HEART FAILURE

Drug delivery using inhaled nanoparticles

“nanoparticles are bio-compatible and well tolerated”

Inhalation of peptide-loaded nanoparticles is a feasible approach for targeted delivery of drugs to the heart, according to a new study published in *Science Translational Medicine*. Drugs for myocardial diseases are currently administered orally or by injection, but these delivery pathways have limitations, such as gastric or hepatic degradation and patient discomfort and inconvenience, particularly for chronic treatment. Nanoparticle inhalation might provide a faster and more effective delivery route than either oral or intravenous administration.

Michele Miragoli, Daniele Catalucci, and colleagues had previously developed biocompatible and biodegradable, negatively charged calcium phosphate nanoparticles (CaPs) that can deliver bioactive

molecules to cardiac cells. The investigators showed *in vitro* that the CaPs (20–50 nm in diameter) can cross the cardiomyocyte cell membrane and release microRNAs inside the cell.

In the present study, the investigators first linked the CaPs to the fluorophore cyanine 7 and delivered the nanoparticles by inhalation to healthy mice. Inhalation was considered a viable delivery method because oxygenated blood from the lungs flows directly to the heart via the pulmonary veins, and because combustion-derived nanoparticles inhaled through polluted air have been detected in the heart, where they are associated with cardiac arrhythmia and dysfunction. Miragoli *et al.* found that inhalation was a more efficient method of targeted delivery to the myocardium than either enteral (gavage) or parenteral (intraperitoneal or intravenous) administration. In rats, no alterations in cardiac excitability and no immunological effects of the CaPs were detected, indicating that the nanoparticles are biocompatible and well tolerated.

The researchers had previously demonstrated the therapeutic effect of a mimetic peptide targeting a subunit of the L-type calcium channel (LTCC), which improved cardiac contractility in animals with diabetic cardiomyopathy. The investigators tested the use of inhaled CaPs to deliver the peptide to the heart.

Mice with streptozotocin-induced diabetic cardiomyopathy were treated via inhalation with CaPs bound to the LTCC mimetic peptide. Targeting of the peptide to cardiomyocytes was effective, and the treatment led to

complete recovery of cardiac function, assessed by echocardiography. The delivered peptide successfully restored LTCC protein levels, ion currents, and channel-related contractile properties. No induction of oxidative stress was observed.

Finally, the investigators demonstrated the feasibility of CaP delivery in pigs. Nebulized CaPs bound to haemagglutinin were delivered to anaesthetized pigs, and a marked haemagglutinin signal was detected in the myocardium 300 min after delivery. No changes in heart rate, blood pressure, cardiac output, left ventricular function, or respiratory function were observed.

If inhaled CaP delivery results in “higher, faster, and more selective cardiac accumulation of CaPs compared to other delivery routes”, the investigators suggest that “delivery of drugs through CaP-facilitated inhalation is thus likely to reduce the amount of required therapeutic compound, which, together with more cardiac-specific delivery, may minimize side effects compared to systemic delivery”.

As part of the EU Horizon 2020 Cupido Project (www.cupidoproject.eu), Miragoli and Catalucci are working to optimize the nanoparticle formulation and initiate a clinical trial. Ultimately, they aim “to develop a nanoparticle-based platform suitable for a cardiac-specific and patient-friendly inhalation delivery of possibly any kind of therapeutic compound”.

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ORIGINAL ARTICLE Miragoli, M. *et al.* Inhalation of peptide-loaded nanoparticles improves heart failure. *Sci. Transl. Med.* **10**, eaan6205 (2018)