Send Orders for Reprints to reprints@benthamscience.net

Current Pharmaceutical Design, 2022, *28*, 468-470

PERSPECTIVE

Nanocarriers Loaded with Oxygen to Improve the Protection of the Heart to be Transplanted

Claudia Penna[1,2,*], Francesco Trotta[3], Roberta Cavalli[4] and Pasquale Pagliaro[1,2,*]

[1]*Department of Clinical and Biological Sciences, University of Turin, 10043 Turin, Italy;* [2]*Istituto Nazionale Ricerche Cardiovascolari, 40126 Bologna, Italy;* [3]*Department of Chemistry, University of Turin, 10125 Turin, Italy;* [4]*Department of Drug Science and Technology, University of Turin, 10125 Turin, Italy*

ARTICLE HISTORY

Received: July 30, 2021
Accepted: October 13, 2021

DOI:
10.2174/1381612827666211109112723

Abstract: In the case of serious cardiovascular diseases, such as refractory heart failure, heart transplantation is the only possible intervention. Currently, the modes of organ transport in hypothermic cardioplegic solution do not allow the implantation of the heart beyond 4-5 hours from the explant. The heart being an organ with a greater consumption of oxygen and high metabolism than the brain, its transport in hypothermic cardioplegic solutions presents critical issues in terms of time and conservation. An ambitious goal of many researchers and clinicians is to minimize the hypoxia of the explanted heart and extend the permanence time in cardioplegic solution without damage from hypoxia. Adequately oxygenating the explanted organs may extend the usability time of the explanted organ. This challenge has been pursued for years with approaches that are often expensive, risky, and/or difficult to use. We propose to consider oxygenated nanocarriers releasing oxygen for a long time. In this way, it will also be possible to use organs from distant countries with respect to the recipient, thus exceeding the canonical 4-5 hours tolerated up to now. In addition to the lack of oxygen, the transplanted organ can undergo the accumulation of catabolites due to the lack of perfusion during transport. Therefore, nanocarriers can also be perfused in adequate solution during organ transportation. A better oxygenation improving the postoperative recovery of the transplanted heart will improve the recipient's quality of life.

Keywords: α-cyclodextrin, α-cyclodextrin nanosponges, cyclic nigerosyl-nigerose, oxygen, hypoxia, reoxygenation, organ transplantation, nanocarriers.

1. INTRODUCTION

In the case of serious cardiovascular diseases (CVD), such as refractory heart failure, heart transplantation is the only possible intervention. In 2014, in the world, 118,127 solid organ transplants have been carried out, of which 6,270 were hearts; a progressive increase in heart transplantation has been observed over the years. The transplantation of solid organs, such as the kidney or the heart, according to the WHO, accounts for only 12% of the total requirement. In 2020, 3,441 organ transplants have been performed in Italy. Every year in Italy, more than 700 patients requiring heart transplants are on waiting list, and only 250-300 transplants are performed each year [1]. In occidental countries, heart transplant activity has been constant over the last ten years. For instance, in Italy, 246 transplants were performed in 2019; this figure represents 1.8% of the total interventions carried out in the period 2010-2019. Despite the discrepancy between supply and demand for hearts to be transplanted, the waiting lists do not increase since those patients that are enrolled and do not receive the heart transplant in time die within a year. It is likely that COVID-19 will increase these numbers. Indeed, pre-existing CVDs are linked to a worse prognosis and increased risk of death in patients with COVID-19. Yet, COVID-19 itself can also induce acute coronary syndrome, arrhythmias, myocardial injury, and venous thromboembolism [2-4].

Hypoxia is a problem for explanted organs, especially for the heart, given its oxygen (O_2)-dependence. Currently, the modes of transport in hypothermic cardioplegic solution do not allow the implantation of the heart beyond 4/5 hours from the explant [5]. An ambitious goal of many researchers and clinicians is to minimize the hypoxia of the explanted heart and extend the permanence time in cardioplegic solution without damage from hypoxia [6, 7].

The insufficient number of heart transplants is due to several reasons, including scarcity of compatible organs, the high oxygen demand of the heart itself which makes it much more delicate than other transplantable organs, significant logistical problems related to organ transport and timing. The heart being an organ with a greater consumption of oxygen and high metabolism than the brain, its transport in hypothermic cardioplegic solutions presents critical issues in terms of time (implantation must be performed within 4-5 hours from heart explant) and conservation. These factors are among the main causes for heart transplants failing to meet the demands and for transplant failure in many cases. If the organ does not reach the recipient in good condition, it determines the death of the recipient as shown by the OPTN/SRTR Heart annual report (2014-2019): 6 months after the transplant, the mortality rate is 6.4%, 7.9% at 1 year, 14.4% at 3 years, and 20.1% at 5 years [7]. Similar trends also occur in pediatric transplants. Furthermore, about 1% of explanted hearts are not used due to the limitations of the organ's conservation and transport system [7]. It is therefore essential to reduce the hypoxic suffering of the explanted organs to facilitate both the transplant and also ensure its success in terms of quality of life of the recipient.

