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ORIGINAL ARTICLE

Key Nanotechnology Breakthroughs in Cardiovascular Disease Therapy

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Abstract

Background: It is justified by the high population's morbidity and mortality rate, as well as the increasing present use of nanoparticles in this pathological context.

Objectives: To describe the main nanotechnology breakthroughs in the field of cardiovascular disease (CVD) and disseminate pertinent information in the literature.

Methods: This is a systematic review conducted between September and October 2021. The review was carried out through basic nature, following the initial script for the selective reading of articles in chronological order to collect relevant and consistent data related to the theme.

Results: It is evidenced the main advances of nanotechnology in the field of CVDs, namely, acute coronary syndromes (ACSs), heart failure (HF), and systemic arterial hypertension (SAH).

Conclusion: The importance of further and deeper studies in this area is emphasized, in order to make the already approved treatments feasible, so they can reach all publics at a low cost.

Keywords: Nanotechnology; Cardiovascular Diseases; Biomedical Technology.

Introduction

According to the World Health Organization in partnership with the Pan American Health Organization, cardiovascular diseases (CVDs) had a high mortality rate exceeding 17 million deaths in 2016, with 31% representing the global status.[1]

CVDs lead the ranking of chronic noncommunicable diseases (NCDs) and are responsible for 71% of deaths worldwide, which impact not only the health field but also the economic sphere, thus becoming a global challenge.[1,2] Along with the advance of cardiovascular problems, there is a significant growth in the nanotechnology field, which is gaining more and more space in the treatment of these diseases, presenting successful and increasingly futuristic results.

Nanotechnology in healthcare is defined by the European Medicines Agency as the use of small structures, smaller than 1,000 nanometers in diameter, that are projected to exhibit specific properties. The discovery of the new allotropic species of carbon known today as fullerenes, and finally the invention of tunneling and atomic force microscopes, have enabled the visualization and manipulation of structures at an atomic level, boosting pure and applied research with nanomaterials.[3,4] The advancement of this nanometric technology started with physicist Richard Feynman[5] and since then has opened a series of opportunities in different scientific fields.[6,7]

In this sense, studies with nanoparticles directed to CVDs have shown increasingly satisfactory results. They were developed with the main focus on primary prevention through early detection and prophylactic treatment, especially of acute coronary syndromes (ACS),

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Central Illustration: Key Nanotechnology Breakthroughs in Cardiovascular Disease Therapy

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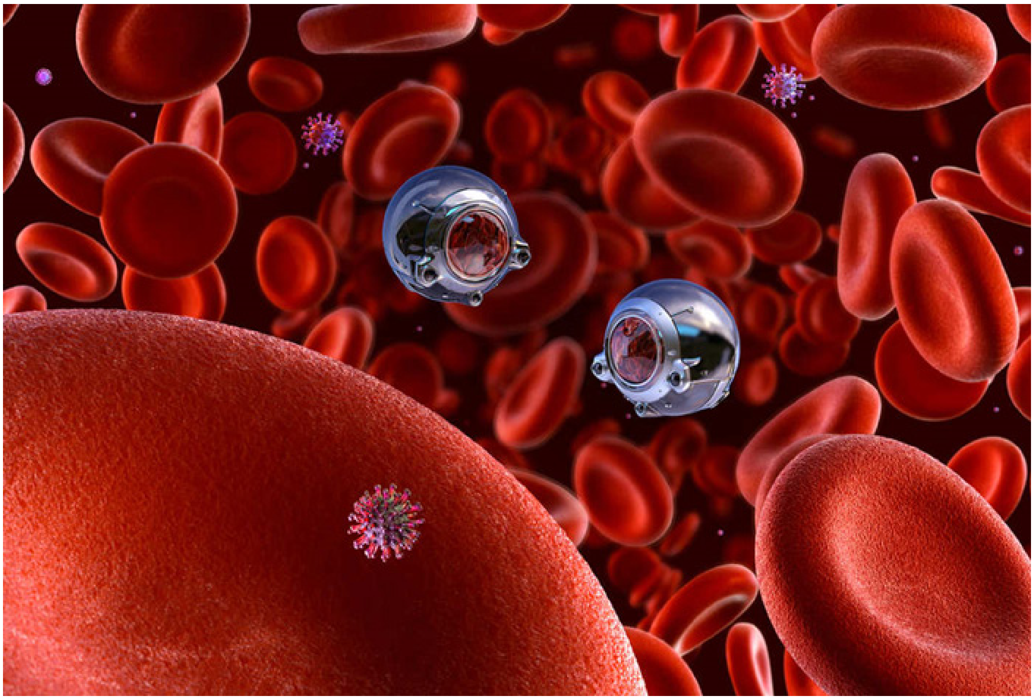

