Cystic Fibrosis Research News

Title:
Antibiofilm and mucolytic action of nitric oxide delivered as a gas or via macromolecular donor using in vitro and ex vivo models

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What was your research question?
Our aim was to directly compare the antibacterial and mucolytic (dissolves or breaks up mucus) efficacy of nitric oxide (NO) delivered as a gas or using a natural biopolymer modified with a NO donor.

Why is this important?
Nitric oxide (NO) is an antibacterial agent in the CF drug development pipeline for treating respiratory infections and is currently being evaluated in phase 2 clinical trials. These clinical trials have demonstrated that intermittent treatment (with intervals) with inhaled NO gas is able to reduce the amount of bacteria and fungi in the lungs of people with CF. Nitric oxide has shown both antibacterial activity against many bacteria and mucolytic action. However, the efficacy of inhaled NO gas is limited by toxicity concerns. We have developed a method to administer NO via nebulization.

What did you do?
We evaluated NO gas or NO nebulization for antibacterial, antibiofilm, and mucolytic efficacy. Nitric oxide gas was flowed across the bacteria solutions, infected tissue, biofilms, mucus, or sputum for 5 hours. Simultaneous experiments were performed with the NO-releasing biopolymer . Using an ex vivo porcine lung model, which is an ethical alternative to traditional

animal models, we evaluated the capacity of both NO gas and the NO-releasing biopolymer to reduce a bacterial *P. aeruginosa* infection. We also assessed the effects of both routes of NO exposure on biofilms, mucus, and CF sputum.

What did you find?

Higher concentrations of NO were achieved when delivered by the NO-releasing biopolymer compared to NO gas. The biopolymer was shown to significantly decrease *P. aeruginosa* viability in the infected tissue model while straight gas had little effect. Similarly, the NO-releasing biopolymer was better than NO gas at reducing biofilm viability at equivalent NO doses. Moreover, the biopolymer reduced the viability of *P. aeruginosa* biofilms (more difficult to treat than individual bacteria) at NO concentrations that were not achievable with NO gas. The mucolytic action of the biopolymer was also greater than direct gas in the treatment of human bronchial epithelial cell mucus and CF sputum.

What does this mean and reasons for caution?

The dual antibacterial and mucolytic action of NO suggests a powerful potential CF therapeutic. Our work indicates that water-soluble NO-releasing biopolymers may be more beneficial than inhaled NO gas at treating respiratory infections and reducing mucus viscosity, though studies in animals and humans are needed to verify these results.

What's next?

To utilize NO-releasing biopolymers as an inhaled therapeutic, the delivery formulation and method must be optimized while maintaining both antibacterial and mucolytic activities. We are currently investigating the best means for delivering NO-releasing biopolymers to regions deep in the lungs to eradicate chronic infections.

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