Feature

Oxygen-generating biomaterials for cardiovascular engineering: unveiling future discoveries

Masoud Mozafari [1,*], **Mohammad E. Barbati** [2]

[1] Research Unit of Health Sciences and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland
[2] Clinic of Vascular and Endovascular Surgery, RWTH Aachen University Hospital, Aachen, Germany

Oxygen-generating biomaterials are emerging as a groundbreaking solution for transforming cardiovascular engineering. These biomaterials generate and release oxygen within various biomedical applications, marking a new frontier in healthcare. Most cardiovascular treatments face a significant challenge, ensuring a consistent oxygen supply to nurture engineered tissues or even implanted devices. Traditional methods relying on passive oxygen diffusion often fall short, hindering functional cardiovascular tissue development. Oxygen-generating biomaterials, incorporating agents like calcium peroxide, provide a controlled oxygen source to the surrounding cells. This innovation potentially enhances cell viability, stimulates growth and boosts metabolic activity crucial for tissue health. Applications include repairing cardiac and vascular tissues, disease modeling, drug testing and personalized medicine, promising tailored treatments. Challenges like material toxicity and oxygen release control need consideration. As research progresses, the use of these innovative biomaterials in clinical translation could reshape cardiovascular healthcare, revolutionizing patient outcomes in heart disease treatment.

Keywords: Oxygen-generating biomaterials; tissue engineering; scaffolds; implants; stents; biomaterials; hypoxia; cardiovascular regeneration

Introduction

Oxygen-generating biomaterials signify a remarkable advancement in the realm of medical science and healthcare innovation.[p1] These biomaterials possess a unique ability to generate and release oxygen when integrated into various structures, ushering in a new era of medical possibilities. Their versatility extends across a broad spectrum of medical procedures, from wound management to tissue regeneration and even cutting-edge cardiovascular implants.[p1] By harnessing the potential of oxygen, these biomaterials offer a crucial resource for cellular and tissue health, enabling accelerated healing, enhanced tissue viability and ultimately improving overall outcomes of treatments.

Engineering oxygen-generating scaffolds, medical implants or integrating such biomaterials in currently available devices stands as a promising frontier poised to revolutionize the treatment of cardiovascular diseases. However, a challenge in the efficacy of functional cardiovascular therapies including regeneration, transplantation or interventional implantable

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devices like stents or valves is ensuring a consistent and sufficient oxygen supply.[p2],[p3] This is precisely where the role of oxygen-generating biomaterials becomes pivotal, presenting a groundbreaking paradigm shift in cardiovascular treatment options.[p4] This feature article delves into the profound significance of oxygen-generating biomaterials, their multifaceted applications within the scope of tissue engineering to address the cardiovascular pathologies and the promising future prospects of this approach.

The oxygen conundrum in cardiovascular engineering

Cardiovascular engineering stands as a compelling frontier, holding the potential to revolutionize the field with its applications in transplantation, interventional implantable devices, disease modeling, drug testing and research. However, a fundamental determinant of the success of these engineered cardiovascular tissues lies in their ability to secure a dependable and sufficient oxygen supply to the cells.[p5] Increased oxygen supply is needed not only during inflammatory and endothelialization processes after implanting a biomaterial in circulatory system but is also crucial for surrounding tissues.[p6],[p7] These tissues are probably either unhealthy before the treatment or inevitably get injured during surgical or interventional implanting process.[p8] It gets even more essential given the exceptional metabolic activity and blood supply of cardiac muscle. The same concerns exist for the intimal layer of vessels that are necrosed or ischemic under atherosclerotic plaque.[p9],[p10] In such circumstances, a continuous and substantial inflow of oxygen is indispensable for maintaining cell viability and optimal functionality.[p11]

Traditionally, researchers have found it really challenging to deliver sufficient oxygen to the cells residing within, under or over the engineered implanted cardiovascular biomaterials. Conventional approaches often resort to passive oxygen diffusion from the surrounding environment, a mechanism that, when closely examined, reveals potential inadequacies in meeting the robust metabolic demands of these tissues.[p12]

Consequently, engineered tissues could confront limitations in terms of cell survival, growth and incorporating into surrounding tissues upon maintaining their functional performance.[p13] In response to this critical oxygen supply concern within engineered cardiovascular tissues, the scientific community is now exploring an ambitious journey, finding innovative solutions with oxygen-generating biomaterials. These meticulously designed biomaterials are engineered with precision to generate and dispense oxygen in a controlled and regulated manner, thereby providing a continuous source of this oxygen to the cells within the newly engineered tissue. This groundbreaking approach crucially addresses the challenge of oxygen deficiency, opening doors to a range of advantages that have the potential to reshape the landscape of cardiovascular engineering. However, it is crucial to approach this innovation with a discerning scientific eye, subjecting it to rigorous evaluation and critical scrutiny to fully comprehend its implications and limitations.