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Nanometric scale figure illustration.[12]

since traditional therapies by pharmacotherapy cause systemic toxicity and percutaneous coronary intervention has high risk for the development of thrombi.[8]

In view of the above, this research aimed to describe the main nanotechnology breakthroughs in the CVD field and disseminate relevant information in the literature, based on the following issue: "What is the effectiveness of the main nanotechnology discoveries in the treatment of CVD?". Thus, the study of this theme is justified by the population's high morbidity and mortality rate, as well as the increasing use of nanoparticles in this pathological context.

Methods

This is a systematic review conducted between September and October 2021. It enables the identification of the most relevant data in a systemic way and then synthesizes them in order to contribute to the formulation of revolutionary proposals in the respective study area.[9,10]

It also presents a descriptive and explanatory qualitative characteristic, which allows the description of several features of the studied fact without evading reality, using for this purpose a variety of information that explains all the content gathered around the problematic, to thereafter make it understandable.[11]

The review was conducted through basic nature, according to the initial script for the selective reading of articles in chronological order to collect relevant and coherent data on the theme. Afterward, the studies were selected and tabulated in electronic media, followed by data simplification and comparison referring to the theme. For the articles search, the subsequent descriptors were chosen: CVDs; Nanotechnology; Nanoparticles; Prevention and Control.

Data were extracted from the databases PubMed/Medline (National Library of Medicine of the National Institutes of Health), SciELO (Scientific Electronic Library Online), and Bireme (Regional Library of Medicine), besides electronic journals and ebooks published between the period 2016 and 2021, not excluding articles selected in a period shorter than this, based on the existence of relevant information. The combination of terms that presented relevant results to the search was "nanotechnology AND heart".

As inclusion criteria, it was used the most recent articles from 2016 on, with the main languages being English, Portuguese, and Spanish, excluding articles published in years before 2016, and that did not associate nanotechnology with the health area. The search resulted in 1,101 articles, of which only 30 fit the study proposal. Of these, 12 were used to address the results and discuss about the main advances of nanotechnology in the field of CVDs.

Results

This study highlighted the main advances of nanotechnology in the CVD field, namely, ACS, heart failure (HF), and systemic arterial hypertension (SAH).

According to the described information, several nanoparticles have been tested in nanomedicine, especially in CVD, either in prevention, early detection, or treatment, enabling the development of nanotechnology[12] products that have minimal adverse effects, especially concerning toxicity levels.

In order to present the studies available in the literature on nanoparticles for CVD treatment, a summary chart was created with the studies selected for this research (Chart 1 - Central Figure).

Discussion

Traditional treatments like drugs and percutaneous coronary intervention for ACS have caused complications such as drug-induced toxicity and the emergence of thrombosis. In this context, products containing nanomaterials have been developed in an attempt to solve these problems.

