Advances in Biotechnology

Chapter 5

Recent Advances in Cardiovascular Diseases and Treatment

Abhilasha Singh*

Department of Medical Biochemistry, University of Madras, Chennai India

Email: abhilasha.iitm@gmail.com

Abstract

Cardiovascular diseases (CVD) are one among the most common causes of death worldwide. There are plethora's of events leading to cardiovascular pathophysiology. Despite, recent advancements in the treatment of cardiovascular diseases, it remains the number one cause of death in the world. While traditional risk factors partially account for the development of CVD, other novel risk factors have recently been implicated. Specifically chronic inflammation has been postulated to play a role in the development and propagation of this disease. Reactive oxygen species (ROS) generated during excessive oxidative stress are the one among responsible for the various inflammatory events in cardiovascular disorders including atherosclerosis, cardiac hypertrophy, cardiomyopathy heart failure, ventricular remodelling, ischemia/reperfusion injury and myocardial infarction. In the last decade, significant advancements in CVD treatment have been made and achieved some curative effects as well. The existing treatment is medical, surgical or a combination of both depending on the extent if severity and clinical presentation of CVD. The collaboration of different science disciplines likely biotechnology and tissue engineering has led to the development of novel therapeutic strategies: Stem cells therapy, Nanotechnology, Robotic surgery and Drugs. These treatment modalities show promising effects in management of CVD and associated conditions to larger extent.

Keywords: Cardiovascular Diseases; Robotics; Nanotechnology; Stem cells

1. Introduction

Cardiovascular diseases are diseases of circulatory system which involves either one or both of the heart and blood vessels (arteries veins and capillaries). The recent advancements in CVD and its physiology have led to a subsequent decrease in the mortality rate in the aged population. [1]. However CVD remains one of the leading causes of death worldwide [2]. There has been a greater focus in research aimed at all aspects of CVD in the last decade. In the recent past there has been significant progress made in developing novel strategies for patients of CVD and its associated complications. These strategies range from new therapeutic targets, drugs to robotic surgery and nanotechnology. This article will summarize the literature evidence on the recent advances ment in cardiovascular disease research with respect to therapeutics and biomarkers. The topics will cover the following headings: robotic surgery, nanotechnology stem cells and other basic research related advancements.

1.1. Robotics

Robotic interventions, the role of non-invasive imaging surgery and radiotherapy have been in use for more than a decade. In cardiology this technique is utilized for surgeries that are dependent on being able to see the exact location within the heart in 3D and having mechanical assistance such as computer-assisted technology or robotic assistance or better imaging and most likely both of these [3]. Further on as this matures and we will have better software technologies, there'll be important improvements in Tran's catheter ways of addressing the cardiac disease. In recent times specifically 2018 onwards this technique have been in use for surgeries like mitral valve repair, coronary artery bypass graft and septal defect closure including transesophageal to assess structural heart disorders especially to guide therapeutic decisions and procedures. The technology is fast evolving with reports emerging about their potential applications in percutaneous coronary interventions and atrial fibrillation ablation [4]. Robotic guided surgery has the potential to limit this radiation exposure. In addition they can also reduce contrast-induced nephrotoxicity and associated mortality in patients [5]. Robotics provides the operator with advantages such as improved ergonomics precision and sometimes shortening of intraoperative time [6]. There have been reports that robot-assisted surgery can shorten the duration of patients hospital stay and will improve patient perception of disease [7].

In terms of patient-related outcomes the robotic-assisted surgery has potential benefits as it can accurately measure the size of the lesions (which can be miscalculated using 2D angiography) which could improve long-term health benfits. Hence they reduce radiation exposure for the surgeon and the patient as well as improve precision by rendering accurate measurements of lesions. In a multicentre study published by Weisz et al. a percutaneous

coronary intervention was performed to patients with coronary artery disease [8]. 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) [9]. They also reported a significant reduction (95%) in operator radiation exposure [9]. Although there are reported benefits for robotically assisted bypass grafting, high costs and long learning curves have slowed down its progress towards becoming used routinely.

