

Nanotechnology, an alternative with promising prospects and advantages for the treatment of cardiovascular diseases

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Abstract: Cardiovascular diseases (CVDs) are one of the most important causes of mortality and affecting the health status of patients. At the same time, CVDs cause a huge health and economic burden to the whole world. Although a variety of therapeutic drugs and measures have been produced to delay the progress of the disease and improve the quality of life of patients, most of the traditional therapeutic strategies can only cure the symptoms and cannot repair or regenerate the damaged ischemic myocardium. In addition, they may bring some unpleasant side effects. Therefore, it is vital to find and explore new technologies and drugs to solve the shortcomings of conventional treatments. Nanotechnology is a new way of using and manipulating the matter at the molecular scale, whose functional organization is measured in nanometers. Because nanoscale phenomena play an important role in cell signal transduction, enzyme action and cell cycle, nanotechnology is closely related to medical research. The application of nanotechnology in the field of medicine provides an alternative and novel direction for the treatment of CVDs, and shows excellent performance in the field of targeted drug therapy and the development of biomaterials. This review will briefly introduce the latest applications of nanotechnology in the diagnosis and treatment of common CVDs.

Keywords: nanotechnology, application, targeted therapy, biomaterials, cardiovascular diseases

Introduction

Nanotechnology is a new way of using and manipulating the matter at the molecular scale, whose functional organization is measured in nanometers.¹ Feynman,² a charismatic, imaginative and witty leader, suggested to people that there are no physical barriers to manipulate individual atoms and molecules, and inspired the development of nanotechnology in his lecture entitled “There’s Plenty of room at bottom”, a profound insight of nanotechnology in 1950s. Smalley et al³ elucidated the structure of nano-macromolecule fullerene, elegant and perfect structure with unique performances, which has attracted intense interest from scientists in exploring other nanomolecular structures. Past decades have witnessed a growth explosion in an attractive field of nanotechnology.⁴

As nanoscale phenomena play an important role in cell signal transduction, enzyme action and cell cycle, nanotechnology is closely related to medical research. Nanotechnology provides a tool for structural analysis at the most important dimensions of organizational structure, atomic and cellular levels, and designs and manufactures synthetic biomaterials on a nanoscale with new treatments and alternative materials emerging. Nanotechnology proposes a biological approach that uses precisely targeted

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nanopharmaceuticals to bind proteins and nucleic acids associated with disease and dysfunction. Nanotechnology also provides tools and techniques for transferring fine organic macromolecules and peptides to the places where they exert effects, protecting them from degradation and immune rejection, and making them cross barriers that prevent macromolecules from passing through them.⁵

Medical nanotechnology has shown an increasing trend in reducing costs and improving the effectiveness of existing drugs, diagnostic reagents, implants, prostheses, patient monitors and individual health care. The actual impact of nanotechnology mainly includes the following aspects:⁵ advanced medical instruments, system biology and therapeutic diagnostic technology, realization of distributed individualized nursing, medical materials, nanoparticles (NPs) for image enhancement, drug delivery, overcoming the natural barrier of drug delivery, implanted immune protection system, advanced restorative science, advanced biosensors and implants for treatment, and defense against disease transmission.

Cardiovascular diseases (CVDs), such as acute myocardial infarction (AMI), hypertension, atherosclerosis, stroke and heart failure, among others, are one of the most hazardous and deadliest diseases, producing stupendous health and economic burdens in the all of the world.⁶

CVDs are the group of pathological disorders that occur in cardiac, valvular and blood vessel tissues associated with heart. In response to various pathological disorders, a variety of therapeutic drugs and measures have been born, contributing to improve the patients' quality of life. However, conventional treatment strategies are not allowed to repair or regenerate damaged ischemic myocardium. Moreover, the use of agents frequently brings about systemic certain side effects. Therefore, these facts force researchers to conduct a variety of studies to find more effective and safer treatments and drugs.⁷⁻⁹

Although there have been several reviews about the application of nanotechnology in CVDs, advances in knowledge and technology are changing rapidly. Moreover, most of the other related reviews focused on the application of nanotechnology to a single disease category, giving readers a deeper understanding of the future of nanotechnology in one aspect. And, this review describes the application of nanotechnology in several common CVDs, not only in depth but also in scope, to make readers understand the application of nanotechnology in CVDs, causing the diffusion of readers' thinking, to stimulate the research of nanotechnology in more fields and promote the development of nanotechnology. This review

will provide a more comprehensive description of the latest advances in the cardiovascular field of NPs. In this review, we call on implementing nanotechnology as a promising and innovative orientation for the treatment of CVDs.

