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JSM Nanotechnology & Nanomedicine

Review Article

Nanomaterials for biomedical applications: Special reference to Life-threatening Diseases

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Submitted: 04 June 2018
Accepted: 25 June 2018
Published: 28 June 2018

ISSN: 2334-1815

Keywords

- Nanomaterials
- Cardiovascular diseases
- Hyperlipidemia
- Hypertension

Abstract

Cardiovascular diseases are a major cause of disability and they are currently responsible for a significant number of deaths in a large percentage of the world population. A large number of therapeutic options have been developed for the management of cardiovascular diseases. However, they are insufficient to stop or significantly reduce the progression of these diseases, and may produce unpleasant side effects. In this situation, the need arises to continue exploring new technologies and strategies in order to overcome the disadvantages and limitations of conventional therapeutic options. Thus, treatment of cardiovascular diseases has become one of the major focuses of scientific and technological development in recent times. More specifically, there have been important advances in the area of nanotechnology and the controlled release of drugs, destined to circumvent many limitations of conventional therapies for the treatment of diseases such as hyperlipidemia, hypertension, myocardial infarction, stroke and thrombosis.

INTRODUCTION

Technological developments are revolutionizing the way healthcare is being delivered. Modern technology has changed the structure and organization of the entire medical field. Nanomedicine is the application of nanotechnology in healthcare; provides variety of promising possibilities to improve medical diagnosis and therapy [1]. It will leading to an affordable higher quality of life for each one. Currently, nanomedicine is a rapidly growing sector and in addition hysterical segment from claiming exploration action that attains the centering for scientists of highest point score notoriety around the globe. In place to dispose of number available tests in the medication about cardiovascular, cancer and a number other diseases, nanomedicines offers an excellent results by its exceptional qualities [2]. Nanomedicine can be defined as the use of molecular entities or particles of a size measurable in nanometers or microns for the diagnosis and treatment of disease [3].

This chapter presents a brief overview of nano-based technologies in cardiovascular nanomedicine. We begin with a concise summery of the limitations in management of cardiovascular disorders (CVDs), pointing on the opportunities for nanotechnology in the field of medicine.

Cardiovascular diseases [CVD]

Cardiovascular Diseases are extensive group of disorders, including disease of the cardiac muscle and of the vascular system supplying blood to the heart, brain, and other vital organs [4]. The primary cause of many of the heart diseases is the development of plaque or fat in the blood vessels and it lead to a stenosis of the blood vessels, reduction in perfusion and insufficient oxygen supply to the organs [5]. The plaque deposition also leads to cardiac arrest and stroke with death or disability as the consequence. Many aspects of cardiovascular diseases are yet not understood. However, the majority of CVD can be attributed to conventional risk factors such as: Hypercholesterolemia, Hyper tension, Obesity, Physical Inactivity, Diabetes mellitus, Genetic predisposition, Lipid abnormalities and Alcohol consumption, etc [6].

Cardiovascular system and functions

Cardiovascular system consists of heart, blood vessels which together maintain a continuous flow of blood around the body [7]. The heart pumps oxygen rich blood from lungs to all part of the body through the net work of arteries and smaller branches called arterioles. The arterioles connected to tiny vessels called capillaries, in capillaries exchange of oxygen and carbon dioxide take place between blood and tissues of the body. Blood returns to heart via capillaries linked with venules, which lead in turn larger veins [8].

Heart: Heart is the central organ of the cardio vascular system. It is a hollow muscular pump. Pumps blood responsible for circulating blood, oxygen and nutrients throughout the

body by means of a regular contraction [9]. The contraction is generated by an electrical activation, which is spread by a wave of bioelectricity that propagates in a coordinated mode throughout the heart [10]. Heart is located in the centre of thorax, between the lungs and directly behind the sternum. A double-walled sac called the pericardium encases the heart, which serves to protect the heart and anchor it inside the chest. Between the outer layer, the parietal pericardium, and the inner layer, the serous pericardium, runs pericardial fluid, which lubricates the heart during contractions and movements of the lungs and diaphragm [11]. The human heart has four chambers: two upper chambers (the atria) and two lower ventricles. The right atrium and right ventricle together make up the "right heart," and the left atrium and left ventricle make up the "left heart." A muscle wall called the septum separates the two sides of the heart. The right and left atria receive the blood entering the heart. The tricuspid valve separates the right atrium from the right ventricle, and the mitral valve separates the left atrium and the left ventricle. The other two heart valves, pulmonic valve, which separates the right ventricle from the pulmonary artery leading to the lungs, and the aortic valve, which separates the left ventricle from the aorta [12] (Figure 1).

Blood vessels

Arteries: An artery is a largest blood vessel that takes the blood away from the heart to the capillaries. Arteries are thick and muscular blood vessels, it contracts and helps to a continuous blood flow throughout the body [13]. Arterial wall consists of three layers: 1). Endothelium, it is a smooth lining inside the arterial wall, 2). Media is the middle part of the artery it made-up of muscles and elastic tissues.3). Adventitia is the outer covering of the artery for the protection (Figure 2). There are two major arteries, Aorta and Pulmonary Artery. Aorta is the largest artery, oxygen rich blood is pumped from the heart into aorta, and it curved up and back from the left ventricle and down in front of the spinal column [14]. At the beginning of aorta two coronary arteries are branched up and divided into a network to supply oxygen and nourishment to the heart muscles. Pulmonary artery carries deoxygenated from the body and are divided as left and right branches from the right ventricle for the transportation of the deoxygenated blood to the lungs [15].

