of the disadvantages that has prevented Fumagillin application is its ability to cause adverse neurocognitive effects at high doses, which is required to achieve a therapeutic effect. Winter *et al*., demonstrated that the Fumagillin can be delivered through αvβ3 integrin targeted nano-delivery system, and can achieve significant antiplaque effects at one-third of the usual dose. Several nanoparticle-based antithrombotic agents have been tested for their potency. d-phenylalanyl-l-prolyl-Larginyl-chloromethyl ketone is a potent antithrombotic agent that is rapidly cleared from the body, thus limiting its clinical use [13]. When combined with a perfluorocarbon-core nanoparticle, it has been shown to have improved antithrombotic action, as shown by Myerson *et al.,* in an animal model study. Peters *et al*., on the other hand used hirudin with fibrin-binding micellar nanoparticles which exhibited greater targeting of fibrin clots in vivo. Collagen IV nanoparticles have been tried in an animal model study and were shown to improve collagen formation while reducing oxidative stress by mimicking Annexin A1 (glucocorticoid regulatory protein) [13]. Nanotechnology has the potential to promote healing by inducing endothelialization of the stent. These nano-modifications have been in the form of a nanofibrous matrix (attracts endothelial cells), polyhedral oligomeric silsesquioxane poly-(carbonate-urea) urethane (improved adherence and proliferation of human endothelial cells), peptide amphiphile-nanofiber coating (for promotion of endothelial cell adhesion), and magnetic nanoparticles (for preferential movement of cells towards the stent). Nanotechnology also has potential applications in finding synthetic alternatives for coronary artery bypass grafts. Researchers have studied the potential of electrospun nanosized fibrous scaffolds, which may prove to be an alternative synthetic graft for

coronary artery bypass graft procedures. Targeting drug-eluting stents in gene therapy is another area where nanotechnology holds promise. Gene-eluting stents can be used to overcome restenosis, in-stent thrombosis, and delayed reendothelialization.



Stem Cell

The stem cells studied in cardiovascular research ranged from bone marrow to adipose tissue to skeletal muscle stem cells. Bone marrow-derived mononuclear cells are the most readily available cells for transplantation in the body. They are easy to identify based on their cell surface markers and can be isolated from the bone marrow [13]. However, their therapeutic potential is low since the harvested cells contain a multitude of cells with a small proportion of stem cells. The bone marrow-derived mesenchymal stem cells are found in even lower concentrations than that of mononuclear cells thus requiring several weeks of maturation with different growth factors in the lab before clinical usage. The adipose-derived stem cells can be surgically harvested from adipose tissues. They are more abundant in comparison to the bone marrow-derived cells [12]. This drastically reduces the time and cost involved in laboratory procedures to culture them for clinical use. The pluripotent stem cells have a high potential for transformation. Although embryos represent the most obvious source of stem cells, their use has ethical concerns and is in debate. Additionally, these cells could potentially face rejection when transplanted to a recipient. However, it is possible to reprogram adult cells and transform them into pluripotent cells (similar properties as embryonic stem cells), thereby being called induced pluripotent stem cells. These cells can be auto-transplanted and therefore would not be rejected [11]. However, due to their transformation potential, unless closely regulated, they can undergo trachomatous (derived from all three germ layers) changes in the body [8]. Due to the risk of trachomatous changes, this area of research requires more work before it can be considered safe for human trials. Another interesting source of stem cells is cardiac stem cells. Although the heart was considered as a static organ (with little or no potential to undergo mitosis during adulthood), recent evidence has shown a different perspective [14]. The heart is now believed to have intrinsic regenerative potential and undergoes constant turnover throughout adult life [14]. The clinical data for stem cell therapy is in its early days with reported literature covering both non-randomized and randomized trials. One non-randomized trial reported improved left ventricular ejection fraction (LVEF) function following injection of mononuclear stem cells in patients with MI within three months. Improved exercise capacity, reduced mortality, and scar tissue are shown in a 5-year follow-up [9]. Several other studies showed similar effects following treatments with mononuclear stem cells after MI. An earlier meta-analysis reported an improvement in LVEF function by 2.99% following bone marrow stem cell transplantation in patients after MI. However, the meta-analysis did not include recent studies that reported no improvement in left ventricular function. In patients suffering from chronic ischemic heart disease, there is reported evidence of improved cardiac function following the use of bone

marrow-derived stem cells. There have been several trials that have studied the clinical efficacy of mesenchymal stem cells [3]. They have reported an improvement in cardiac function and relative safety in the use of mesenchymal stem cells. Cardiac-derived stem cells have also undergone clinical testing and have shown promising results. Stem cell therapy continues to be a promising treatment modality for coronary artery disease (both acute and chronic). The experimental and clinical studies have shown promising results. However, further research is needed to understand the exact mechanisms of action and the ideal source of stem cells to derive optimum benefit and to further our understanding [8]. Several challenges have to be overcome (such as long-term safety and route of administration), but the direction of current research looks promising.