Roles of NPs in CVDs

Owing to their unique size, physical properties and chemical composition, NPs are able to deliver targeted drugs through blood and tissue flow. It can also be cleared in tissues and organs long enough to enhance imaging or perform other unique nanoscale functions. Hence, NPs are mainly used for enhanced medical imaging, targeted delivery to kill pathological cells, and targeted delivery of drugs.¹⁰

NPs in diagnosis and treatment of coronary artery disease (CAD)

CAD is the process of atherosclerotic plaque gathering on the inner wall of the coronary artery, causing the stenosis of the cavity, reducing the compliance of the vascular wall, and gradually or abruptly causing the loss of the blood supply of partial myocardium.¹¹ Atherosclerosis is a chronic disease characterized by thickening of the arterial wall and inflammation of atherosclerotic plaques.¹² A heart attack would occur with coronary arteries blocked completely by atherosclerosis. During this process, hypoxia of cardiomyocytes (CMs) triggers a series of complex and interrelated physiological responses involving various cells, cytokines and extracellular matrix (ECM). All of these processes lead to the loss of cardiac function, accompanied by fibrous scars to replace the myocardium.⁷

The most frequent cause of coronary thrombosis is the shedding or rupture of the atherosclerotic plaque.¹³ The plaques, called as "vulnerable", are apt to rupture due to certain characteristics, involving the appearance of multitudinous inflammatory cells and a large necrotic core with a flimsy fibrous cap, reduced smooth muscle cells (SMCs), and a decreased ECM, plaque bleeding and calcification, among others.¹⁴

At present, the common diagnostic methods of CAD are electrocardiography (ECG), stress echocardiography, coronary computed tomography angiography, coronary angiography (CAG) and MRI. However, these conventional methods do not identify such "vulnerable plaques."^{15,16} With the improvement of diagnostic requirements and technologies, molecular imaging of CVDs based on nanotechnology is emerging to detect certain targets, such as macrophages, oxidized low-density lipoprotein (oxLDL), microvessels, etc.¹⁷

Aikawa et al¹⁸ used a cross-linked iron oxide fluorescent NP to simultaneously image macrophages for determination of inflammatory response in atherosclerotic plaques.¹⁸ Due to the absence of fluorine (¹⁹F) background in targeted tissue, observed signals of ¹⁹F perfluorocarbons NPs from MRI permit a spatial resolution and a fine specificity to demonstrate inflammation progress.¹⁹ In addition, the combined utilization of intravascular ultrasound and photoacoustic (IVUS/IVPA) imaging with gold NPs as contrast agents to co-localize with active macrophages in plaques as described by Yeager et al.²⁰ Therefore, the progression and fragility of atherosclerotic plaques can be judged by detecting the content, infiltration and proliferation of macrophages.

Apoptosis and oxLDL play an important role in triggering and promoting plaque rupture. Various approaches, such as agents labeled with radioisotopes (¹²³I, ¹²⁴I, ^{99m}Tc, and ¹⁸F) and superparamagnetic particles (iron oxide and gadolinium) for positron emission tomography (PET), single-photon emission computed tomography, or MRI, have come to the fore to image certain targets associated with apoptosis and oxLDL in demarcating plaques in risk for rupture.^{21–23}

Microvessels at the bottom of atherosclerotic plaque independently associated with plaque rupture, suggesting a contributory role for neo-vessel generation in the process of plaque growth, hemorrhage and rupture.²⁴ Integrin $\alpha v \beta 3$, a key mediator of angiogenesis, has been targeted by using a gadolinium-coated perfluorocarbon nanomaterial (containing 90,000 separate gadolinium chelates) derivatized with an arginine–glycine–aspartic acid peptidomimetic.²⁵ At the same time, more and more research will combine diagnostic and therapeutic partners to gradually develop diagnostic therapies and evaluate treatment effects in a various ways.²⁶ One study²⁷ used multimodal imaging to examine the permeability of blood vessel walls and the accumulation of fluorescently labeled liposomal NPs in atherosclerotic plaques. It was found that there is a strong correlation between the permeability established by *in vivo* dynamic contrast-enhanced MRI and NP plaque accumulation throughout the vessel wall. This suggests that we may be able to understand the degree of damage and inflammation of the blood vessel wall through the accumulation of NPs. Therefore, the cardiovascular imaging methods based on nanotechnology provide the feasibility for early diagnosis and differentiation of fragile plaque, and provide the basis for early prevention and treatment of atherosclerotic plaque.

Atherosclerosis is a chronic progress, and current therapies targeted for every phase mainly include two treatment options: 1) no-invasive medical therapy focusing on reduc-

ing the burden of atherosclerotic plaque and stabilizing vulnerable plaques and 2) invasive revascularization therapy including percutaneous coronary interventions or coronary artery bypass graft surgery.^{28–30} Nanotechnology can be used for the treatment of atherosclerosis by increasing the circulation time of the whole body, reducing the systemic cytotoxicity of drugs, enhancing the solubility of the drug, lowering the required dose, combining the diagnosis and treatment of drugs to form theranostics, and increasing the cumulateness of the drug at the specific site.³¹