Veins: Veins carry blood towards heart. Most of the veins located near the skeletal muscles. Vena cava are the largest vein in the body. They are not as muscular like arteries, but they contain valves to prevent the back flow of blood. The structure of the vein is similar to arteries but they are thin and les flexible [16]. The structure of veins is similar to that of arteries, again consisting of three layers: 1).

Tunica Adventitia: This is the strong outer covering of arteries and veins which consists of connective tissues, collagen and elastic fibres. 2).

Tunica Media: This is the middle layer and consists of smooth muscle and elastic fibres. This layer is thinner in veins.3).**Tunica Intima:** This is the inner layer which is in direct contact with the blood flowing through the vein. It consists of smooth endothelial cells. The hollow centre through which blood flows is called the lumen. Veins also contain valves which prevent the back flow of blood and aid venous return.

Capillaries: Capillaries are the smallest blood vessels. It connects arterioles with venules.

Circulatory systems

A body has two circulatory systems,

Pulmonary circulation: Deoxygenated blood drains from the body into the right ventricle to the pulmonary arteries, and is further divided as small pulmonary capillaries in the lungs [17]. The blood deliberately flow through the capillaries, thus provide the gas exchange between the walls of capillaries and the alveoli. After the oxygenation process the oxygen rich blood leaves through pulmonary vein and to heart through the left atrium, then fills the is pumped into the left ventricle so that it pumped to systemic circulation heart [18].

Systemic circulation: The system which sends oxygenated blood from the heart to all the other parts of the body and tissues through systemic capillaries, then the CO_2 rich blood flows through venules and reached to vena cava [19]. Deoxygenated blood from the upper body part returns to the heart through the superior vena cava and blood from lower body part through inferior vena cava. Both the vena cava pumps the blood to right atrium and to right ventricle for the pulmonary circulation [20] (Figure 3)

MAJOR CARDIOVASCULAR DISEASES

CVD is the diseases that affect the heart, blood vessel circulatory system. Cardiovascular disease include,

1. Coronary heart disease (heart attack)
2. Cerebro vascular disease (stroke and TIA)

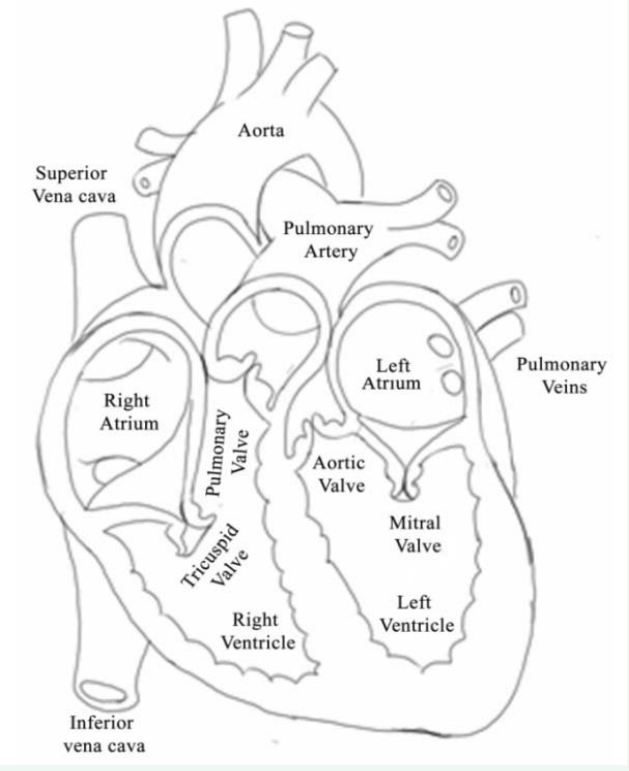

Figure 1 The Heart.

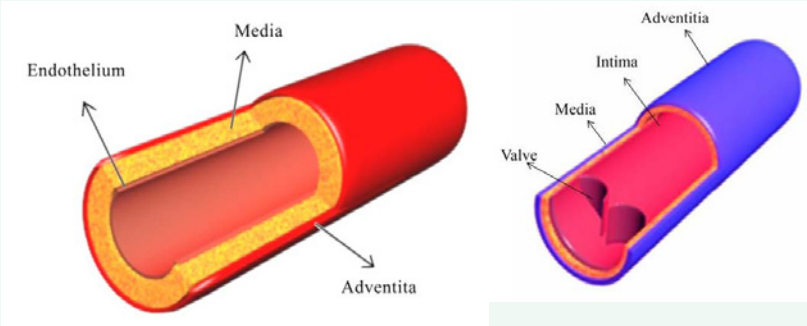

Figure 2 Structure of an Artery and vein.