For this purpose, we propose oxygenated nanocarriers (NC-O_2) that are able to slowly release O_2 for a long time. Different formulations can be used to make the NC-O_2 nanocarriers, such as native α-cyclodextrin, branched α-cyclodextrin polymer, α-cyclodextrin nanosponges, and cyclic nigerosyl-nigerose, which can prove to be innovative tools for oxygen delivery in a controlled manner. Data obtained in several cellular models (*e.g.*, cardiomyocytes and endothelial cells) show that NC-O_2 can reduce cell mortality in hypoxia/reoxygenation models [8, 9].

*Address correspondence to these authors at the Department of Clinical and Biological Sciences, University of Turin, Regione Gonzole 10, 10043 Orbassano (TO), Italy; E-mails: pasquale.pagliaro@unito.it; claudia.penna@unito.it

1873-4286/22 $65.00+.00

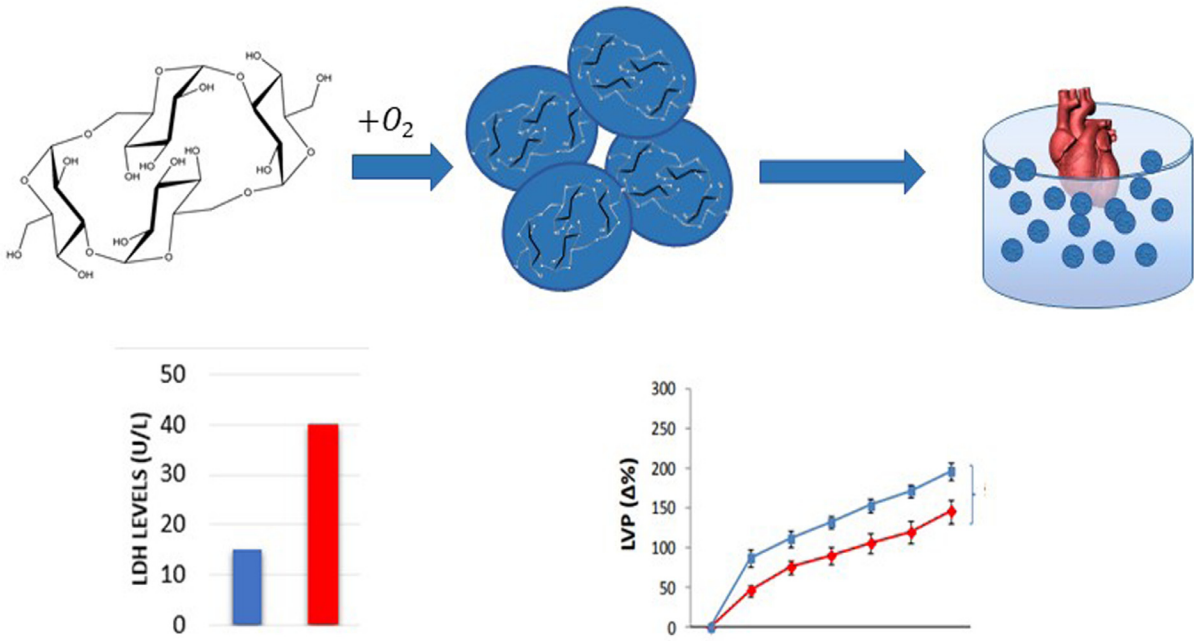

Fig. (1). Nanocarriers charged with oxygen (O_2) to reduce the damage of the explanted heart. By natural decomposition, they release O_2. The limitation of damage may be indicated by reduced lactate dehydrogenase (LDH) release and by improved cardiac performance, as suggested by improved left ventricular pressure (LVP). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Therefore, we propose that NC-O_2 nanocarriers can be: a) added to the cardioplegic solution and infused directly into the donor's coronary arteries at the time of explantation to enable them to enter the cells and provide a reserve of O_2, and b) added to the cold solution to release O_2 during the transport of the heart (Fig. **1**).

NC-O_2, similarly to extracellular vesicles, has the therapeutic potential to limit the damage caused by hypoxia and reperfusion [10]. Of course, a reduction in ischemia reperfusion injury will improve the performance of the transplanted heart and, if required, extend the time between explantation and implantation.