High-dose statins whose effects of the reduction in morbidity and mortality in CAD have been observed are limited owing to off-target side effect.³² However, Broz et al depicted that pravastatin-loaded nanometer-sized vesicles functionalized by oligonucleotides to target macrophages can allow high-dose therapy for decreasing toxicity in other tissues and improving efficacy.³³ Equally, fumagillin, an effective antiangiogenic drug, has been illustrated as having the potential of delivery via paramagnetic NPs targeted by integrin to reduce systemic side effects.³⁴ Inflammatory monocytes/macrophages play a vital role in progress of atherogenesis and rupture of the atherosclerotic plaque. Nakashiro et al³⁵ utilized a bioabsorbable NP to delivery pioglitazone (peroxisome proliferator-activated receptor- γ agonist, inhibiting inflammatory reaction) into circulating monocytes, which can regulate inflammatory reaction and prevent atherosclerotic plaque ruptures.³⁵ The immune system plays an indelible role in the development of atherosclerosis, and the characteristics of immune cells are different. Some studies have combined the different physical and chemical properties of NPs and different immune cells to form a NP library. The endogenous high-density lipoprotein-based NP library can preferentially deliver therapeutic drugs to macrophages in atherosclerotic plaques, achieve targeted delivery of drugs, and also open a new path for targeted delivery of NP drugs.³⁶ In addition, hirulog, a natural thrombin inhibitor derived from hirudin, has been conjugated onto micellar NPs to inhibit further fibrin clots from forming after coronary artery occlusion caused by thrombosis due to plaque degeneration and rupture.³⁷ Of course, the proresolving activity and efficacy of NP drugs during treatment are also well thought out. Kamaly et al³⁸ have shown that sub-100-nm NPs are proresolving in the body, and NPs containing anti-inflammatory peptide Ac2-26 show more obvious advantages in neutrophil recruitment and enhanced resolution, and targeted NPs delivery can improve the structure of the target site. Therefore, proresolving nanomedicine therapy has a promising future in the application of chronic inflammatory diseases such as atherosclerosis.

Restenosis after coronary artery angioplasty is affected by mechanical injury, inflammation responses and deferred endothelial healing during angioplasty. Therefore, inhibition of vascular thrombosis and restenosis is the primary factor determining long-term success of stent placement.³⁹ To solve these problems, drug-eluting stents (DES) were invented, especially DES coated with NPs that can help locate previously ineffective drugs in interesting epitopes and produce the desired results. Nakano et al elicited a delivery platform with NP-eluting stent to target prevention of restenosis and improvement of endothelial recovery.⁴⁰ Tsukie et al verified that pitavastatin-NP-eluting stent on reducing in-stent restenosis has the same efficiency as sirolimus-eluting stent, but the effect of delayed endothelial healing was not observed. On the contrary, it was observed at the sirolimus-eluting stent site.⁴¹

These nanotechnology platforms have potential for more efficient and safer equipment in the future targeting CAD. Table 1 summarizes some of the significant advances in NPs used in CAD.

Application of NPs in hypertension

Hypertension, a disease whose incidence increases with the improvement of quality of life, is not only a disease in itself but also a risk factor for many other CVDs. Increased arterial blood pressure increases the heart's load, and it also causes certain damage to other organs such as brain, eyes, kidney, and so on. Over time, a series of hypertension-related diseases, such as heart enlargement, ischemic cardiomyopathy, myocardial infarction, heart failure, stroke, renal dysfunction and retinopathy will appear subsequently.

Table 1 Some advances in nanoparticles used in CAD

Drug/nanoparticle	Target region	Objection	Prime target	Year/reference
Ligand-decorated liposome nanoparticles	Activated platelet	Human and rat	Platelet-targeted delivery of drugs and imaging probes	2010 ¹²⁴
Liposomes containing alendronate	Coronary artery	–	Reduce circulating monocytes and inhibit experimental restenosis	2012 ¹²⁵
Liposome nanocarriers to delivery BH4	Prevention of early atherosclerotic lesion formation	Mouse	Prevention of early atherosclerotic lesion formation	2015 ¹²⁶
Gd-containing immunomicelles	Macrophages in atherosclerosis	Murine	Detection of macrophage-rich plaques	2006 ¹²⁷
Lipid-polymeric nanoparticles loaded with paclitaxel	Coronary artery	Rat	Treatment of injured vasculature due to PCI	2011 ¹²⁸
PLGA nanoparticles containing alendronate	Coronary artery	Rabbit	Depletion of circulating monocytes, inhibition of macrophages proliferation and restenosis	2009 ¹²⁹
Mn G8 dendrimers	Oxidation-specific epitopes	Mouse	Detection of atherosclerotic plaques	2015 ¹³⁰
Tadpole dendrimer loaded with siRNA	AT1R	Rat	Improvement of cardiac function recovery	2013 ¹³¹
Rapamycin-loaded gel-like nanoparticles	Carotid artery	Rat	Prevention of neointimal hyperplasia and reendothelialization of vascular injury	2008 ¹³²
MNP-loaded primary ECs	Gene expression	Lewis inbred rats	Reendothelialization by the implant and alleviating neointimal hyperplasia	2015 ¹³³
Paclitaxel-loaded MNPs	Carotid stent	Rat	Inhibition of in-stent restenosis	2010 ¹³⁴
HDL covered by liposomes	Aortic cholesterol contents	Cholesterol-fed rabbits	Reduction of aortic plaque volume and cholesterol content	2010 ¹³⁵
Colloidal nanoparticles-loaded thrombin	Acute arterial	Mouse	Localized treatment of acute thrombosis	2011 ¹³⁶
Superparamagnetic nanoparticles derived from fluorophores	Areas of atheroma	Rabbit	Identification of biologically high-risk atheroma	2017 ¹³⁷
PDLLA nanoparticles containing sirolimus	Smooth muscle cells	–	Inhibiting the proliferation of smooth muscle cells and speeding up the proliferation of endothelial cells	2018 ¹³⁸

Abbreviations: AT1R, angiotensin II (Ang II) type I receptor; BH4, tetrahydrobiopterin; CAD, coronary artery disease; ECs, endothelial cells; Gd, gadolinium; HDL, high-density lipoprotein; MNP, magnetic nanoparticle; Mn, manganese; PCI, percutaneous coronary interventions; PDLLA, polymer poly (DL-lactide); PLGA, poly-(lactic-co-glycolic) acid; siRNA, small-interfering RNA.

