

Nitric oxide and phosphodiesterase-5 inhibitors: possible treatments for COVID-19 in diabetes

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Key words: type 2 diabetes, pulmonary microcirculation, COVID-19, nitric oxide, phosphodiesterase-5 inhibitor

Individuals with type 2 diabetes, hypertension and obesity have poor outcomes from coronavirus-19 (COVID-19). The presence of microvascular disease (retinopathy, microalbuminuria or neuropathy) is an independent risk factor for early death in COVID-19. Microvascular dysfunction is a systemic condition which includes pulmonary manifestations. Impaired gas transfer, due to microangiopathy in type 2 diabetes, suggests that individuals will be vulnerable to the pro-inflammatory state and microthrombi characteristic of 'endothelitis' in COVID-19. Drugs that improve blood flow in the intrapulmonary peri-alveolar microcirculation – namely, nitric oxide or phosphodiesterase-5 inhibitors – are therefore promising candidates for clinical trials in COVID-19.

A concerning feature of the coronavirus disease-19 (COVID-19) pandemic has been the adverse outcomes observed in individuals with diabetes, obesity and hypertension.^{1–3} People with diabetes are more likely to experience severe outcomes of hospitalisation (odds ratio 2.67, 95% CI 1.91 to 3.74),¹ with mortality rates near 10%.³ A publication comprising 7,336 patients showed the risk of fatal outcome from COVID-19 was up to 50% higher in patients with diabetes.⁴ In unadjusted analyses, higher glycated haemoglobin (HbA_{1c}) was associated with worse hospital outcomes in type 2 diabetes.⁴ However, in multivariable analyses of a large series from France,⁵ glycaemic control (HbA_{1c}) was not significant whereas the presence of macro- and/or microvascular disease are independent risk factors for early death in people with diabetes hospitalised for COVID-19. HbA_{1c} rep-

resents glycaemic exposure over the preceding 3 months whereas microvascular burden is a marker of metabolic dysfunction over an individual's lifetime.⁶ Microvascular dysfunction, in particular, is also attracting attention as a pathogenetic mechanism in COVID-19. Viral entry into pneumocytes leads to immune activation and a pro-inflammatory state in the adjacent endothelial cells of the microcirculation.⁷ Microthrombi contribute further to the impediment of microvascular blood flow through the lung.⁸ COVID-19 has therefore been considered an 'endothelitis'.⁷

The classic triad of microvascular complications of diabetes (retinopathy, neuropathy and nephropathy) are manifestations of much wider, systemic microvascular dysfunction which also affect vascular beds located in the brain, heart and lung.^{6,9} Reduced lung volumes in diabetes, determined by forced expiratory volume in 1 second (FEV₁) and vital capacity, relate to the presence of diabetes microvascular complications and glycaemic exposure,¹⁰ even after adjustment for smoking and gender. Obesity and hypertension themselves contribute to microangiopathy, with inter-relationships between impaired microvascular function, hypertension and insulin resistance.⁶

The transfer capacity of the lung (TL_{CO}) is a measure of the capacity for diffusion of oxygen across the alveolus into the microvasculature. It has been shown that, in non-smokers with type 2 diabetes but no overt cardiopulmonary disease, TL_{CO} was lower than in age-matched healthy controls – even after adjusting for cardiac output.¹¹ Importantly, individuals with evidence of microvascular dysfunction (retinopathy, microalbuminuria or neuropathy) had worse TL_{CO}.¹¹ Impairment of alveolar-capillary recruitment was evident regardless of obesity status, and suggested that parenchymal changes could impede opening or distention of alveolar capillaries. There is significant 'redundancy' of the pulmonary circulation, such that nearly 50% of gas transfer may be lost before measures of blood oxygenation diminish.¹² Therefore, the lower TL_{CO} seen in diabetes^{11,13,14} would be unlikely to manifest clinically unless a huge stressor was applied to the system. COVID-19 infection is just such a stressor. Severe COVID-19 pneumonia produces diffuse alveolar damage and widespread endothelial dysfunction and microthrombi result in matched and unmatched ventilation/perfusion (V/Q) defects, for which an individual with preceding pulmonary microangiopathy would be ill-prepared. Unlike sepsis syndromes, blood pressure and the macrocirculation appear relatively unaffected by COVID-19.¹⁵ To summarise: a drug that could improve peri-hilar microvascular recruitment may therefore improve oxygenation.