The use of magnetic and polyfunctional nanoparticles containing poly-Lactic-co-glycolic acid, with the ability to encapsulate and deliver peptides in specific sites of action through penetration into the bloodstream and subsequently into the myocardial tissue, has shown significant results, specifically in AMI, because they are able to modulate the genes that are involved in the inflammatory process, reflecting on improvements in the atherosclerotic process.[6]

Furthermore, a protective action developed by controlled release polymeric nanoparticles named Col-IV IL-10 NP22, which imitates the role of interleukin 10, was identified with atherosclerotic plaque, reducing necrosis present in lesions involving low-density lipoprotein, showing its future use is feasible.[13] Another modality of nanomaterial called amphiphilic polymers based on sugar molecules (SBAP) promotes a unidirectional activity acting in the stabilization of liposomal structures, aiming to act both in the prevention and treatment of atherosclerosis.[6]

Regarding pharmacology, the use of nanocarriers, responsible for involving the drug and prolonging its half-life, acts in the location of organic dysfunction, making such release occur in the intracellular medium improving the pharmacokinetic and pharmacodynamic action of the drug. Thus, the use of nanocarriers has been discussed in the treatment of thrombosis and embolism, based on the biophysical attraction of the friction force caused by the narrowing of the vessel, which would decrease the use of antithrombolytics and consequently their adverse effects.[6]

Also aiming at the early diagnosis of AMI and ACS, highly sensitive In_2O_3 nanoribbon biosensors are under development, being able to detect alterations in up to 45 minutes, from concentrations below 1 pg/mL in the case of troponin I, demonstrating a great potential for early identification of AMI.[14]

A study using carbon nanotubes, also to detect markers such as myoglobin, troponin I, creatine kinase-myoglobin binding (CK-MB), showed high affinity for these, and no specific response when tested with other types of proteins.[15-24] Still, with regard to early detection of AMI through immunochromatography test using magnetic nanoparticles, it is possible to detect in up to two minutes the elevation of troponin and CK-MB in patients with severe AMI, thus promising to revolutionize the detection, and consequently, the early treatment of this pathology.[25]

Another study from 2020, used metal nanoparticles to detect troponin T using a drop-casting method, and demonstrated a 250% increase in threshold sensitivity with detection of 0.1 ug/ml, proving efficacy in early identification of this biomarker, in the face of AMI. [26]

Gold nanoparticles embedded in hydrogel-based scaffold structures have also been tested revealing great potential to regenerate cardiac tissue.[17] Another study also demonstrated that collagen hydrogels associated with carbon nanotubes promote improved cardiomyocyte functionality.[20]

Regarding gold nanoparticles, the literature cites a study that used such material embedded in an extracellular matrix derived from cholecyst in scaffold format for cardiac tissue engineering. Corroborating other articles,

Chart 1 - Score of the main nanoparticles studied in the literature. São Paulo, SP, Brazil, 2021.

AUTHORS	STUDY/METHOD	NANOPARTICLE STUDIED	STUDY RESULT
Vélez-Reséndiz et al. 2018[8]	In vitro and In vivo	Magnetic nanoparticles of Poly Lactic-co-Glycolic Acid	Modulation of genes involved in the inflammatory process of atherosclerosis
Kamaly et al. 2016[13]	In vitro and Ex vivo	Polymeric nanoparticles Col-IV IL-10 NP22	Prevention of atherosclerotic plaque formation and reduction of necrosis in advanced lesions
Liu et al. 2016[14]	Scalable manufacturing method	In_2O_3 nanoribbon	Troponin I uptake below 1 pg/ml in 45 min
Matta et al. 2016[15]	Nanomaterial fabrication by chemoresistive detection method	Carbon nanotubes	High sensitivity for detection of troponin, CK-MB and myoglobin at 50 fg/ml
Amezcua et al. 2016[16]	Literature review	Electro-wired nanoscaffolding Nanoporous Patches	Regeneration of damaged myocytes and stimulation of contractility in AMI and HF
Baei et al. 2021[17]	Laboratory method	Gold nanoparticles embedded in hydrogel scaffolds	Promising proposal for cardiac tissue regeneration
Wang et al. 2016[18]	In vivo	Polypyrrole nanoparticles	Improved ejection fraction by 50% and reduced infarct length by 42.6
Mou et al. 2018[19]	In vitro	Iron nanoparticles	Increased electrochemical junctions, and decreased structures related to cardiac mechanics
Yu et al. 2017[20]	Manufacturing method	Collagen hydrogels	Improved cardiomyocyte function
Nair et al. 2017[21]	Heart Tissue Engineering (Manufacturing method)	Gold nanoparticles	Promising in the cardiac myoblast growth and proliferation; low probability of causing cellular toxicity.
Navaei et al. 2017[22]	Manufacturing method	Hydrogel GelMA incorporated into GNR	Organization and improvement of cardiac cell function
Sacks et al. 2016[23]	Immunoassay sandwich	Nano-Gold Chip	Early identification of HF in hypertensive patients by elevated autoantibodies.