According to WHO, 1 billion people were suffering from hypertension in 2008, and the mortality rates of ischemic heart disease and stroke resulted by hypertension were 45% and 51%, respectively.⁴²

At present, the main clinical antihypertensive drugs can be divided into the following categories: angiotensin-converting enzyme inhibitors, calcium channel blockers (CCBs), angiotensin II receptor blockers, central sympathomimetic drugs, diuretics, alpha blockers, beta blockers and vasodilator.⁴³ However, the majority of these antihypertension drugs show some defects, such as poor water solubility, low bioavailability, short half-life and so on.⁴² At the same time, because of the high dosing frequency and long-term use, some undesirable side effects are coming up, such as dry cough caused by captopril, male breast hyperplasia caused by spironolactone, etc. In order to use these drugs effectively and safely, it is necessary to provide a drug delivery system with low doses, increased bioavailability, increased selectivity and reduced adverse effects. As mentioned above, some NPs-based oral drug management systems provide alternative strategies for overcoming these difficulties.⁴⁴

So far, the NPs used in the treatment of hypertension mainly include nanoemulsion, liposome, polymeric NPs, solid lipid NPs (SLNs) and nanostructured lipid carriers. One example is the formulation of olmesartan medoxomil (OM) in the nanoemulsion system designed to reduce its adverse solubility and bioavailability. Olmesartan, playing a role in lowering blood pressure by selectively blocking of angiotensin II-AT1 receptor, shows poorly oral bioabsorptivity and availability restricted by poor water solubility and permeability.

The pharmacokinetic study of OM nanoemulsion that was carried out to detect changes in plasma concentration of active olmesartan in rats after oral administration indicated 2.8 times increase compared with the conventional dose; furthermore, the effect of antihypertension demonstrated better and longer with three times reduction in the routine dose. This finding indicates that OM nanoemulsion can significantly improve its bioactivity by increasing its solubility, thereby enhancing its bioavailability and promoting the improvement of clinical application.⁴⁵ Other nanoemulsion containing a variety of drugs, such as ramipril, amlodipine, valsartan, lacidipine, carvedilol and so on, have been shown to increase the bioavailability and antihypertensive efficacy of these drugs to varying degrees.⁴⁶⁻⁵⁰

In addition to nanoemulsion, many additional formulations can be designed using nanotechnology to improve the efficacy and safety of antihypertensive drugs. Liposomes

containing lacidipine, a hydrophobe CCB, also have been considered as a promising strategy to improve the bioavailability of insoluble drugs.⁵¹ Shah et al,⁵² indicated that felodipine-loaded poly-(lactic-co-glycolic) acid (PLGA) NPs can control blood pressure and change ECG for extended duration by bypassing the prophase metabolism and providing sustained drug release.⁵² Moreover, Niaz et al⁵³ elaborated the new polymer nanowire is a new type of antihypertensive drug (angiotensin-converting enzyme inhibitor, beta blockers, and CCB) with stable, high cation and even dispersion. It has good encapsulation efficiency. The hydrophilicity of chitosan as a biological carrier helps to improve the oral bioavailability of antihypertension drugs.⁵³ Dudhipala et al⁵⁴ devised a nisoldipine SLN whose peak serum concentration (C_{max}) and AUC_{total} are significantly higher than oral drug suspension (12.55 ± 0.6 mg/mL vs 7.53 ± 0.13 mg/mL, 96.15 ± 3.92 mg/mL/h vs 44.13 ± 2.90 mg/mL/h, respectively). Additionally, the removal rate of nisoldipine in SLN formulation is relatively slow, which makes biological half-life ($t_{1/2}$) and mean residence time of SLN formulation higher. The oral bioavailability of SLN preparation was 2.17 times higher than that of suspension.⁵⁴ However, SLN has some limitations, such as the formation of solid lipid into crystal as time goes on, thereby reducing the encapsulation efficiency and the amount of drug loading with time, which led to the development of nanostructured lipid carrier composed of liquid lipids. Ranpise et al⁵⁵ developed a nanostructured lipid carrier containing lercanidipine hydrochloride, a poorly water-soluble drug, with a relative bioavailability of only 10%. In vitro release studies have shown that the release rate of the drug in the acid buffer pH 1.2 is 19.36%, indicating that the drug in the nanostructured lipid carrier is still encapsulated under the acidic pH condition. In vitro studies showed that the release rate of drugs increased from 10% to 60.54% in 24 hours. In vivo, pharmacodynamic studies showed that nanostructured lipid carriers could release lercanidipine hydrochloride in a controlled manner for a longer time compared with ordinary drugs.⁵⁵

Furthermore, the limitations of the current nitric oxide (NO) delivery systems and rapid degradation of siRNA upon administration for gene therapy stimulate an enormous interest in the development of compounds that produce such vasoactive substances in a controlled and sustained manner to treat CVDs such as hypertension. Cabrales et al⁵⁶ prepared NO-releasing NPs using a new platform based on hydrogel/glass hybrid NPs. This nanomaterial maintains a stable form of NO or NO precursor (nitrite) during drying, while exposed to moisture, these NPs slowly release the treatment level

of NO. After the administration of this NO NP, circulating NO level can reduce the average arterial blood pressure and increase the NO exhaled concentration in a few hours.⁵⁶ NPs can be proposed as a delivery system to prevent the degradation of siRNA by endonuclease and exonuclease in blood, serum and cells. Liposome is a cationic liposome made of DOTAP (N-[1-(2,3-dioleoyloxy)]-N-N-N trimethyl ammonium propane). The expression of β 1-adrenergic receptor can be reduced by intravenous administration, and the blood pressure is controlled for 12 days.⁴²