Improved cellular and molecular function

Intriguingly, the impact of oxygen-generating biomaterials on cellular and molecular function within engineered cardiovascular tissues warrants meticulous scientific examination.[p14] These biomaterials have exhibited a substantial capacity to enhance cell viability, constituting a pivotal advancement in the realm of cardiovascular engineering. By ensuring a continuous and reliable oxygen supply, these biomaterials create an environment conducive to the flourishing of cardiovascular cells, ultimately translating into elevated rates of cell survival and the overall quality of the engineered tissue.

Furthermore, a key dimension of cardiac engineering resides in the realm of cell proliferation. Oxygen-generating biomaterials have demonstrated their prowess in stimulating increased cell division, thereby enabling the expansion of the cellular population within the engineered tissues. This dynamic process stands as a fundamental milestone, essential for achieving the desired tissue thickness and functional attributes.[p15] It is worth noting that oxygen operates as one of the most important players in cellular metabolism, exerting a significant influence over a spectrum of metabolic processes, including energy generation and biosynthesis.

Oxygen-generating biomaterials enhance oxygen availability, which in turn elevates metabolic activity in cells. This metabolic boost is essential for maintaining cellular function, supporting ATP production and facilitating biosynthetic processes, all of which are crucial for tissue vitality. The increased oxygenation can also help reduce hypoxia-induced apoptosis and necrosis, further supporting tissue health.[p15] This underscores the transformative potential of these biomaterials in improving outcomes for cardiovascular engineering by promoting cell survival, proliferation and functionality. However, it is crucial for the scientific community to rigorously investigate these advancements, examining the underlying mechanisms, optimal oxygen release rates, potential cytotoxicity of byproducts and long-term effects on tissue integration and performance to fully understand their benefits and any limitations.

Insights into oxygen production mechanisms

Understanding how oxygen-generating biomaterials work requires a detailed look at their composition and function. These biomaterials consist of two main components: a scaffold or matrix and an oxygen-releasing agent. The matrix provides structural support, whereas the oxygen-releasing agent produces and releases oxygen into the surrounding area (Figure 1). One common class of oxygen-releasing agents is peroxides. Solid inorganic peroxides like calcium, magnesium and sodium peroxides are pivotal for oxygen release in biomedical applications, primarily through hydrolysis reactions upon contact with water. Calcium peroxide (CaO_2), magnesium peroxide (MgO_2) and sodium percarbonate ($Na_2CO_3{\cdot}3H_2O_2$) undergo hydrolytic decomposition, yielding oxygen (O_2) and hydrogen peroxide (H_2O_2)[p13]:

$$CaO_2(s) + 2H_2O \rightarrow Ca(OH)_2(s) + H_2O_2;$$

$$MgO_2(s) + 2H2O \rightarrow Mg(OH)_2(s) + H_2O_2;$$

$$(Na_2CO_3)_2{\cdot}3H_2O_2 \rightarrow 4Na^+ + 2CO_3^{-2} + 3H_2O_2.$$

The resulting H_2O_2 further decomposes to release oxygen and water:

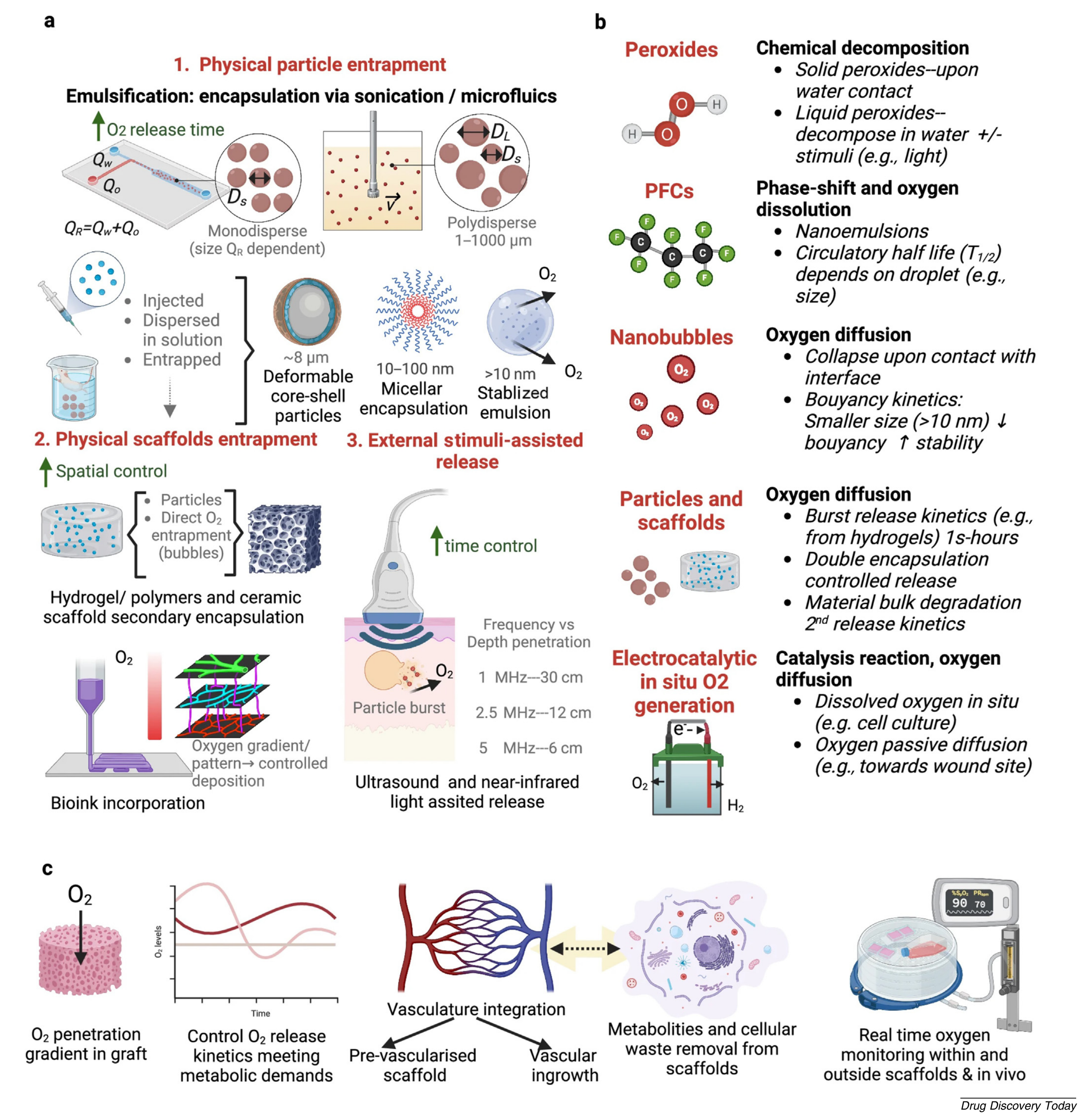

FIGURE 1

(a) Strategies for oxygen-controlled release. This panel illustrates various strategies for controlling oxygen release within biomaterials. These include physical entrapment in emulsions of uniform size, such as those generated by microfluidics, or in polydispersed particles the size of which is dependent on the velocity and shear forces within the system. These particles can form structures like micelles or multilayered particles. Other strategies involve encapsulating oxygen-releasing agents within scaffolds or employing stimuli-responsive release mechanisms to ensure precise oxygen delivery. **(b)** Core mechanisms of oxygen release in biomaterials and devices. This panel depicts the fundamental mechanisms by which biomaterials and devices generate and release oxygen. These mechanisms are crucial for maintaining optimal oxygen levels within engineered tissues, thereby supporting cell survival, function and overall tissue health. The controlled release of oxygen is achieved through various chemical and physical processes designed to meet the metabolic demands of the tissue. **(c)** Remaining challenges in oxygen tissue engineering. This panel highlights the ongoing challenges in the field of oxygen tissue engineering. Key issues include ensuring consistent and controlled oxygen release over extended periods, preventing the formation of harmful byproducts such as reactive oxygen species (ROS) and integrating oxygen-generating biomaterials seamlessly into existing tissue engineering frameworks. Addressing these challenges is crucial for advancing the efficacy and safety of oxygen-releasing biomaterials in clinical applications. Reprinted, with permission, from (p30).