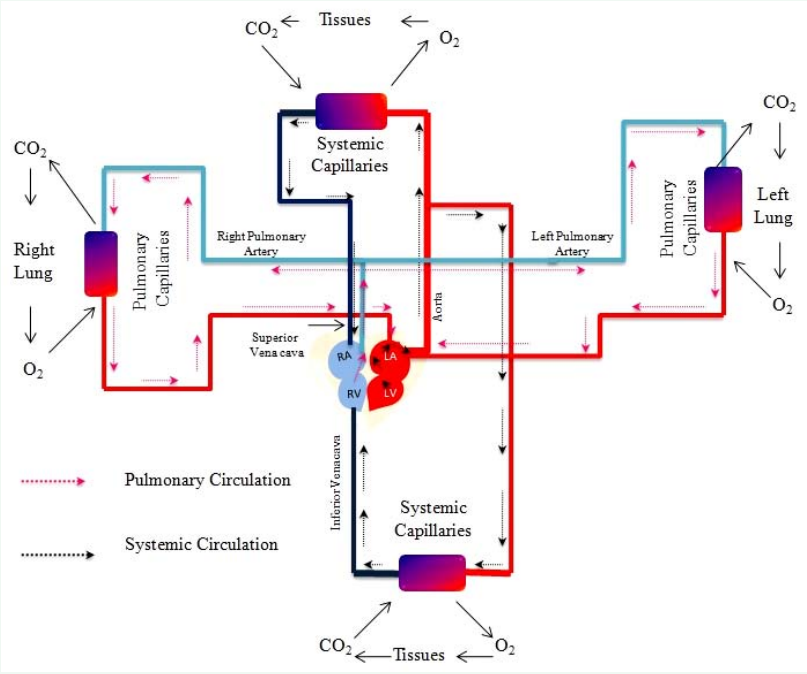

Figure 3 Circulatory systems.

3. Congestive heart failure.
4. Congenital cardiovascular defects.
5. Atherosclerosis
6. Rheumatic heart disease

Coronary heart disease (heart attack)

Coronary heart disease (CHD) also known as Ischemic Heart Disease, is a disease in which a waxy substance called plaque builds up inside the coronary arteries. The blood vessels are narrowed or blocked due to the deposition of cholesterol or plaque on their walls. This reduces the supply of oxygen and nutrients to the heart muscles. This may eventually result in a portion of the heart being suddenly deprived of its blood supply leading to the death of that area of heart tissue, resulting in a heart attack [21]. Ischemic Heart Disease is the most common cause of death in many countries around the world. The primary symptoms of IHD are angina and acute myocardial infarction.

Angina: It is the characteristic pain of CHD. Angina is chest pain or discomfort caused when your heart muscle doesn't get enough oxygen-rich blood. The discomfort also can occur in shoulders, arms, neck, jaw, or back. Angina pain may even feel like indigestion. It is caused by atherosclerosis leading to stenosis (partial occlusion) of one or more coronary arteries [22]. There are many types of angina, including micro vascular angina, Prinzmetal's angina, stable angina, unstable angina and variant angina.

Acute myocardial infarction (AMI): Acute myocardial infarction (AMI) commonly known as a heart attack occurs when blood flow decreases or stops to a part of the heart, causing damage to the muscle [23]. The most prominent risk factors for myocardial infarction are older age, actively smoking, high blood pressure, diabetes mellitus, and total cholesterol and high-density lipoprotein levels. Many risk factors of myocardial infarction are shared with coronary artery disease, the primary cause of myocardial infarction the total occlusion of a major

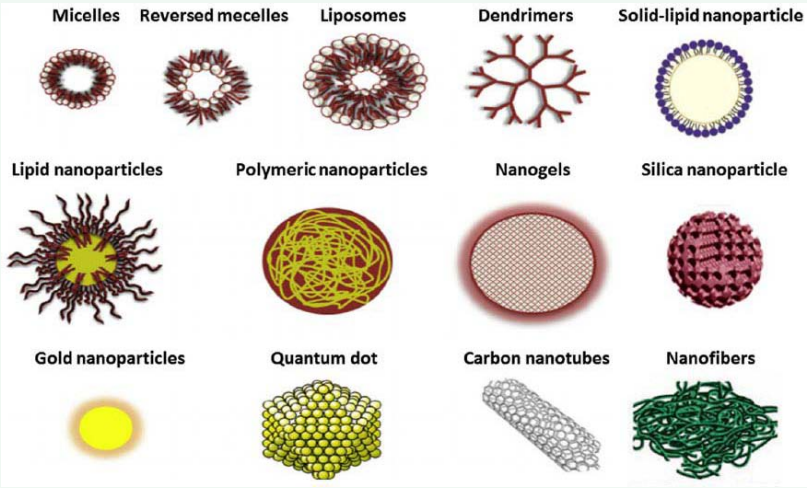

Figure 4 Different types of Nanosystems used in biomedical Applications.

coronary artery with a complete lack of oxygen and nutrients leading to cardiac muscle necrosis. The most prominent risk factors for myocardial infarction are older age, actively smoking, high blood pressure, diabetes mellitus, and total cholesterol and high-density lipoprotein levels. Many risk factors of myocardial infarction are shared with coronary artery disease, the primary cause of myocardial infarction.

Cerebro vascular disease (stroke and TIA)

Stroke: Stroke is a disease that affects the arteries leading to and within the brain. Its often called "brain attack". It is the major cause of death and a leading cause of disability in many of the cases. A stroke occurs when a blood vessel that carries oxygen and nutrients to the brain is either blocked by a clot or bursts (or ruptures). When it occurs, part of the brain will not able acquires enough blood and oxygen so it results the damage and death of brain cells.