NPs and pulmonary hypertension

Pulmonary arterial hypertension (PAH) is a highly threatening and progressive disease characterized by increased pulmonary vascular resistance and increased pulmonary artery pressure. Continuous increase of pulmonary vascular resistance leads to pulmonary vasoconstriction and structural remodeling, which further affects the right heart function and ultimately leads to right heart failure and death.⁵⁷ The common targeted drugs for PAH include prostacyclin (prostaglandin I₂), endothelin receptor antagonists, phosphodiesterase type-5 inhibitors and a soluble guanylate cyclase stimulator. These vasodilators have shown certain effectiveness in the past applications.⁵⁸ However, due to the poor bioavailability and side effects of the drugs, their overall therapeutic ability is limited. In order to solve these problems, the drug delivery system mediated by NPs can be used as a novel alternative strategy.

Bosentan, a selective and competitive antagonist of endothelin receptor, has been designed to nanosuspensions for enhancing solubility and absorption by an increase of its contact surface. The study showed that the solubility of bosentan NPs increases seven times higher than coarse bosentan.⁵⁷ Akagi et al⁵⁹ described a PLGA NP incorporated with beraprost (a prostacyclin analog) that significantly reduced pulmonary vascular resistance and inhibited pulmonary vascular remodeling in rat models. Beraprost-NPs also improved the survival rate of rat model and decreased the occurrence of side effects.⁵⁹ Also, in another study, authors reported that imatinib-incorporated NPs exhibited more significant inhibition of pulmonary arterial smooth muscle cells proliferation than imatinib (a tyrosine kinase inhibitor) after intratracheal administration.⁶⁰ Other studies have shown consistent results, including various NPs that incorporate with pitavastatin, fasudil and oligonucleotides, which have shown better effects on inhibiting pulmonary vascular remodeling, inducing the decline of PAH, and improving survival rates.^{61–63} Therefore, this platform based on nanotechnology can serve as a novel alternative tool for improving the effectiveness and alleviating side effects of treatment of PAH.

Application of NPs for treating atrial fibrillation (AF)

AF is the most common clinical arrhythmia, accounting for approximately one-third of all arrhythmia-related inpatients. AF significantly affects morbidity and mortality in patients as the result of the high risk of stroke.⁶⁴ Catheter ablation has become a major treatment for drug refractory AF. However, the success and maintenance of cardioversion has been limited by a lack of sufficient understanding of the mechanisms for the occurrence and maintenance of AF. Yu et al⁶⁵ proposed a novel ablation strategy utilizing functionalized magnetic NPs (MNPs). Previous animal experiments have demonstrated that ganglionated plexi (GP) plays an important role in the occurrence and maintenance of AF, and clinical evidence also suggested that the main GP ablation can increase the success of standard pulmonary vein isolation by catheter ablation for treating AF.⁶⁶ Selective ablation of GP requires their accurate location. At present, the location of target GP is achieved by detecting the sites where high-frequency stimulation slows down heart rate and then ablation at that site, that is, endocardial catheter technique. Better methods to identify and ablate these focal neural networks can be used as an auxiliary therapy for conventional cryoablation or radiofrequency ablation.

Inspiringly, Yu et al⁶⁵ described a technique using superparamagnetic Fe₃O₄ NPs that were coated with thermoresponsive polymeric hydrogel (shell) when contacting body temperature in vivo to release neurotoxic agent contained therein. The results showed that in six dogs in which MNPs were injected directly into the anterior right GP, the sinoatrial node slowing response induced by high frequency stimulation was significantly inhibited (40%±8% at baseline; 21%±9% at 2 hours), and the lowest voltage of high frequency stimulation inducing AF was increased significantly (5.9±0.8 V at baseline; 10.2±0.9 V at 2 hours). In the other four dogs, MNPs were injected into the circumflex artery supplying the inferior right GP (IRGP) and were attracted to IRGP by magnets sutured on the epicardial surface, which inhibited the function of IRGP and decreased the ventricular rate. These results demonstrate that targeted delivery of drugs based on nanotechnology may have a promising future in the treatment of AF.

