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Nitric oxide dosed in short bursts at high concentrations may protect against Covid 19

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ABSTRACT

It has long been suggested that NO may inhibit an early stage in viral replication. Furthermore, *in vitro* tests have shown that NO inhibits the replication cycle of severe acute respiratory syndrome coronavirus. Despite smoking being listed as a risk factor to contract Covid-19, only a low proportion of the smokers suffered from SARS-corona infection in China 2003, and from Covid-19 in China, Europe and the US. We hypothesize, that the intermittent bursts of high NO concentration in cigarette smoke may be a mechanism in protecting against the virus. Mainstream smoke from cigarettes contains NO at peak concentrations of between about 250 ppm and 1350 ppm in each puff as compared to medicinal use of no more than 80 to a maximum of 160 ppm. The diffusion of NO through the cell wall to reach the virus should be significantly more effective at the very high NO concentration in the smoke, according to classic laws of physics. The only oxide of nitrogen in the mainstream smoke is NO, and the NO_2 concentration that is inhaled is very low or undetectable, and methemoglobin levels are lower in smokers than non-smokers, reasonably explained by the breaths of air in between the puffs that wash out the NO. Specialized iNO machines can now be developed to provide the drug intermittently in short bursts at high concentration dose, which would then provide both a preventative drug for those at high risk, as well as an effective treatment, without the health hazards associated with smoking.

In this commentary we present a hypothesis that inhaled nitric oxide, iNO, delivered in short bursts at a high concentration, has a protective effect against Covid-19.

It has long been suggested that NO may inhibit an early stage in viral replication and thus prevent viral spread, promoting viral clearance and recovery of the host [1]. In a recent letter, Ignarro assumed this to apply also to inhalation of NO (iNO) [2], supported by findings in a previous SARS-corona epidemic. One of the authors of this commentary treated SARS patients in Beijing with iNO in a limited number of patients [3]. iNO dramatically improved arterial oxygenation, expressed as arterial oxygen tension, PaO_2, divided by the inspired oxygen fraction, FIO_2, within 2–3 days. The PaO_2/FIO_2 ratio increased from a mean of 97–260 mmHg and, as shown in Fig. 1, the transcutaneous O_2 saturation increased and respiratory support was at the same time reduced or discontinued. The 270% increase in the PaO_2/FIO_2 ratio is many times larger than commonly seen when treating ARDS patients with iNO, where an improvement by 20% is considered significant [4]. A similar low PaO_2/FIO_2 ratio (110 mmHg) was also reported in another study with a larger number of patients [5]. This suggests that the SARS patients benefitted more by iNO with marked decrease in shunt through non-ventilated lung regions than in "typical" ARDS. It turned out that pulmonary infiltrates were also reduced, suggesting an effect on the SARS pneumonia [3]. Furthermore, *in vitro* tests have shown that NO inhibits the replication cycle of severe acute respiratory syndrome coronavirus [6,7]. So, in addition to improved oxygenation, NO killed the SARS Corona virus in cell culture tests. The new pandemic, Covid-19, transmitted by the SARS-CoV-2 virus, has also caused severe impairment in oxygenation of blood. The PaO_2/FIO_2 ratio was as low as a median 77 mmHg in Covid-19 in a study from Wuhan, China, where the outbreak started [8].

Smoking is listed as a risk factor to contract Covid-19, since developing an acute lung infection on top of chronic obstructive pulmonary

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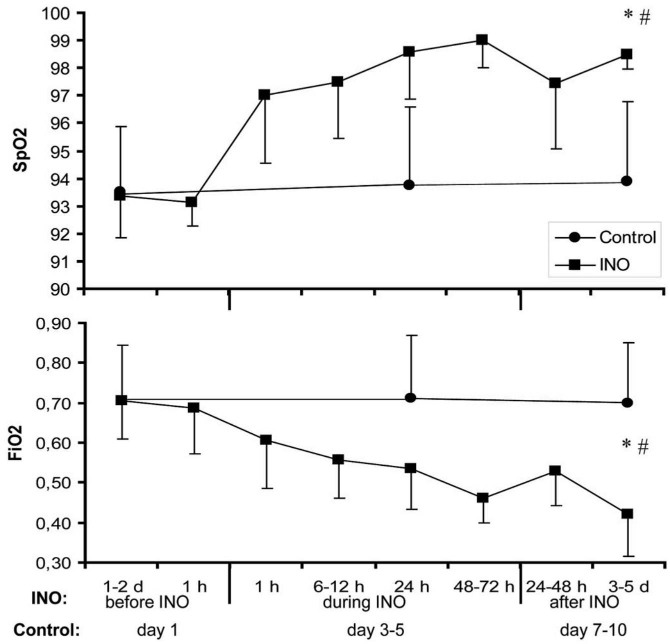