Transient ischaemic attack [TIA]: The blood supply to the brain is interrupted for a short period of time. It is often called a 'mini-stroke', as the signs are the same as those of a stroke, but they do not last as long. The signs of a TIA may disappear in a few minutes and last no longer than 24 hours. They are often a warning that a stroke may occur.

Congestive heart failure

It is the condition at which the pumping power of the heart is weaker than normal. Thus damaged or overworked heart muscle is incapable to maintain a regular blood circulation. At this condition blood deliberately flows through the heart and body and pressure in the heart increases. As a result, the heart cannot pump enough oxygen and nutrients to the tissues. The chambers of the heart may respond by stretching to hold more blood to pump through the body or by becoming stiff and thickened. This helps a regular blood circulation, but due to the weak heart muscles the pumping efficiency is less. As a result, the kidneys may respond by causing the body to retain fluid (water) and salt. If fluid builds up in the arms, legs, ankles, feet, lungs, or other organs, the body becomes congested, and congestive heart failure is the term used to describe the condition [24].

Congenital cardiovascular defects.

Congenital heart defects are the structural problems of the heart from anomalous formation of the heart or major blood vessel and are present at birth. These defects change the normal flow of blood through the heart.

There are many types of congenital heart defects.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the arterial wall by an imbalanced lipid metabolism and a dysfunctional inflammatory response .Atherosclerosis, also called hardening or blockage of the arteries, is a very common condition affecting the arteries, the thick-walled, high-pressure blood vessels that carry fresh oxygen-rich blood from the heart to the rest of the body. In atherosclerosis, plaque builds up in the walls of arteries, causing thickening and loss of elasticity. As plaque accumulates, it hardens and may diminish blood flow, causing stable angina, or it may rupture, producing either temporary occlusion (unstable angina) or permanent occlusion (myocardial infarction) [25].

Therapeutic Benefits of Nanotechnology for the Cardiovascular Diseases

Cardiovascular diseases and neurovascular diseases are most common causes of death in developed and developing countries respectively; stroke is the most common cause of permanent disability in both adults and children. Nanotechnology offers new opening of therapeutic and diagnostic strategies for cardiovascular diseases. Surgery is one of the preeminent methods to treating CVD when the other interventional methods such as angioplasty, have failed. Traditional surgical procedures involve opening of chest and connecting the patient to cardiopulmonary bypass machine and arresting the heart. Various surgical procedures can lead undesirable disturbance the central nerve system and gastro intestinal complications [26]. Cardiovascular applications of nanoparticles can be considered be under four broad categories: in vitro studies and diagnosis cardiovascular imaging, Nano therapeutics and drug delivery,

and nano implants. Therefore, there is pressing a need to develop novel techniques such as nanotechnology for the early detection and treatment of several CVD .Nanotechnology offers advantages for CVD mainly in four areas:

1. Targeted therapeutics: delivering drugs where they are needed.

2. Tissue engineering and regenerative medicine: building new tissues to replace defective valves, damaged heart muscle, blocked blood vessels [27], etc

3. Molecular imaging: using "smart" imaging agents that identify disease more specifically

4. Biosensors and diagnostics: improved diagnostic devices for the laboratory, and implantable sensors to detect problems inside the body [28].

Molecular mechanisms underlying pathological conditions such as plaque formation still remain unclear, thus the early detection is difficult, leading to a high rate of morbidity and mortality. Greater significance of nanotechnology for diagnostic and imaging tools, marker and contrast agents are permits the goal of detecting disease at its primary stages (Table 1).

Types of nanoparticles for medicinal Applications

There are several different types of nanoparticles, each of which can be personalized to a definite application [29]. They can be classified into several categories, according to their structure (*i.e.*, nanospheres, nano capsules, nanotubes and colloidal carriers such as liposomes [30], or dendrimers), physicochemical properties (i.e., pH sensitive, magnetic, stealth nanoparticles) and the materials used for its synthesis (i.e., natural, synthetic, hybrid, or gold nanoparticles) [31,32]. Different types of nanoparticles which are used in biomedical field are shown in Figure 4. Nanoparticles can achieve controlled drug release, targeting and increase the effectiveness or bioavailability of many diagnostic or therapeutic agents. These include liposomes, micelles, iron oxide particles, magnetic nanoparticles quantum dots, dendrimers, and lipoproteins. Structurally, nanoparticles consist of a shell that can be engineered to have the desired properties, with the interior of the shell available for carrying other molecules such as drugs. Nanoparticles such as quantum dots have a solid core to which other molecules can be attached to produce the desired functionality [33,34] (Table 2).

Nanotechnology based diagnosis

Advancements of technological innovations like nanotechnology and nuclear medicine etc., permits the diagnostics have easier and more accurate. Currently, several methods of imaging allow for technicians and physicians to examine the anatomy of the patient without any invasive procedures. Minimally invasive surgeries, especially within the disciplines of cardiovascular and thoracic surgery, have also become more common in recent years [36]. Medical imaging plays an important role in health care. Molecular imaging and image guided system are now become an essential tool for diagnosis. Generally the imaging tools could only detect the changes on the tissues, and the help of contrast agent or markers are absolutely identified site of diseases [37]. Recently the improved function of positron emission tomography and magnetic resonance techniques along with the advancement of nanotechnology permits the early detection of diseases. Integration of nanotechnology and medical imaging pave a revolution in diagnosis.