$$2H_2O_2 \rightarrow O_2 + 2H_2O.$$

Additionally, liquid peroxides such as hydrogen peroxide (H_2O_2) can also release oxygen catalyzed by ferrous ions (Fe^{2+}) in the absence of catalase:

$$H_2O_2(aq) + 2Fe^{3+}(aq) \rightarrow O_2(g) + 2Fe^{2+}(aq) + 2H^+(aq);$$

$$H_2O_2(aq) + 2Fe^{2+}(aq) + 2H^+(aq) \rightarrow 2H_2O(l) + 2Fe^{3+}(aq).$$

Fluorinated compounds like perfluorocarbons (PFCs) are also employed as oxygen carriers in biomedical applications, using their high oxygen-dissolving capacity and diffusion mechanisms to deliver oxygen effectively in tissue culture and therapeutic treatments.[p13] These compounds slowly break down to release oxygen gas in a controlled manner, matching the needs of the surrounding cells.

The optimization of these formulations to enhance their limited miscibility has been explored by using nanoemulsions as foundational formulations. Key emulsion parameters, including droplet sizes, fabrication methods and the selection of surfactants, significantly influence stability and shelf-life (Figure 1). By fine-tuning these parameters, researchers aim to achieve a more stable and effective oxygen-release system. This controlled and gradual release of oxygen is vital for supporting cellular metabolism, promoting cell survival and maintaining overall tissue health in engineered cardiovascular tissues. Ensuring a sustained oxygen supply helps mitigate hypoxic conditions, which are detrimental to tissue regeneration and function. However, it is crucial that the oxygen release has a steady rate that matches the metabolic needs of the cells within the tissue. This precise regulation ensures a constant supply of oxygen, which is essential for the successful application of oxygen-generating biomaterials.

In this well-balanced environment, an optimal microenvironment is created, promoting the growth and maturation of cardiovascular tissues and improving the performance of implants. However, it is important for the scientific community to explore the mechanism of action of these oxygen-generating biomaterials further and tailor it based on the required function and specification of the application. For instance, cardiac valves, aortic grafts and various types of stents (coronary, peripheral and cerebrovascular) each have distinct requirements. This is because of their different functions and locations within the cardiovascular system. Similarly, implants in arteries face different conditions than those in veins. Arterial implants are exposed to high-pressure, pulsatile, oxygen-rich blood, whereas venous implants encounter low-pressure blood with less oxygen.[p16] By understanding their intricacies and behaviors, researchers can unlock their full potential and address any challenges with precision and clarity.

Oxygen-generating biomaterials for cardiovascular engineering

The potential of oxygen-generating biomaterials in cardiovascular engineering is groundbreaking, offering new solutions for many applications (Figure 2). Oxygen-generating biomaterials are key to repairing and regenerating damaged