Fig. 1. Effect of inhaled nitric oxide (INO) on oxygen saturation (SpO_2), measured by pulse oximetry, (upper panel), and the inspired oxygen fraction (F_IO_2) (lower panel) in six SARS patients and eight control patients with similar severity of the disease, during mechanical ventilation for a week or more. Note the improved SpO_2 in the patients receiving INO, while at the same time F_IO_2 could be reduced. No change was seen in the control patients.
*#: significant difference between INO and control patients ($p < 0.05$)
From Chen et al., 2004 [3]. By permission of the publisher.

disease, COPD, is presumed to increase the burden on the lung. Smokers who contracted SARS in 2002–3 and Covid-19 today, had a poorer outcome [5,8]. This is in line with the report by the FDA in April 2020 that "People who smoke cigarettes may be at increased risk from Covid-19, and may have worse outcomes from Covid-19."

However, an unexpected finding was that only a low proportion of the smokers, 8%, suffered from SARS-corona infection in China 2003 [9], and in general below 10% from Covid-19 in a review of different studies in China [10]. This is much less than the proportion of male smokers in China, 52% [11], and men seem to contract the disease more frequently than women. This data implies that about 80% of the male smokers in China were protected against SARS-CoV-2 virus, but that the accumulating chronic effects of smoking increased the risk if the patient contracts the disease. High protection has also been reported in different studies in France, USA and Italy with smokers contracting Covid-19 of 5–6% and the reference population of smokers being 25.4% in the French study [12], 13.7% in the American (New York) study [13], and 14.9% in the Italian (mainly the Milan area) study [14]. Despite these results from four different countries, there is reluctance to state that smoking may be protective against Covid-19 and a meta-analysis of 19 studies concluded that smoking is a risk factor for the progression of Covid-19 [15]. However, what the meta-analysis actually shows is that if the smoker contracts Covid-19, the patient will get worse than a non-smoker, not that relatively more smokers contract the disease. The reluctance may be due to a general opposition to smoking and fear of using tobacco to prevent the ongoing pandemic [16,17].

It is not generally known that mainstream smoke from cigarettes contains NO at peak concentrations of between about 250 ppm and 1350 ppm in each puff [18,19]. The wide variation depends primarily upon the brand. The very high NO concentration in cigarette smoke as compared to medicinal use of no more than 80 to a maximum of 160 ppm, is presumably tolerated only because it is present for a single puff and then followed by numerous breaths of fresh air before the next puff. NO given as a single burst provides a similar NO intake over time, as a lower dose given continuously, since for example, 1000 ppm given for 1 breath followed by 10 breaths of air between doses is equivalent to 100 ppm given continuously. Moreover, the diffusion of NO through the cell wall to reach the virus should be significantly more effective with bursts at the very high NO concentration in the smoke, according to classic laws of physics. The only oxide of nitrogen in the mainstream smoke is NO, and the NO_2 concentration that is inhaled is very low or undetectable [20], therefore it's well-known airway irritating effect is absent or minor. Expired, endogenously produced NO, in the 0.012–0.025 ppm range [21] is known to be reduced in smokers [22], but the approximately 100,000 times higher concentrations produced by the cigarette puff more than compensates for the decrease in endogenous production. Moreover, methemoglobin levels are, if anything, lower in smokers than non-smokers [23], and the low levels can be reasonably explained by the breaths of air in between the puffs that wash out the NO.

We hypothesize, in view of our knowledge of NO and positive experience with NO inhalation in the SARS epidemic, that the intermittent bursts of high NO concentration in cigarette smoke may be a likely mechanism in protecting against the virus. To copy the intermittent high NO concentration by breathing in NO from a gas tank is problematic, since NO_2 will build up during dilution with air to potentially toxic concentrations. Pulsed short bursts of high NO concentration will require a delivery system for inhaled NO that is independent on supply from a gas tank. Such a tankless system does exist [24], and has been approved by the US FDA.

It may be recalled that there are also other components in the cigarette smoke: nicotine, carbon monoxide (another potential antiviral molecule) and many other more or less toxic components or compounds. A clinical trial has, at the time of this publication, started in France on the assumption that it is the nicotine which is the source of the protection via downregulation of the angiotensin converting enzyme-2 (ACE-2). But this mechanism has recently been questioned after the demonstration of increased airway expression of ACE-2 in smokers [25,26]. To what extent carbon monoxide and other toxic compounds play a role is not clear.

All taken together, the fact that about 56–80% fewer smokers are contracting Covid-19 in independent studies in China, Europe and the US, should stimulate an understanding of the mechanisms behind the protective effect. It seems likely from the evidence presented here that intermittent high dose NO is that compound. Specialized iNO machines can now be developed to provide the drug intermittently in short bursts at high concentration, which would then provide both a preventative drug for those at high risk, as well as an effective treatment, without the health hazards associated with smoking.

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Declaration of competing interest

The authors declare they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.niox.2020.06.005.

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