***In Vitro* diagnosis:** Nanotechnology has been used to enhance *in vitro* studies in various fields of medicine. *In vitro* diagnostic testing (IVD) has become a fundamental tool in clinical practice for diagnosing and monitoring of diseases, as well as providing prognosis and predicting treatment response. IVD is used to assess the potential risk of developing a disease or disorder and to guide patient management. *In vitro* diagnosis for the medical applications has usually been laborious work. Samples from the patient's body [blood, other fluids tissues etc], it could be taken hours, days or weeks and labor intensive. Technological innovations in the in the electronic industry have led to the development of smaller, faster and economical devices and do not require any special skills; which can supply exact results by a single measurement. A variety of nanoanalytical tools such as scanning probe microscopy, imaging mass spectrometry, and advanced ultrasound technologies offer new opportunities for *in vitro* diagnostics, similar to molecular pathology or reading highly integrated ultra-sensitive biochips [38]. Nanostructures such as nanotubes, Nanowires, etc. have found application *in vitro* diagnostic studies such as detection of viral infections. E.g.: *in vitro* assays are utilized for HIV, malaria or cardiac markers detections, and genetic screening to detect mutations and polymorphisms [2].

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Biomarkers in cardiovascular disease: Biomarkers are an important tool in clinical application to specify a variety of health or disease characteristics, together with the intensity or type of exposure to an environmental factor, genetic susceptibility, genetic responses to exposures, markers of subclinical or clinical disease, or indicators of response to therapy and to improve patient care [39]. It can act as surrogate end points. Thus biomarkers can be defined as "a characteristic that is objectively

measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"[40]. For example, biomarkers have showed that a significant impact in early detection of sub-clinical disease (*e.g.*, prostate specific antigen screening for prostate cancer)[41], diagnosis of acute or chronic syndromes (*e.g.*, B-type natriuretic peptide in heart failure), risk stratification (*e.g.*, cardiac troponin in acute coronary syndromes) and monitoring of disease or therapy (*e.g.*, hemoglobin A1c in diabetes mellitus) [42]. The use of nanotechnology also makes availability for ultrasensitive detection of proteins and other biomarkers. The capability to rapidly secure sensitive measurements of multiple key cardiac biomarkers promises to revolutionize clinical diagnosis. Local inflammation in the vessel wall plays a key role in the development of atherosclerosis [43]. Therefore, inflammatory biomarker could be prognostic biomarkers in CVD. Epidemiological and clinical studies have shown strong and consistent relationship between biomarkers of inflammation, evaluated by high sensitivity C-reactive protein (HsCRP), and risk of cardiovascular events in patients with cardiovasculary especially ischemic heart disease. However, when HsCRP is used in general population studies, HsCRP does not always seem to have a significant prognostic value in detecting future cardiovascular disease [44].

Bio-nano chips: A new era in CVD diagnostics is emerging, empowered by new advances in promising lab-on-a-chip technologies such as the P-BNC. The union between minimally invasive or noninvasive sampling methods with a portable microchip sensor device that performs sensitive and multiplexed analysis of CVD biomarkers may open up new avenues of more efficient and cost-effective clinical care for cardiac patients [45].

Nanosensors: Nanosensors in medicinal research are emerging, and particularly in heart ailments. Cardiovascular diseases necessitate rapid concern and quick treatment. Nano sensors are designed such a way as to detect a heart attack by calculating the stress reaction in the heart and converting it into an ECG signal. Nanosensors are able to wirelessly covey the signal to physicians for rapid diagnosis and treatment [46]. These sensors are less cost and can be used by individuals with cardiac disease at all times [47].

Devices arranged with nano materials are used for both prior processing and sensing analysis. Two or three chips are being elaborated for use in medical monitoring or diagnostics. First chip is associated with analyte preliminary processing and sensing structures, it will be made by the nanofab created. Rest of the chips would be with standard microcontrollers. Nanosensors have a silicon or polymeric filters with nano sized sieving structures; micro liquid systems for bio-object sorting; a micro PCR; single chip electrophoresis system; a single chip (with outward light source) SPR system with micro scale substance and catalytic sensors with deep submicron structures for better functionality and response time [48].

Nanotechnology based Imaging

Cardiovascular imaging techniques need to rising their ability to capture and accumulate substantial amounts of information. Recent computational techniques and nanotechnology, in the field of medicine machine learning, offer new approaches of imaging data available for investigation. The most promising area however, is the nanomaterial based improved clinical imaging, especially in nanoimaging of cardiovascular diseases [49]. The general imaging techniques and implantable devices are come under in this category. The major benefits of molecular imaging for *in vivo* diagnostics are the early detection of diseases and the monitoring actual stages, of disease including cancer metastasis, it leading to proper assessment of therapeutic and surgical efficacy [50]. *In vivo* molecular diagnosis performed by improved positron emission tomography (Quantitative PET) and by advanced applications of magnetic resonance techniques such as MRS and MRSI diffusion spectroscopy (d-MRI), and functional magnetic resonance (f-MRI), all these techniques permits study of human biochemical process in various organs, tissues and cells [51]. However the applications of advanced techniques like nano imaging methods provide less toxicity and patient compliance. Nano imaging now becomes popular because of exclusive properties. Some recent studies proves that the

Table 1: Major constraints of treating CVD and potential advantages of nanotechnology in the area of CVD treatment.