NPs application in the treatment of AMI

After myocardial infarction, the cardiac function is continuously impaired due to the low proliferation and limited self-repair ability of myocardial cells. Conventional myocardial blood supply restoration cannot repair the apoptotic CMs. Therefore, stem cell therapy has emerged as a new treatment

method.⁶⁷ However, despite the great development of this therapy, the delivery of targeted stem cells and the tracking or detection of their proliferation still need efforts to optimize. In order to overcome these shortcomings, new methods are needed to achieve high concentration cells in damaged tissues and to monitor their proliferation and survival. MRI has become a reliable and safe technology for tracking these cells. However, it is important that the sensitivity and success of this technology largely depend on the contrast medium used. Iron oxide superparamagnetic NPs, due to their unique magnetic properties and favorable biocompatibility, can be used to direct and monitor the therapeutic effects of stem cells on AMI. It has been recognized as one of the most promising contrast agents for stem cell markers.^{68,69}

Additionally, Binsalamah et al⁷⁰ applied a chitosan-alginate NP containing placental growth factor (PIGF), a key molecule in angiogenesis and vasculogenesis, to improve cardiac function at the site of AMI. The results demonstrated that using NPs as a carrier instead of direct injection of PIGF in the treatment of AMI can provide a sustained release of PIGF and enhance the positive effects of growth factors on acute myocardial ischemia.⁷⁰

Moreover, Nakano et al⁴⁰ have proposed a PLGA NP incorporated with irbesartan (an angiotensin II receptor blockers) to inhibit the recruitment of inflammatory monocytes which contribute to myocardial ischemia–reperfusion injury, further decreasing the infarct size and meliorating left ventricular remodeling.⁷¹ In a similar manner, Galagudza et al⁷² designed a silica NPs loaded with adenosine (a prototype cardioprotective agent) to reduce infarct size while reducing hypotension and slow heart rate from systemic adenosine use.⁷² Of special interest, another study found that phosphatidylserine-presenting liposomes could act as an anti-inflammatory effect by mimicking apoptosis cells being swallowed by macrophages and following that the macrophages secreted high levels of anti-inflammatory cytokines and regulated the expression of certain receptors markers.⁷³

Roles of NPs in other CVDs

As a new drug delivery platform, NPs also perform well in many other CVDs. Fullerene NPs significantly protect brain cells from ischemia or reperfusion injury caused by cerebral infarction by scavenging free radicals from oxidative stress. At the same time, certain NPs can be combined with some neuroprotective drugs to greatly promote permeability and make it more smoothly cross the blood–brain barrier to play a vital role in the treatment of ischemic stroke.^{74–76} Of course, NPs can also target thrombolytic drugs, such

as tissue plasminogen activator after thromboembolism, to play the role of rapid recanalization of occluded blood vessels and alleviate the inefficiency and many side effects of systemic medication, including the high risk of bleeding complications.⁷⁷ NPs as a drug-releasing platform for perivascular drug delivery have stirred up the recent research in nanomedicine to restrain intimal hyperplasia (IH) after open vascular reconstructions in treatment of atherosclerosis, such as application in IH antiproliferation of saphenous vein grafts.⁷⁸

In short, NPs have shown excellent properties in the transportation of many drugs and have a promising prospect of application.

Nanomaterials for CVDs

After myocardial infarction, cardiac myocyte apoptosis, myofibroblast and macrophage migration to the infarct site to repair the heart tissue resulting in scar tissue, affect the systolic function of the heart and eventually cause heart failure.⁷⁹ Heart transplantation is the most effective treatment for patients with heart failure when they reach the final stage of heart failure. However, due to the lack of heart donors and immune rejection, very few people are lucky to receive transplantation treatment.⁸⁰ In order to overcome these bottlenecks, cell-based therapy and tissue engineering have gradually become a hot research direction.^{81,82} Tissue engineering is an interdisciplinary field that aims to create biomimetic materials that generate scaffolds that usually seed with cells to produce or repair functional organs. Nanomaterials are usually made from metals, ceramics, polymers, organic materials or composites, because they are synthesized on a nanoscale scale, with a significant increase in surface area–volume ratio and roughness, thus enhancing mechanical, electrical, optical, catalytic and magnetic properties. It is clear that the superior material properties of nanomaterials have shown the most promising results in cardiac myocyte tissue engineering.⁸³

Nanomaterials are usually classified, according to their origin, as natural or synthetic biomaterials. It is known that natural biomaterials mainly found in the ECM, including collagen, fibrin and hyaluronan, have nanoscale dimensions.⁷⁹ The nanofiber scaffolds incorporated with these materials by electrospinning have been used for cardiac tissue engineering applications, showing higher percentage of cellular attachment and the availability of multiple focal sticky points.⁷⁹ Nevertheless, in some cases, the shortcomings of these materials should be carefully considered. Proteases in organisms degrade natural substances too quickly, limiting the use of these materials as long-term implants.⁸⁴ In particular, these materials may

contribute to fibrosis, foreign body reactions together with oxidative stress and immune response when used in vivo.

The application of synthetic materials in many occasions provides a better control of the eventual effects due to their facile fabrication and widely modified mechanical properties. Structure, pore size and orientation, mechanical strength, degradation methods and so on can be optimized according to the actual demand. Poly (ethylene glycol) (PEG), a US Food and Drug Administration-approved polymer, is regularly used for scaffolds that can offer cellular structural support and guide tissue regeneration. Kim et al⁸⁵ introduced a CM substrate that was made of PEG with nanopillar topography and they found that cell adhesion was apparently increased on PEG nanopillars as compared to conventional PEG substrate and that nanopatterned substrate stimulated cell–cell binding in colonizing CMs. Later, another study⁸⁶ that used PEG hydrogels to determine whether CMs could be guided by nanomorphology embedded on the substrate showed that compared with the random orientation on the pattern-free nanopopography substrate, the uniform CM orientation is allowed on the PEG substrate with patterned nanomorphology. It is also important to observe the larger cell diameters on the patterned substrate, which indicates that the nanomorphology affects the cell size.