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Br J Diabetes 2020;**20**:ONLINE AHEAD OF PUBLICATION
<https://doi.org/10.15277/bjd.2020.257>

Nitric oxide

Vascular nitric oxide (NO) is critical for normal vasodilatation and endothelial function. Endogenous vascular NO production is lower in males and declines with ageing.¹⁶ Dietary interventions including nitrate¹⁷ and polyphenols such as flavanols or anthocyanins¹⁸ are potent means to enhance NO bioavailability via endothelial NO synthase (eNOS) in healthy people, and even in people with vascular disease and type 2 diabetes.¹⁹ The effect of NO is mediated by the intracellular second messenger cyclic guanosine monophosphate (cGMP). The major cGMP-degrading phosphodiesterase (PDE) is PDE5, which is abundantly expressed in normal lung tissue.²⁰ In 2004, during the SARS-coronavirus (SARS-CoV) outbreak, an open-label study of six patients in the ICU suggested that low-dose inhaled NO for three days could shorten the time of ventilatory support (compared with eight controls).²¹ Contemporaneous *in vitro* studies suggested a direct effect of NO on the replication cycle of the SARS coronavirus: the NO donor compound S-nitroso-N-acetylpenicillamine increased survival rate in SARS-CoV infected epithelial cells.²² Based on these same principles of action, trials are underway for the use of inhaled NO to prevent deterioration of mild/moderate COVID²³ and to treat established severe disease.²⁴ Inhaled NO appears preferable to another pulmonary vasodilator, epoprostenol (a prostacyclin analogue), because the latter is nebulised and requires an inline filter that must be changed every four hours. This would increase the number of times the ventilator circuit has to be opened, thereby increasing the risk of viral transmission to staff.

PDE5 inhibition

PDE5 inhibition results in increased cGMP levels and prolongs its vasodilating effects in the pulmonary vasculature. Acute administration of a single oral dose of sildenafil causes a significant decrease in mean pulmonary artery pressure and pulmonary vascular resistance, with minimal to no effect on mean arterial pressure.²⁰ It may also lead to minimal improvement in cardiac output.²⁰ Sildenafil and tadalafil have therefore proved to be a valuable treatment for pulmonary arterial hypertension, a condition characterised by endothelial dysfunction, cell proliferation and vascular remodelling of the pulmonary arteries.²⁰ Similarly, COVID-19 may lead to diffuse pulmonary intravascular coagulopathy with ventricular stress induced by pulmonary hypertension.²⁵

A further attribute of PDE5 inhibition in COVID could be to offset the ramifications of COVID-19 on angiotensin converting enzyme-2 (ACE2) expression. COVID-19 decreases surface expression of ACE2 during infection. Therefore, angiotensin II is less liable to be degraded to angiotensin-(1–7) by ACE2. Angiotensin II, acting through PDE5, causes vasoconstriction.²⁶ A tablet preparation that improves NO action in the intrapulmonary vasculature is therefore an attractive option for COVID-19. At the time of publication, one pilot study is evaluating the role of sildenafil in patients with COVID-19 (NCT04304313). This trial, and those of inhaled NO, are restricted to hospitalised patients, albeit with a broad range of disease severity. In view of their mechanism of action, speculatively, PDE5 inhibitors would be of most benefit in those with evidence of pulmonary hypertension or right ventricular dysfunction.



Key messages

- Impaired gas transfer due to microangiopathy has been reported in type 2 diabetes
- The presence of diabetic microvascular disease is an independent risk factor for early death in COVID-19
- COVID-19 can lead to microthrombi in pulmonary microvasculature
- Drugs that improve blood flow in the intrapulmonary peri-alveolar microcirculation (nitric oxide or phosphodiesterase-5 inhibitors) are being tested in clinical trials in COVID-19

Based on the background information outlined above, we propose that modulation of NO availability either via direct application, stimulation of eNOS activity or by enhancing downstream signalling by PDE5 inhibition should be considered in treatment trials of COVID-19 infection in diabetes due to their potential to offset the adverse effects of pulmonary microangiopathy.

Author contributions Conceptualisation: MBW, PV. Writing original draft: MBW, PV, PK. Writing, review and editing: CH, MDF.

Conflict of interest None

Funding None

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