1.2. Nanotechnology

Nanotechnology has been revolutionizing several fields of medicine. It involves the engineering of nano-scale molecules with distinctly different properties than bulk molecules of the same composition. These inherent differences provide distinct benefits which are strong reasons for the boom in nanotechnology research. This technology has been studied in CVD for its potential benefits in medical [non-invasive and invasive] treatment modalities, drug delivery applications, percutaneous coronary interventions gene therapy and coronary artery bypass graft [10]. Nanotechnology have shown potential benefits when used in percutaneous coronary intervention. They have been studied for their ability to release drugs as well as promote healing and reduce restenosis. 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 [11]. 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 [12]. 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]. Nano modifications have also helped research scientists in targeting specific drug delivery of collagen IV chondroitin sulphate tissue factor or stents and several nano-coatings in the form of hyaluronic acid (which carries plasmid DNA) nano-biohybrid hydrogel (which carries Tat peptide and DNA) and poly lactic-*co*-glycolic acid nanoparticles (which carries PDGF receptor-β antisense RNA) have been extensively studied in animal models with promising results [14]. Nanotechnology has led to an interesting and promising direction in the treatment of CVD. It has shown promising potential in delivering drugs that are otherwise limited by their pharmacokinetics. Its potential application in stent and gene based therapy are useful for future therapeutics based on these modifications. Further randomized controlled trials need to be conducted to establish strong evidence to support the use of these newer technologies for CVD treatments.

1.3. Stem Cells

Stem cells technology have emerged as an important research target on developmental

morphological and physiological processes that govern tissue and organ formation, maintenance regeneration and repair[15]. Human heart is largely incompatible in replenishing or regenerating lost cardiomyocytes [16]. The therapeutic applications of stem cells is a promising and rapidly emerging branch of regenerative medicine in which stem cell-based treatments could be applied to treat and cure many aggressive and lethal diseases in humans [17]. Recent investigations were carried out with ex vivo expanded or differentiated embryonic stem cells and stem cell-derived from fully functional progeny as well as adult stem/progenitor cells. These have provided accumulating evidence supporting their potential role in the treatment of various genetic and degenerative disorders [18]. Research in CVD has shown to replenish myocardial damage by increasing the blood supply during ischemic conditions of the heart. In recent scenario both vascular growth factors and stem cells have generated a lot of interest for treatment in CVD subjects [19]. The apex and atria of the heart constitute the homing sites of cardiac stem/progenitor cells (CSCs), that are able to give rise to three major cell types of the myocardium-cardiomyocytes, smooth muscles and vascular endothelial cells-in physiologic and pathological conditions [20]. The rationale behind this therapeutic approach is to improve the blood supply to ischemic areas of the heart by stem cells and promote cardiac cell regeneration. This can be achieved in one of two ways: by a direct effect of the stem cells or by paracrine factors secreted by these stem cells [21]. In this regard hematopoietic stem cells have been of great interest especially for mononuclear cells and endothelial progenitor cells. Studies conducted using these cells for various forms of ischemic heart disease (such as acute myocardial infarction (MI) and chronic ischemic heart disease) have been contradictory although some studies have demonstrated a beneficial effect in such patients [22]. Adipose derived stem cells are another form of stem cells utilised for studies. A novel alternative is the creation of induced pluripotent stem cells of which adult cells are transformed into pluripotent stem cells similar to embryonic stem cells [23]. Although it offers a promising alternative, concerns of cancerous transformation of the undifferentiated stem cells have to be taken into account, before they can be tried in human subjects. The stem cells studied in cardiovascular research ranged from bone marrow to adipose tissue to skeletal muscle stem cells. Bone marrow (BM) - 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 [24]. However their therapeutic potential is low since the harvested cells contain a multitude of cells with a small proportion of stem cells [25]. BM stroma and the vascular walls of peripheral tissues also contain the multipotent EPCs and MSCs localized in perivascular niches that are able to generate mature endothelial cells and diverse mesenchymal cell lineages including osteoblasts, chondrocytes, adipocytes and myoblasts [26]. The BM and vascular wall-resident and circulating EPCs, as well as EPCs, derived from ESCs fetal liver and adult stem cells present multiple important clinical interests. EPCs can be utilised to treat diverse vascular disorders because of their significant high migratory potential through blood and their capacity to differentiate into new endothelial cells that can contribute to promoting

neo-angiogenesis and endothelium repair at distant sites of organ or tissue damage.