Improving the postoperative recovery of the transplanted heart will improve the recipient's quality of life. Adequately oxygenating the explanted organs and extending the usability time of the explanted organ is a challenge that has been pursued for years with approaches that are often expensive, risky, and/or impractical to use. The approach to NC-O_2 nanocarriers is inexpensive, of low risk, and easily usable in any transplant center in the world. Improving oxygenation will make it possible to use better preserved and better-performing hearts, thereby extending the time between the explantation and implantation.

The NC-O_2 nanocarriers proposed by us have considerable versatility; they can be sterilized by adding to the cardioplegic solution which will reduce the risk of infections, and they can be naturally decomposed so that they release oxygen, thereby prolonging the time of stay of the heart in hypothermic cardioplegic solution. In this way, it will be possible to use organs from distant regions with respect to the recipient, thus exceeding the canonical 4-5 hours tolerated up to now.

In addition to the lack of oxygen, the transplanted organ can undergo the accumulation of catabolites due to the lack of perfusion during transport. To overcome this problem, researchers have proposed continuous perfusion of the explanted heart with the blood of the donor using a complex system of perfusion and oxygenation [11]. The NC-O_2 nanocarrier proposed by us can also be continuously perfused in a sterile, cardioplegic/hypothermic solution that makes this approach less problematic. Perfusion transport in association with hypothermic protection and the presence of oxygen could limit damage, allowing better recovery of the transplanted organ and greater chances of success in functional terms. In this context, NC-O_2 could prove to be superior to the hemoglobin substitutes tested experimentally without brilliant results [12-14]. The hemoglobin substitutes remove nitric oxide (a potent endogenous vasodilator [12-14]), which is not the case with NC-O_2.

Clearly, this approach cannot solve many of the problems of transplantation [6], such as refusal by relatives of the potential donor; however, a greater awareness that the donor organ will have a greater chance of success could, theoretically, limit this problem and, perhaps it could give more time to donor relatives to decide whether to donate or not.

NC-O_2 nanocarriers are still being studied in our laboratories with experimental approaches and are not yet a clinical reality [8, 9, 15]. We hope to see these tools in the clinical arena in the future and to be able to appreciate their efficacy in CVD, as already the case for other nanocarriers in cancer [16, 17].

The release of activated oxygen from an ultrasound-activated oxygen generation nanosystem is an alternative method that has been proposed to reduce hypoxia and oxidative stress after myocardial infarction [18]. In this study, the survival of heart cells in hypoxic conditions was found to be substantially improved and the damage in the infarcted myocardial tissue to be reduced. Recently, ultrasound irradiation has also been proposed for a combination with

photodynamic therapy and chemotherapy by using albumin "Nanoglue"-based nanotheranostics. The combination approach is very promising and can achieve effectiveness in different clinical fields [19].

Recently, various nanoparticle approaches have been proposed to mimic the morphological and electrophysiological characteristics of native heart tissue for a better regenerative outcome. An overview, which provides an emphasis and discussion of the latest reports on these innovative nanoconstructs for cardiac tissue engineering, has been reported in the minireview by Kankala *et al.* [20].

CONCLUSION

Our preliminary data [8, 9] suggest that oxygenated nanocarriers given just before the heart is explanted as well as during heart transportation, either in a static position or added in a perfusion system, may improve organ conservation and performance after transplantation. Nanoconstructs for cardiac tissue engineering and controlled oxygen delivery are a promising field and represent a powerful tool to fight against many pathological conditions, including CVD. Appropriate experiments must be performed to ascertain the effectiveness and mechanism of protection of NC-O_2 nanocarriers before they are translated to the clinic.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was supported by ex 60%-RILO (MUR) and by progetto B/2021/0159 (Fondo Beneficenza San Paolo).

CONFLICT OF INTEREST

Dr. Pasquale Pagliaro is the Editorial Board Member for the journal Current Pharmaceutical Design.

ACKNOWLEDGEMENTS

The authors acknowledge Fondo di beneficenza San Paolo for the support.

REFERENCES

[1] Regional Transplant Center, Piedmont Region. Available from: 2020www.trapianti.salute.gov.it

[2] Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 2020; 17(9): 543-58. http://dx.doi.org/10.1038/s41569-020-0413-9 PMID: 32690910

[3] Pagliaro P, Thairi C, Alloatti G, Penna C. Angiotensin-converting enzyme 2: a key enzyme in key organs. J Cardiovasc Med (Hagerstown) 2022; 23(1): 1-11. http://dx.doi.org/10.2459/JCM.0000000000001218 PMID: 34091532

[4] Lionetti V, Bollini S, Coppini R, *et al.* Understanding the heart-brain axis response in COVID-19 patients: A suggestive perspective for therapeutic development. Pharmacol Res 2021; 168: 105581. http://dx.doi.org/10.1016/j.phrs.2021.105581 PMID: 33781873

[5] Pagliaro P, Aragno M, Penna C. Role of temperature in myocardial ischemic injury and protection by conditioning. Cond Med 2020; 3(1): 31-46.