Polyglycolic acid (PGA) and polycaprolactone (PCL) are also promising candidates for scaffolding since they have some advantages such as desirable degradation rates all while being nontoxic, biocompatible, hydrophilic and low cost, but also has soft and flexible characteristics. Aghdam et al⁸⁷ fabricated PCL:PGA nanofibrous scaffold by electrospinning for studying cell attachment and proliferation of cardiac progenitor cells. They found that after 6 days of culture on the scaffold of PCL:PGA with weight ratio of 65:35, the cell viability was the highest and attributed to the enhancement of hydrophilicity. Equally important, PLGA has been diffusely used for tissue engineering applications for combining the advantages of poly-lactic acid and PGA. Simon-Yarza et al⁸⁸ used PLGA to prepare nanofiber scaffolds containing Neuregulin-1 (Nrg), a cardioactive growth factor. The results showed Nrg-containing fibers have effective adhesion, integration and biocompatibility with damaged heart tissue and that an increase of M2:M1 macrophage ratio after implantation suggests that tissue remodeling is induced. Scaffolds made of other nanomaterials, such as polypyrrole,⁸⁹ carbon nanotubes^{90–92} and electrospun poly(glycerol sebacate),⁹³ have shown excellent performance in tissue engineering of CMs.

Another approach for treating injured heart tissue after a heart attack is to use engineered cardiac tissue patch, which

is usually produced by implanting heart cells into a three-dimensional scaffold of porous biomaterials.⁹⁴ One study⁹⁵ described that compared with the traditional polymer matrix, the carbon nanofibers embedded in PLGA make the growth of CMs more robust and that 50:50 PLGA to carbon nanofibers composite ratios at PLGA density of 0.025 g/mL enhanced CM function by mimicking heart tissue tensile strength and conductivity and enhancing the adsorption of proteins known to promote CMs function. Moreover, Malki et al⁹⁶ developed a engineered cardiac patch composed of albumin electrospun fibers and gold nanorods with cardiac cell seeded in. When localized on the myocardium and irradiated with near infrared laser (808 nm), this patch can absorb light and convert it into heat power, which changes the molecular structure of the fibrous scaffold locally, and makes it attached to the wall of the heart strongly but safely.

Of course, injectable scaffolds are favored by researchers for their simple and minimally invasive procedures because they can be injected through syringes or catheters. One study conducted by Lin et al⁹⁷ demonstrated that when injecting self-assembling peptide nanofibers into myocardium, they can enhance the thickness of infarcted myocardium and inhibit ventricular remodeling, whereas the implantation of nanofibers containing autologous bone marrow mononuclear cell improves cell retention and cardiac functions after MI in pigs.⁹⁷ Another common method is to prepare injectable gel from acellular ECM. For example, Singelyn et al⁹⁸ extracted and decellularized porcine cardiac tissue to form myocardial matrix with the ability to self-assemble to form a nanofibrous structure in vivo. It can also be used to delivery stem cells⁹⁹ or cell factors¹⁰⁰ to repair infarcted myocardium and improve cardiac function. Injectable materials are likely to be exemplary techniques for cardiac tissue engineering because of their ease of use, but there are still many obstacles to overcome, such as the correct guidance of the infarct area and the control of the arrival of the final stent geometry. Transporting materials through ducts can avoid invasive surgery, reduce patient recovery time and infection opportunities. Infarcted areas after myocardial infarction are unstable, and intramyocardial injection may increase the risk of ventricular rupture, leading to safety problems in patients with AMI.¹⁰¹

Of course, nanomaterials are not only used in myocardial tissue engineering but also have outstanding applications in other cardiovascular fields. In one study, authors demonstrated that a nanopolyplex as a delivery platform of a mitogen-activated protein kinase–activated protein kinase 2 inhibitory peptide into vascular graft intima can significantly increase long-term patency by inhibition of inflammatory

Table 2 A brief summary of the application of nanotechnology to cardiovascular disease

Coronary artery disease	Hypertension	Pulmonary hypertension
<ul style="list-style-type: none"> • Nanoparticles for diagnosis: iron oxide fluorescent, 19F perfluorocarbons, gold, gadolinium-coated perfluorocarbon • Nanoparticles for therapy: pravastatin, fumagillin, pioglitazone, anti-inflammatory peptide 	<ul style="list-style-type: none"> • Nanoemulsion: olmesartan medoxomil, ramipril, amlodipine, valsartan, lacidipine, carvedilol • Lipotomes: lacidipine, siRNA • Nanowire: ACEI, BBS, CCB • Nanostructured lipid carrier: lercanidipine • Hydrogel/glass hybrid: nitric oxide • Nanoparticles: felodipine 	<ul style="list-style-type: none"> • Nanosuspensions: bosentan • Nanoparticles: beraprost, imatinib, pitavastatin, fasudil, oligonucleotides
Atrial fibrillation	Acute myocardial infarction	Ischemic stroke
<ul style="list-style-type: none"> • Superparamagnetic Fe₃O₄ nanoparticles loaded with neurotoxic agent • Nanomaterials: Parylene-C with dexamethasone and amiodarone 	<ul style="list-style-type: none"> • Diagnosis: iron oxide superparamagnetic nanoparticles • Nanoparticles: PIGF, irbesartan, adenosine, phosphatidylserine • Nanomaterials: PEG, PGA, PCL, PLA, PLGA, PPy, peptides nanofibers 	<ul style="list-style-type: none"> • Nanoparticles: tPA, hirulog