The adipose derived stem cells can be surgically harvested from adipose tissues. They are more abundant in comparison to the bone marrow-derived cells. This drastically reduces the time and cost involved in laboratory procedures to culture them for clinical use [27]. 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 can not be rejected. However due to their transformation potential, unless closely regulated they can undergo teratomatous (derived from all three germ layers) changes in the body [28]. Due to the risk of teratomatous changes this area of research requires more work before they can be considered safe for human trials. Another interesting source of stem cells are cardiac stem cells. Cardiac stem cells (CSC's)or their further differentiated progeny which represents a cell replacement therapy of aged or dysfunctional CSCs and regeneration of cardiomyocytes and coronary vessels is emerging as an area of great interest to many researchers. The experimental and clinical studies have shown promising results [29]. 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 add our understanding.

1.4. Drugs

Drugs for CVD patients (such as hypercholesterolemia) has been statins and fibrates though they are capable of bringing curative effects but are lifelong dependent medications. Recent research has led to various drug developments for CVD patients. One such class of drugs referred to patients suffering from CVD are oral antithrombotic medications such as aspirin and clopidogrel [30]. Oral anti-coagulants group consists of the drugs: ximelagatran, darexaban dabigatran, rivaroxaban and apixaban [31]. Of which dabigatran, edoxaban, rivaroxaban apixaban are FDA approved for clinical use. Dabigatran is a competitive inhibitor of thrombin while edoxaban, rivaroxaban and apixaban are inhibitors of clotting factor Xa. However use of dabigatran in CVD patients was confirmed in phase 2 trial for ischemic events in patients at higher doses of the drug (110 and 150 mg) but with increased bleeding risk [32].

An important protein that controls the regulation of LDL (which is a key regulator in hypercholesterolemia) is proprotein convertase subtilisin/kexin type 9 (PCSK9) [33]. They function to reduce the number of LDL receptors thereby decreasing LDL cholesterol levels in the blood [34]. Another major drug which could act as blocker for PCSK9 is Alirocumab which is a monoclonal antibody (produced by recombinant DNA technology) [35]. The studies with

Alirocumab reported a reduction in LDL cholesterol levels ranging from 28% to 65% depending on the route of administration [36]. Since high levels of LDL levels are linked to CVD the use of Alirocumab reduced adverse cardiovascular events by 15–48% [36]. Another class of drugs recently studied for the treatment of heart failure is the angiotensin receptor-neprilysin inhibitor (ARNi) which contains a combination of sacubitril and valsartan commonly referred to as the LCZ696 or ARNi [37]. The valsartan portion is a drug of the angiotensin receptor blocker family as well as angiotensin II receptor antagonist, while the sacubitril component is neprilysin inhibitor [38]. This drug is proven treatment for heart failure than Angiotensin-converting enzyme (ACE) inhibitors [39].

2. Conclusion

Research progress has led to significant advancements in therapeutic approach despite cardiovascular diseases remain one of the most common causes of mortality and morbidity worldwide. Recent significant inter-collaborative efforts of researchers, clinicians and other health professionals have led to multi-faceted and novel strategies to be developed for CVD and its treatment. Though some of these strategic interventions have strong evidence supporting their clinical use while others still in the experimental trial stage. The early evidence are being available for some of these novel treatment modalities and the results are promising and hold the potential to become alternatives to current treatment options in the future. Since we are dwelling in the era of evidence-based medicine and treatment perspective, further evidence in the form of clinical trials and long term follow up studies are much needed before these novel strategies enter into mainstream treatment practice. With sustained continued efforts the future for CVD therapeutics looks substantially promising.

3. Abbreviations

CVD	Cardio vascular disease
ARNi	Angiotensin receptor-neprilysin inhibitor
PCSK9	Proprotein convertase subtilisin/kexin type 9
BM	Bone Marrow
LDL	Low-density lipoprotein
LCZ696	Combination of sacubitril and valsartan
EPCs	Endothelial Progenitor Cells
MSc	Mesenchyme Stem cells
MI	Acute myocardial infarction
CSCs	Cardiac Stem Cells

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