Limitations of treating CVD	Advantages of Nanotechnology in the treatment of CVD
Early Detection	Early detection
Diagnosis	Specific therapeutics
Precise Monitoring	Nano vectors
Imaging	Nanosensors
Specific Surgery	Blood pool imaging
Appropriate Therapeutics	Nano optics
Tissue Regeneration	Nanostructured stents
Side effects	Nano robotics

Table 2: A brief overview of each of these categories is summarized [35].

Types of Nanoparticles	Characteristics	Applications
Polymeric nanoparticles	Solid or encapsulated nanoparticles composed of natural or synthetic polymers.	Biodegradable in nature. Minimum retention within body.
Inorganic nanoparticles	Mainly metallic solid nanoparticles	Special optical, magnetic, electro chemical properties. Applied in drug delivery, tissue engineering and diagnostics

use of nanoparticle as tracers or contrast agents. Fluorescent nanoparticles such as quantum dots and dye dropped silica nanoparticles offers more intense fluorescent light emission and can target a specific cell or tissue. The fluorescent can be tuned for specific imaging purposes. Thus they are expected to be a suitable for the imaging of living cells [52]. The biocompatibility and targeting efficiency of the system can be improved by nanoparticle coating.

Characteristics of Nanoparticles for cardiovascular imaging

Cardiovascular imaging is the most significant diagnostic tools for cardiovascular diseases. Nanoparticles could be unique providers in the field of the medical imaging [53], due to their exceptional features as follows:

Biocompatible size distribution: This is another aspect fulfilled by nanoparticles for bio-medical imaging.

Image contrasting ability: Paramagnetic nanoparticles are magnetic resonance imaging (MRI) contrast agents. Iodinated nanoparticles can be used as computed tomography (CT) contrast agents, whereas quantum dots can act as fluorescent enhancers.

Surface tuneable property: Nanosurface can be modified with the molecules of choice. Thus, it is possible to conjugate a nanomaterial with multimodal entity, for example, target specific molecules (targeted delivery), imaging probes and/or therapeutic molecules.

Stability and high penetration power: Contrast enhancer nanomaterials are much more stable than a chemical image probe.

Half life: In case of carrier nanoforms, used as image contrast agents, the half life of the chemical image probes is also increased due to their conjugation with nanoparticles [54].

Types of Cardiovascular imaging

Echocardiography: When an echo is performed, the transducer (probe) sends ultrasound waves into patient's body, and then receives echogenic beams, which the machine uses to produce an ultrasound image. In order to obtain good quality images, the sound waves need a "window" (between ribs,) to travel through [55].

The sound wave also loses strength the farther it has to travel. Sometimes it is very difficult to obtain good windows due to patients' chest size and shape, rib spaces, lungs, patient immobility, breast implants etc. Currently the utilization of ultrasonic contrast is an important nanotechnological system for enhancing the perception of the cardiovascular structures in patients with poor acoustic window.[56]

The use of ultrasonic contrast agents is now an established nanotechnological technique for enhanced visualization of the cardiac structures in patients with poor echocardiograph windows. Ultrasonic contrast agents consist of micro bubbles of high molecular weight gas such as per fluorocarbon within a thin shell made of protein (albumin) or lipid. These micro bubbles undergo oscillation due to resonance in an ultrasound beam and are highly echogenic. As a result, they significantly enhance the delineation of structures such as the myocardial wall segments, aneurysm, or a thrombus [57]. Ultrasound contrast agents containing micro bubbles affixed with targeting ligands could significantly increase the sensitivity and specificity of echocardiography and ultrasonography. Kaufmann et al. used contrast-enhanced ultrasound to image and quantify inflammatory atherosclerotic plaques containing VCAM-1. In this study, the investigators used micro bubbles containing an antibody to VCAM-1 to localize the contrast agent to the plaques rich in VCAM-1[58]. Hamilton et al., reported that, Nanoparticles can also be useful for detecting left ventricular thrombus, in this study they demonstrated that liposomes containing antibodies to fibrinogen enhanced the echogenicity of the apical left ventricular thrombus in an animal model [59].

Computed tomography: Nanoparticles can be used for imaging specific targets on computed tomography [60]. Currently, there is no reliable method of noninvasively evaluating atherosclerotic plaques in patients with coronary and peripheral vascular disease. Nanotechnology can facilitate the study of plaque composition noninvasively. Hyafil and coworkers detected macrophages within atherosclerotic plaques in rabbits using iodinated nanoparticles dispersed with surfactant [61]. These nanoparticles accumulated within the macrophages and were visualized by computed tomography. Nanoparticles could help improve the accuracy of imaging of atherosclerotic plaques. Furthermore, by obviating or minimizing the need for traditional contrast agents, nanoparticle based contrast agents can eliminate the risks associated with traditional contrast agents. Spectral computed tomography in which contrast agents based on nanoparticles containing heavy metals such as gold or bismuth offer enhaced accuracy and efficiency of the imaging process while reducing the risks involved.