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; BBS, beta blockers; CCBs, calcium channel blockers; PCL, polycaprolactone; PEG, poly (ethylene glycol); PGA, polyglycolic acid; PLA, poly-lactic acid; PLGA, poly-(lactic-co-glycolic) acid; PPy, polypyrrole; PIGF, placental growth factor; tPA, tissue plasminogen activator.

response and cellular proliferation.¹⁰² Collagen, a natural nanostructural biodegradable material, seems to be more suitable for the manufacture of the external scaffold, because it not only plays a protective role for venous bridges in arterial environments but also helps to reduce IH with features of low immunogenicity and excellent biocompatibility, porous structure and desired permeability.¹⁰³ Li et al¹⁰⁴ studied the effects of external scaffolds made of collagen on venous graft hemodynamics and IH and the results demonstrated that the rabbit arteriovenous graft coated with collagen external scaffold showed higher blood velocity and blood flow, thinner intima and media, and smaller diameter. Moreover, the external scaffolds made of other collagen or polymer have been widely used in the study of inhibiting the neointimal proliferation and maintaining the fluidity of vein grafts, and have shown remarkable effect and gratifying application prospect.¹⁰⁵ What's more interesting is that nanomaterials can also be used to treat and prevent AF. A nanostructured film fabricated with Parylene-C was loaded with dexamethasone and amiodarone, and then was localized to epicardium of rabbit model to inhibit perioperative inflammation and AF.¹⁰⁶ The results demonstrated that the nanostructured Parylene-C films possess the capacity to release lastingly drug delivery, and most notably to reduce inflammatory reaction, epicardial neotissue fibrosis and occurrence of AF. A brief summary of the application of nanotechnology to CVDs is shown in Table 2.

Application of nanotechnology in cardiac and cardiothoracic surgery robots

The combination of endoscopy and advanced control technology makes robotic-assisted surgery possible.^{107,108}

Robotics is not based on nanoscale robots that flow through the body, but on sensors, imaging, navigation, brakes, etc., which are based on nanotechnology to enhance the ability of surgeons. The surgical robot technology, especially the robot which can be controlled by magnet at the end of the catheter, has a great influence on cardiothoracic operation and intubation in cardiovascular surgery.^{109,110} The remote image-guided magnetic catheter guidance system has been used in ablation operation for the treatment of AF^{111,112} and tachycardia.¹¹³⁻¹¹⁵ Robotic-assisted catheter technology has also been widely used in mitral valve repair,^{116,117} and robotics have been used in minimally invasive surgery to treat coronary artery stenosis^{118,119} or to assist in navigation in thickened hypertrophic obstructive cardiomyopathy with septum myectomy,¹²⁰ which is associated with sudden cardiac death syndrome.

The tracking and compensation of beating heart activity using robot technology can be regarded as a great challenge to robotics. In recent years, it has met this requirement to a large extent, but even so, there is still room for development. This is due to the application of increasingly sophisticated mathematical methods and adaptive control strategies for robot tracking and movement.¹²¹ The realization of these real-time advanced computing methods depends on the advance of fast computing, electronic control, sensors and actuators based on nanotechnology. As these abilities continue to develop, new theories of control will emerge that will be applied to tracking the movements of the heart, eyes and other parts of the body for the purpose of surgery, treatment and diagnosis.¹²²

Conclusion and prospects

Nanotechnology as a new type of science provides a bright prospect and hope for clinicians to achieve the goals that until recently seemed impossible to achieve, but it is still necessary

to further deepen knowledge and increase the application of nanotechnology. Nanomedicine has great potential in the treatment of CAD. Effective nanodrug delivery systems for different drugs are being developed. However, the problems facing their implementation are many, for instance, non-determinacy of the age of a nanomaterial in a biological cell, no sufficient information about the biological safety of NPs at the cellular level, and direct toxicity inside the living cell based on the chemical makeup. At the same time, nanomaterials may also produce allergic reactions, inflammation and increased angiogenic intima in the body. In addition, DES may cause deformities and injuries, and some clinical disasters have occurred. Therefore, more and more studies consider combining nanotechnology and gene therapy methods (eg, pDNA and RNAi) to modify gene expression and generate signaling molecules to inhibit the growth of diseased cells and hyperplasia, and cause apoptosis. Thereby fundamentally solving the disease progression.¹⁷ In addition, although nanotechnology has achieved pleasing results in CVDs, it is still mostly in the experimental stage, and for patients with severe myocardial damage, it cannot completely repair the damaged myocardium, so many patients who cannot receive heart transplant eventually die from heart failure. Therefore, more and more scientists try to combine the superiority of nanotechnology with stem cells or gene therapy, so-called tissue engineering or genetic engineering, to provide a bright future for the diagnosis and treatment of CVDs.^{26,123} Therefore, the clinical application of nanotechnology should be carefully evaluated through randomized trials. Collaborative research between biomedical engineers and clinicians is essential for the development of practical and effective treatment of nanoscale models.

Overall, there is still a long road ahead for research and clinical translations in application of nanotechnology. Great progress in nanomedicine has greatly improved the current treatment of CVDs. With the shrinking of treatment and the expansion of scientific curiosity, the future of CVDs treatment is indeed very exciting.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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