5.1. 3-D PRINTING

Cardiac conditions often require 3-D imaging such as magnetic resonance imaging, computerized tomography, and 3-D echography to diagnose and treat these conditions [6]. The limitations to this are that though these images are in 3-D, they are viewed on a 2-D computer screen or films. Although it could be sufficient for some cardiac procedures, the current imaging modalities are not effective for more complex interventions. 3-D printing has a potential role in CAD as it cannot only overcome these limitations but also allow for complete visualization, tactile sense, education, and surgical planning as well as simulation [15]. 3-D printing involves additive manufacturing of a model using 3-D data from imaging modalities. Scientists are starting to see the full potential of 3-D printing as the technology continues to evolve. In the field of cardiology, it has tremendous potential in the treatment of congenital defects, cardiac tumors, cardiomyopathy, functional flow models, valvular heart diseases, stent placement for CAD, and other cardiac surgeries [14]. 3-D printing allows the visualization of 3-D printed hearts with coronary arteries to visualize the extent of occlusion and stenosis in CAD patients. These models can be used in a pulsatile flow loop environment, not only to visualize and understand complex flow patterns but also to simulate interventions. 3-D printed models are also useful in CAD research to compare imaging and treatment modalities [7]. One in vitro study mimicking a clinical scenario proved that 3-D printing could be more effective in planning and treating complex situations (bifurcation lesions) that require stent placement.

5.2. Drugs

CAD patients are often on supportive, therapeutic, and lifelong medication for the condition itself and co-morbidities (such as hypercholesterolemia). There have been recent advances in drug development for CAD patients. One class of drugs taken by patients suffering from CAD are oral antithrombotic medications such as aspirin and clopidogrel [2]. A few years ago, a group of drugs collectively termed novel oral anti-coagulants were discovered. This group consists of the following drugs: ximelagatran, darexaban, dabigatran, rivaroxaban, and apixaban. Of these, dabigatran, edoxaban, rivaroxaban, and apixaban are approved for clinical use. Dabigatran is a competitive inhibitor of thrombin while edoxaban, rivaroxaban, and apixaban are inhibitors of clotting factor Xa. The use of dabigatran in CAD patients was studied in a phase 2 trial [1]. The results revealed that ischemic events in patients were significantly reduced at higher doses of the drug (110 and 150 mg), but this benefit was counteracted with a four-fold increase in bleeding risk. However, the trials concluded that lower-dose therapy could be used without a significant increase in bleeding risk [8]. These results were confirmed in several phase III trials. Since high LDL levels are linked to CAD, the use of Alirocumab reduced adverse cardiovascular events by 15–48%. Another drug that was recently developed for the treatment of heart failure is the angiotensin receptor-neprilysin inhibitor (ARNi) [7]. This drug contains a combination of sacubitril and valsartan, commonly referred to as the LCZ696 or ARNi. The valsartan portion is a drug of the angiotensin receptor blocker family as well as angiotensin II receptor antagonist, while the sacubitril component is a neprilysin inhibitor [9]. This drug has proven to be more effective in the treatment of heart failure than traditional Angiotensin-converting enzyme (ACE) inhibitors[4]. Although initial trials are promising, the results of phase III clinical trials are being awaited.

CONCLUSION

Despite great progress in cardiovascular research, CAD remains one of the most common causes of morbidity and mortality worldwide. However, significant inter-collaborative efforts between researchers, clinicians, and other related professionals have led to multi-faceted and novel strategies to be developed to treat CAD and its associated conditions. Though some of these strategies have strong evidence supporting their clinical use, some others are still in the experimental stage. Despite only early evidence being available on some of these novel treatment modalities, the results are promising and hold the potential to become alternatives to current treatment options in the future. Since we live in the era of evidence-based medicine, further evidence in the form of clinical trials and long-term follow-up studies are required before these novel treatment strategies enter into mainstream practice. With sustained continued efforts, the future of CAD therapeutics looks substantially promising.

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