Magnetic resonance imaging: Cardiac magnetic resonance (MR) imaging is being increasingly utilized in the management of a variety of cardiovascular disease such as ischemic and nonischemic cardiomyopathy, coronary artery disease, assessment of left ventricular function, assessment of valvular abnormalities, etc. A continuous cardiac movement is significant limitation in cardiac MRI procedure. Nanoparticles could significantly enhance the applicability of MR to cardiovascular imaging. Various nanoparticles are utilized for identifying the vulnerable plaque and for identifying the early stages of cardiac diseases such as atherosclerosis. Super paramagnetic iron oxide particles accumulate in macrophages in atherosclerotic plaques, which could then be visualized on magnetic resonance imaging. Nanoparticles containing antibodies to oxidation specific epitopes such as oxidized low-density lipoproteins (LDL) were used to identify plaques containing oxidized LDL.

Other magnetic nanomaterials, such as paramagnetic contrast agents (i.e., gadolinium chelates) used in the enhancement of T1 contrast, and manganese nanoparticles], have also been used to provide a broader range of magnetic nanoparticles for use in cardiovascular imaging. However the majority of clinically used MRI contrast agents are based on gadolinium ions, which are highly toxic in a free form and thus have to be chelated. Chelation reduces the toxicity of gadolinium ions, it also reduces the number of coordination sites resulting in a low relaxivity of less

than 4 mM $^{-1}$ s $^{-1}$at a magnetic field strength of 1.41 T, and thus decreased contrast efficiency [62].

Nuclear imaging: Nuclear imaging is a commonly used tool to assess for myocardial ischemia and viability. Nanotechnology may enhance the utility of this diagnostic modality by improving its sensitivity and specificity. Nuclear imaging using nanoparticles may also provide information on presence of active ischemia and inflammation and its response to treatment. Nahrendorf et al., were able to image and quantify macrophage content in aortic aneurysms on Positron Emission Tomography-Computed Tomography using macrophage and monocyte targeted nanoparticles labeled with fluorine-18. By enabling targeted imaging, nanotechnology may also result in a reduction in the radiation dose required in nuclear imaging studies. Radio labeled liposomes and lipoproteins have also been used to study atherosclerotic lesions in experimental models. Positron emission tomography has become invaluable in studying biochemical processes such as myocardial fatty acid metabolism *in vivo*. Nanoparticles can considerably enhance the specificity and the ease with which these physiologic processes can be studied using this imaging modality.

Multimodality imaging: Nanoparticles thus show enormous potential in increasing the accuracy and efficacy of cardiovascular imaging techniques. A pivotal advantage of nanotechnology in imaging is the possibility to design nanoparticles that can be visualized via multiple modalities such as (positron emission tomography) PET, MRI, and optical imaging positron emission tomography is combined with computed tomography. The physiologic information obtained from the former is complemented by the anatomic information obtained from the computed tomography. The clinical utility of the results thus obtained is vastly greater than that from either modality alone. Nanoparticle based imaging agents can potentially increase the applicability of such multimodality imaging to clinical practice while reducing the adverse effects, time and cost involved.

Nanotechnology based therapeutics for cardiovascular diseases

Nanoscience and nanotechnologies application have a huge potential to bring benefits in, medicine and pharmacy. Since most of these applications are primarily focused on improving human health [28]. Nanotechnology has given rise to a innovative area called nanomedicine. The purpose of nanotechnology in the bio medical field include the prevention of life threatening situation by a proper monitoring, diagnosing, repairing diseases and damaged tissues in living system using appropriate medical assistance i.e. the effective supply of suitable therapeutics [63]. The overall goal of nanomedicine is to diagnose as accurately and early as possible, to treat as effectively as with negligible side effects. The main advantage of nanomedicine is earlier detection of a disease, leading to less severe and costly therapeutic demands, and an improved clinical result.

TARGETED DRUG DELIVERY

The most important clinical applications of nanotechnology are in area of pharmaceutical development and pharmaceutical nanoparticles have gained great importance for the treatment of CVD. In pharmaceutical technology and biomedicine, nanoparticles are typically defined as particles with diameter from 1 to 100 nm and have been exploited for both diagnostic and therapeutic purposes. The ideal size of nanoparticles used as drug delivery systems ranges from 10 to 100 nm. Targeted drug delivery refers to the process in which only a specific organ or tissue in the body is exposed to the therapeutic agent. The rest of the body remains unexposed to the drug, unlike in systemic administration of a medication. Targeted nanoparticle based therapy has already become part of the management of certain cancers.

The drugs formulated in nanoparticles for the treatment of CVD are summarized here Endothelial-selective delivery of therapeutic agents would provide a useful tool for modifying vascular function in various cardiovascular diseases and several research groups are interested in this targeting approach [28]. Kona et al., developed a novel nano particulate drug delivery system that mimics platelets binding to the injured vessel wall under physiological flow conditions. Glycoprotein Ib (GPIb) was chosen as the targeting ligand and conjugated to nanoparticles because its role in platelet adhesion to the vascular wall under high shear flow conditions is well-recognized. Dexamethasone-loaded biodegradable poly-(d,llactic-co-glycolic acid) (PLGA) nanoparticles were formulated using a standard emulsion method. The results demonstrate that conjugation of GPIb to PLGA nanoparticles increased particle adhesion onto targeted surfaces and increased cellular uptake of these nanoparticles by activated endothelial cells under shear stresses. In addition, these nanoparticles also provided a controlled release of the model drug. Therefore, these drug-loaded, GPIb-conjugated PLGA nanoparticles could be used as a targeted and controlled drug delivery system to the site of vascular injury for treatment of cardiovascular diseases [64].