[6] Guide to the quality and safety of organs for transplantation. Available from: https://freepub.edqm.eu/publications

[7] Colvin M, Smith JM, Ahn Y, *et al.* OPTN/SRTR 2019 Annual Data Report: Heart. Am J Transplant 2021; 21 (Suppl. 2): 356-440. http://dx.doi.org/10.1111/ajt.16492 PMID: 33595196

[8] Femminò S, Penna C, Bessone F, *et al*. α-Cyclodextrin and α-cyclodextrin polymers as oxygen nanocarriers to limit hypoxia/reoxygenation injury: Implications from an *in vitro* model. Polymers (Basel). 2018; 10(2): 211. doi:10.3390/polym10020211

[9] Penna C, Femminò S, Caldera F, *et al*. Cyclic nigerosyl-nigerose as oxygen nanocarrier to protect cellular models from hypoxia/reoxygenation injury: Implications from an *in vitro* model. Int J Mol Sci. 2021; 22(8):4208. doi:10.3390/ijms22084208

[10] Alfì E, Thairi C, Femminò S, *et al.* Extracellular vesicles (EVs) in ischemic conditioning and angiogenesis: Focus on endothelial derived EVs. Vascul Pharmacol 2021; 140: 106873. http://dx.doi.org/10.1016/j.vph.2021.106873 PMID: 33992781

[11] Chew HC. The donor heart and organ perfusion technology. J Thoracic Dis 2019; 11(Suppl 6): S938-45. http://dx.doi.org/10.21037/jtd.2019.02.59

[12] Terraneo L. Hemoglobin extravasation in the brain of rats exchange-transfused with hemoglobin-based oxygen carriers. Artificial cells, nanomedicine, and biotechnology 2017; 45(4): 710-6. http://dx.doi.org/10.1080/21691401.2016.1263640

[13] Pagliaro P. Differential biological effects of products of nitric oxide (NO) synthase: it is not enough to say NO. Life Sci 2003; 73(17): 2137-49. http://dx.doi.org/10.1016/S0024-3205(03)00593-9 PMID: 12927585

[14] Yu B. Hemoglobin-based red blood cell substitutes and nitric oxide. Trends Cardiovasc Med 2009; 28(9): 784-94. http://dx.doi.org/10.1016/j.tcm.2009.06.004

[15] Cavalli R, Akhter AK, Bisazza A, Giustetto P, Trotta F, Vavia P. Nanosponge formulations as oxygen delivery systems. Int J Pharm. 2010; 402(1-2): 254-257. doi:10.1016/j.ijpharm.2010.09.025

[16] Haider N, Fatima S, Taha M, *et al.* Nanomedicines in diagnosis and treatment of cancer: An update. Curr Pharm Des 2020; 26(11): 1216-31. http://dx.doi.org/10.2174/1381612826666200318170716 PMID: 32188379

[17] Ansari MA, Chung I-M, Rajakumar G, *et al.* Current nanoparticle approaches in nose to brain drug delivery and anticancer therapy - a review. Curr Pharm Des 2020; 26(11): 1128-37. http://dx.doi.org/10.2174/1381612826666200116153912 PMID: 31951165

[18] Fu H, Fu J, Ma S, Wang H, Lv S, Hao Y. An ultrasound activated oxygen generation nanosystem specifically alleviates myocardial hypoxemia and promotes cell survival following acute myocardial infarction. J Mater Chem B Mater Biol Med 2020; 8(28): 6059-68. http://dx.doi.org/10.1039/D0TB00859A PMID: 32697256

[19] Zhang Y, Wan Y, Chen Y. Ultrasound-enhanced chemo-photodynamic combination therapy by using albumin "Nanoglue"-based nanotheranostics. ACS Nano 2020; 14(5): 5560-9. http://dx.doi.org/10.1021/acsnano.9b09827

[20] Kankala RK, Zhu K, Sun XN, Liu CG, Wang SB. Cardiac tissue engineering on the nanoscale. ACS Biomaterials Science & Engineering 2018; 4(3): 800-18. http://dx.doi.org/10.1021/acsbiomaterials.7b00913