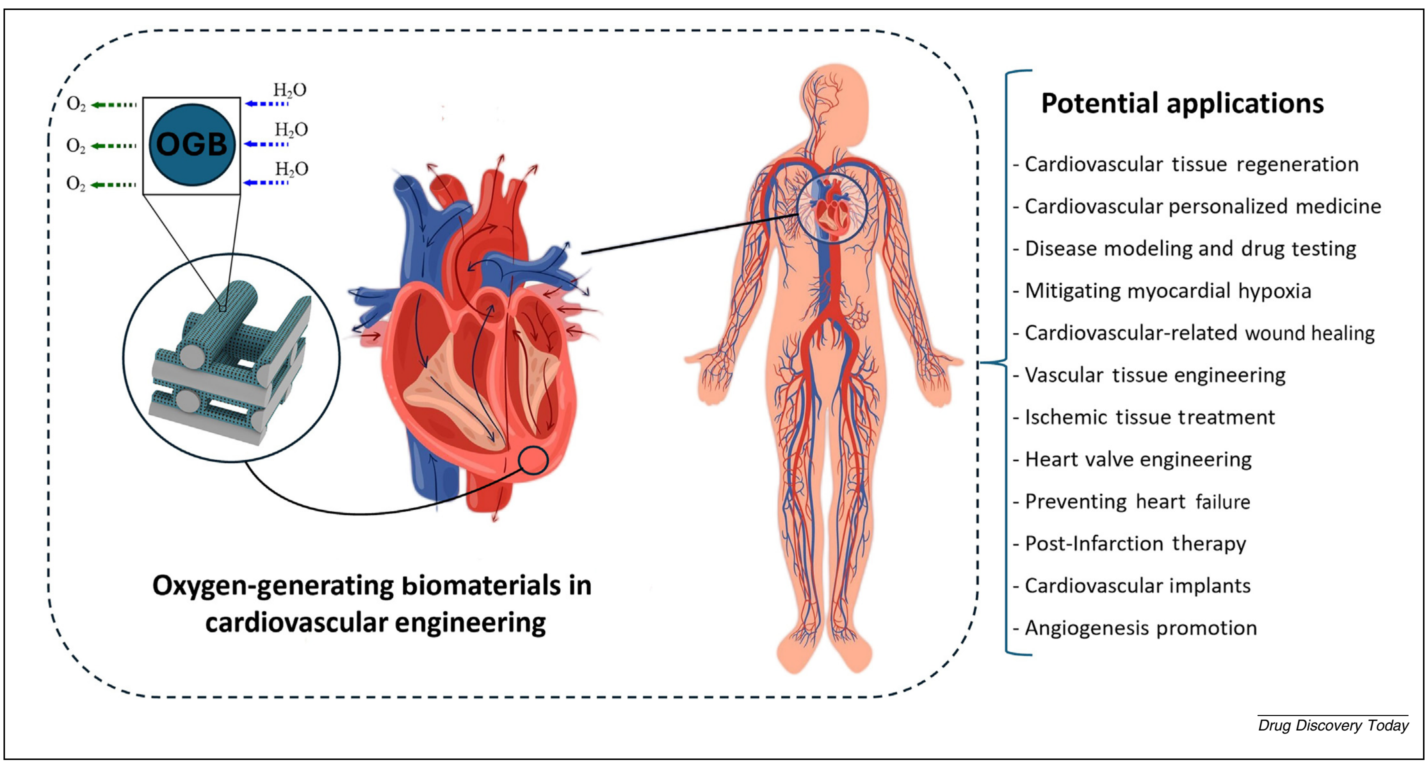

FIGURE 2
Applications of oxygen-generating biomaterials in cardiovascular engineering. This figure illustrates the diverse applications of oxygen-generating biomaterials in cardiovascular applications. Each application represents a distinct therapeutic approach leveraging oxygen-releasing properties to enhance tissue regeneration, function and overall patient outcomes in cardiovascular care.

cardiovascular tissues or replacing the nonrepairable tissues. These biomaterials can be used to make patches, constructs or grafts implanted into damaged areas of the circulatory system. The steady release of oxygen helps the healing process and promotes the growth of strong, healthy tissue, providing hope for better and longer favorable outcomes in treatment of cardiovascular diseases.[(p17)]

The integration of oxygen-generating biomaterials in cardiovascular tissue engineering stands as a pivotal advancement in biomedical research. These biomaterials facilitate the creation of disease-specific tissues that closely mimic physiological conditions of the heart and blood vessels. Through controlled oxygen release, these engineered tissues replicate the complex microenvironments of cardiovascular diseases, offering valuable insights into disease progression and treatment efficacy in a controlled laboratory setting.[(p18)] This approach enhances the accuracy of drug testing, potentially reducing reliance on animal models and improving the translatability of findings to clinical trials. Overall, oxygen-generating biomaterials represent a promising frontier in enhancing our understanding of cardiovascular pathophysiology and advancing therapeutic interventions.