NANOVECTOR FOR CARDIOVASCULAR DISEASE TREATMENT

A "Nanovector" is a nanoscale particle or system, having nanoscale components, which is used for the delivery of therapeutic or contrast agents. Nanovectors are being investigated and developed as carriers for personalized therapeutic and imaging contrast agents based on the anticipated advantage of enhanced homing to the diseased site (such as atherosclerotic plaque, cancer lesions, etc.) [65]. This homing behavior relies on the nanoparticles' ability to cross various obstacles, the so-called "bio-barriers," located between the administration site and the target organ [66]. The presence of multiple biological barriers that effectively prevent the administered drug or imaging agent from reaching its target tissue. The disease tissue accumulation of a molecularly targeted and specific agent administered in a solution is extremely low, drug molecules reaching their site of action. As a result, significantly higher doses of an agent have to be administered to achieve an adequate therapeutic response, thus results a very narrow the efficacy –toxicity range. For example Doxorubicin, [which possesses prominent cardio toxic effects].

Nanovector can be divided into the three main subcategories (generations) [67]. The active targeting of nanovector for CVDs are capable to facilitate an exact delivery of drug into the target cells, should posses a prolonged effect of the drug, and reduction of the shear effects of blood flow [28].

The first generation of nanovectors includes nanoparticles that reach the disease site using passive mechanisms. The main subclass in this category is the liposomes [68]. The second generation of nanovectors is comprised of delivery systems with an additional functionality, including: (1) targeting of the disease site through ligands that specifically bind to receptors uniquely- or over-expressed in the tumor microenvironment; (2) advanced functionalities, including co-delivery of multiple therapeutics or imaging agents, or triggered or controlled release of therapeutic agents [69]. The third generation of nanovector has the ability to perform a time sequence of functions through the use of multiple nano-based components that synergistically provide distinct functionalities.

NANOFABRICATED MATERIALS FOR THE DESIGN OF MEDICAL DEVICES FOR CVDS

Nanomaterials are de fined as materials comprised of basic components within a confined dimensionality, yielding a host of unique physicochemical properties not present in the bulk material. Realizing the full potential of nanotechnology as it pertains to cardiovascular disease diagnosis and therapy requires the ability to fabricate nanoscale devices and materials with a high degree of precision and accuracy. Eventual goals for the development of nanofabricated materials in cardiovascular medicine include control of infection and thrombosis, modification of cellular adhesion, and control of drug delivery [70].

FABRICATION OF NANOTEXTURED STENTS

Restenosis is the recurrence of stenosis, a narrowing of a blood vessel, results a constrained blood flow. Restenosis usually pertains to an artery or other large blood vessel that has become narrowed, received treatment to clear the blockage and subsequently become renarrowed [71]. Coronary artery stents have been shown to reduce Restenosis following balloon angioplasty. However, in-stent Restenosis still remains problematic and affects up to 60% of patients who receive a coronary stent implant. Restenosis associated with the movement of soft muscle. These stents have reduced the necessity for repeat angioplasty procedures due to restenosis by 70-80% [72].

However, the anti proliferative drugs released from the stents also restrain normal re-endothelialization of the vessel, rendering it vulnerable to thrombosis, which requires treatment with anti-platelet drugs. Nanotextured stent coatings, such as hydroxyapatite and titania, have been applied to enhance endothelial cell attachment and proliferation to promote re-endothelialization of vessel walls [73].These types of coatings have been prepared by using a sol-gel process, in which a colloidal suspension (sol) of metal or ceramic is applied to a surface. The preferential evaporation of the solvent after dip or spray coating drives self-condensation of the solute into a uniform thin- film nano phase by increasing the concentration of solute in the solution until it exceeds the critical micelle concentration. This process forms a porous, highly textured coating from the solute [74].

CONCLUSION

Management of patients with cardiovascular diseases has specific challenges stemming from the unique patho anatomic characteristics of the cardiovascular system. Important limitations in the current diagnostic and therapeutic modalities include mechanistic limitations due to the size of the vessels or location of culprit lesions and substrates, imperfect resolution, and lack of specificity in detection and modification of pathophysiological changes. Nanoparticles have the potential to overcome each of these limitations owing to their ability for targeted binding and drug delivery. Furthermore, nanoparticles can also contribute to our understanding of various disease processes by facilitating the visualization and study of the key early events in these conditions. At the same time, because of targeted delivery nanoparticles make it feasible to avoid or minimize adverse effects by reducing the total dose delivered and ensuring localized drug delivery without systemic exposure. In view of these attributes of nanoparticles, one can expect to see an increasingly prominent role of nanoparticles in the study, diagnosis and treatment of a multitude of cardiovascular diseases.

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Cite this article

Luke M (2018) Nanomaterials for biomedical applications: Special reference to Life-threatening Diseases. JSM Nanotechnol Nanomed 6(1): 1062.