**Central Figure - Source: Prepared by the authors (2021). *ACS: acute coronary syndromes; HF: heart failure; SAH: systemic arterial hypertension; AMI: acute myocardial infarction; CK-MB: creatine kinase-myoglobin binding; GelMA: gelatin methacryloyl; GNR :*

it presented promising results, revealing that it is suitable for the growth and proliferation of cardiomyoblasts, with a low probability of causing cellular toxicity.[21-27]

According to information contained in a 2018 article on nanotechnology-associated progenitor cell therapy, there was an increase from a previous 1%, to 100% of myocyte regeneration, emphasizing the benefits brought by the use of nanoparticles.[5]

A study with unique features developed an ultrasound-activated oxygen-generating nanosystem that can release O2 specifically into the infarcted cardiomyocyte, relieving hypoxemia and protecting the surrounding tissue after the AMI episode, as well as reducing oxidative stress.[28]

When it comes to HF, the idea of using cardiovascular tissues by engineering process with nanomaterials has been widely discussed. Scaffolds have demonstrated the potential to regenerate damaged myocytes and stimulate their contractile function, and patches have improved strength and conductivity in addition to recruiting proteins that help cardiac cell function.[16-22] Another cardiac marker whose detection has been tested is the B-natriuretic peptide, which has proven to be highly sensitive in the early identification of early-stage HF. The articles also point out that the use of gold nanoparticles is efficient in HF patients, as it favors a more efficient delivery of the drug at its site of action, improving myocardial contractility. [29]

Following this reasoning, researchers have been investing in nanomaterials, such as the plasmonic nano-gold platform, suggesting that it may be useful and early identifies HF in hypertensive individuals through the elevation of autoantibodies. In this sense, a study using this nano platform showed that troponin I, annexin-A5, and ADRBK1 were detected with high sensitivity and are related to left ventricular dysfunction in SAH patients, and can also be studied in other cases of heart disease.[30]

Therefore, despite the many cited benefits with the use of nanotechnology, more studies are needed in this field to evaluate the toxicological effects that these nanomaterials can cause in the body since the excretion of these substances occurs mostly by renal or hepatobiliary route, in addition to minimize the risks since such strategies can revolutionize nanomedicine.[19-31]

Conclusion

Advances in the nanotechnology area have shown that experiments have significantly impacted the prevention, early diagnosis, and treatment of several diseases, especially in the field of CVD. Most of the experiments were carried out in animals and showed promising results, giving greater security to advance in researches with human beings.

Hence, this discovery has been breaking paradigms and generating new therapeutic possibilities for cardiac patients with a high degree of efficacy and minimum risk of cytotoxicity, being evidenced, through the increment of nanoparticles, a lower mortality rate, contributing to increase the survival of this population and prevent the onset of cardiovascular complications through early detection. Finally, it is emphasized the importance of further studies in this area, in order to make the already approved treatments feasible, so they can reach all publics at a low cost.

Author Contributions

Conception and design of the research and acquisition of data: Lemos FA; analysis and interpretation of the data: Lemos FA, Silva KB, Campos CC, Santos UG, Barauna GB, Marques BM, Dourado JS; writing of the manuscript: Lemos FA, Silva KB, Campos CC, Marques BM, Dourado JS; critical revision of the manuscript for intellectual content: Lemos FA, Campos CC, Silva AF.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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