A new era emerges with patient-specific cardiovascular implantables that can be crafted using oxygen-generating biomaterials. In some cases, these biomaterials enable researchers to use a patient's own cells to develop cardiovascular tissues that closely resemble the individual's unique physiology.[(p19)] This innovative method not only offers tailored treatment options but also holds promise for more-effective and precisely targeted therapies. By mimicking the patient's specific biological parameters and disease characteristics, these advancements aim to transform cardiac and vascular care. This approach marks a significant step toward personalized medicine, where treatments can be customized to meet the distinct requirements of each patient.[(p20),(p21)]

The heart's vital functions heavily depend on a continuous supply of oxygen. When this supply diminishes, myocardial hypoxia – a dangerous condition – can lead to ischemic injuries and impaired cardiac function. In a recent pioneering effort, researchers have developed oxygen-generating microparticles to address this challenge.[(p4)] These microparticles, made from poly-D,L-lactic-co-glycolic acid (PLGA) and calcium peroxide (CPO), release oxygen steadily for >24 h. This innovative research holds promise for reducing myocardial injuries, improving cardiac function and influencing gene expression. It has the potential to transform cardiac care, especially in transplantation and tissue engineering applications.[(p22),(p23)] The implications of these developments are profound, extending to a spectrum of biomedical applications. Of paramount significance is the potential to extend the window for heart transplantation by reducing ischemic injuries. The tangible reduction in myocardial injuries following heart procurement in *ex vivo* heart models underscores the real-world relevance of CPO microparticles.[(p24)] This research heralds a new epoch in cardiac care, offering renewed hope for enhanced patient outcomes in critical cardiac conditions, and holds the promise of reshaping the landscape of cardiac medicine from bench to bedside.

The future of cardiovascular treatment options with oxygen-generating biomaterials

Looking ahead, the role of oxygen-generating biomaterials in cardiovascular engineering is poised for transformative advancements. Exciting developments and possibilities are on the horizon. Ongoing research aims to revolutionize biomaterial designs, enhancing oxygen delivery to unprecedented levels. Next-generation designs could feature multilayered scaffolds with precisely engineered oxygen-release rates, promising precise control over the oxygen environment in engineered tissues.[(p25)] Such advancements hold great potential for optimizing tissue development and functionality in cardiac and vascular applications.

Nanotechnology is emerging as a game-changer in boosting the capabilities of oxygen-generating biomaterials. Integrating nanoparticles into these biomaterials shows promise in enhancing oxygen release efficiency and delivery to cells, potentially improving tissue performance and functionality. It even opens the door for a new type of implantable devices other than the currently available valve, stent and graft endoprosthesis. It is just a matter of further innovation and time to develop small implantable devices to put in the hypoxic area of cardiac muscle to prevent its necrosis and fibrotic tissue formation. Such implantable devices can increase cellular oxygen levels in areas with lack of blood supply due to acute vascular occlusion; or giving time to these tissues that cannot be saved with revascularization interventions until enough collateralization of surrounding arterioles achieved during the healing process after myocardial infarction. Addressing myocardial hypoxia remains a significant goal, with oxygen-generating nanobiomaterials offering sustained oxygen release over extended periods. Ongoing refinements focus on balancing oxygen release with pH changes in cell culture media to maintain optimal conditions. Research indicates that oxygen-generating agents support contractile functions even under hypoxic conditions, enhancing contraction stress in engineered cardiac tissues and downregulating HIF-1α expression, crucial for cellular responses to hypoxia.[(p4)] These future developments represent significant breakthroughs that could not only rescue cardiovascular tissue but also protect other vital organs dependent on oxygenation, even when proper vascularization is lacking. Such promising innovations have the potential to redefine cardiovascular healthcare strategies in multiple ways and dramatically improve patient outcomes.

Existing challenges toward clinical translation

The prospect of clinically translating oxygen-generating biomaterials for cardiovascular engineering is nothing short of thrilling. As research continues to amass evidence of their safety and efficacy, these biomaterials inch closer to becoming a beacon of hope for patients grappling with cardiovascular diseases. Functional cardiac tissue constructs, vascular grafts and stents crafted or covered using oxygen-generating biomaterials have the potential to become standard elements of cardiovascular engineering. Yet, the integration of oxygen-generating agents beckons as a promising avenue for addressing pressing challenges. However, the path to success is intricate and necessitates meticulous consideration of scientific complexities (Figure 1).

Foremost among these challenges is the inherent toxicity associated with the materials employed for oxygen delivery. When introduced into the body, especially at higher concentrations, the specter of adverse effects looms large. To surmount this obstacle, biomedical research is vigorously exploring innovative design approaches. A compelling facet underlines the need for a cautious approach to selecting oxygen-generating agents. Unlike borrowing concepts from unrelated fields, a more-tailored approach is imperative owing to stark disparities in physiological responses within the human body. For instance, agents like CPO, seemingly benign in environmental contexts, exhibit notably different effects when directly implanted within the human system. Hence, comprehensive studies are mandated to delineate the therapeutic windows for each oxygen-generating agent, ensuring their potential benefits while minimizing potential harm.

To pave the way for clinical adoption, exhaustive assessments spanning genotoxicity, teratogenicity, systemic toxicity and pharmacokinetics are prerequisites. Additionally, controlling the release of metal ions to prevent undesirable physiological manifestations is paramount. Intermediate products of oxygen generation, such as hydrogen peroxide (H_2O_2) and reactive oxygen species (ROS), tread a fine line between benefit and harm.[p26] To mitigate potential adverse effects, ingenious strategies, including the integration of antioxidant enzymes like catalase into the systems, are being explored.[p27]

The field of bioprinting, a crucial aspect of tissue engineering, is met with several challenges that need to be addressed to improve its effectiveness. One significant issue is the premature generation of oxygen during the preparation of bioinks, which can compromise the integrity and functionality of the printed constructs. To overcome this, innovative encapsulation techniques are being developed. One such method is stimuli-responsive oxygen release, which enables controlled oxygen delivery in response to specific microenvironmental triggers (Figure 1). A promising approach involves using microbubble-enhanced ultrasound to facilitate on-demand oxygen release precisely where and when it is needed. Additionally, the use of smart biomaterials that release oxygen in response to microenvironmental stimuli is being explored to provide a more controlled and sustained oxygen supply. Moreover, the spatiotemporal effects of oxygen-generating biomaterials on stem cell fate within bioprinted constructs is an area that warrants further investigation. Understanding how these materials influence stem cell differentiation, proliferation and overall tissue development is crucial for advancing the field. Such insights could lead to more-effective and -reliable bioprinted tissues and organs for therapeutic applications.

By addressing these challenges and exploring new techniques, the potential of bioprinting can be significantly enhanced, paving the way for innovative solutions.[p28] In the context of cardiovascular applications, the risk of hyperoxygenation in local tissues is another looming concern. Studies have hinted at potential complications, and the design of biomaterials with tightly controlled oxygen-release kinetics emerges as a potential solution.[p29] The journey of oxygen-generating biomaterials in cardiovascular engineering is a multifaceted odyssey laden with scientific intricacies. Researchers are pursuing innovative solutions to harness the potential of these biomaterials while ensuring their safety and efficacy.

Concluding remarks

Oxygen-generating biomaterials stand as vanguards in propelling the frontiers of cardiovascular engineering. By squarely addressing the crucial challenge of oxygen supply, these innovative biomaterials illuminate a promising pathway toward the development of functional, robust tissues suitable for transplantation and implantation in various applications. With the relentless march of research and technological innovation, the future of cardiovascular engineering gleams with immense potential. Personalized therapies and the long-anticipated clinical translation of these oxygen-generating biomaterials loom on the horizon, promising to reshape this landscape. As our exploration of the capacities of oxygen-generating biomaterials continues, we stride ever closer to a transformative shift in cardiovascular healthcare. The promise of these biomaterials in enhancing cardiac and vascular tissue function, resilience and adaptability fuels our journey forward. The coming years hold the potential to revolutionize how we perceive and address cardiovascular diseases, offering new hope to countless individuals in need.

Conflicts of interest

There are no conflicts of interest to declare.

CRediT authorship contribution statement

Masoud Mozafari: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Mohammad E. Barbati:** Investigation, Writing – review & editing.

Data availability

No data was used for the research described in the article.

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Masoud Mozafari [1,*], Mohammad E. Barbati [2]

[1] Research Unit of Health Sciences and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland
[2] Clinic of Vascular and Endovascular Surgery, RWTH Aachen University Hospital, Aachen, Germany
* *Corresponding author: Mozafari M. (mozafari.masoud@gmail.com, masoud.mozafari@oulu.fi).*