


Neuroimmune interactions and COVID-19 in lung transplant recipients

Joan Arenas-Prat 


Neurogenic inflammation has a well-recognized role in the regulation of the inflammatory response to a variety of noxious stimuli, including infections. At the lung level, this response is driven by the vagus nerve by means of modulation of parasympathetic pathways that can induce bronchospasm, mucus secretion, fluid extravasation and vasodilation. Besides parasympathetic vagal fibres, these noxious stimuli activate afferent sensory C-fibres and initiate defensive reflexes that ensure airway integrity; however, they can also release inflammatory neuropeptides such as substance P or calcitonin gene-related peptide (CGRP). In a recent Perspective (De Virgiliis, F. & Di Giovanni, S. Lung innervation in the eye of a cytokine storm: neuroimmune interactions and COVID-19. *Nat. Rev. Neurol.* **16**, 645–652 (2020))¹, Francesco De Virgiliis and Simone Di Giovanni suggest a new strategy based on targeted modulation of vagal fibres to treat the life-threatening inflammatory reaction secondary to SARS-CoV-2 infection.

According to this novel therapeutic approach, based on the concept of the neuroimmune unit, patients who have undergone lung transplantation would be expected to have more adverse outcomes from COVID-19 owing to abolition of the anti-inflammatory effect of the vagus nerve by complete denervation of the lungs² — including sensory, sympathetic and parasympathetic fibres — as a result of the transplant surgery. Consistent with the authors' model, a recent multicentre study showed that, although lung transplant recipients have a clinical presentation of SARS-CoV-2 infection similar to that of the general population, they have a worse prognosis and higher mortality compared with non-transplanted patients³. However, lung transplantation also results in elimination of sensory C-fibres, which would block the release of inflammatory neuropeptides such as substance P and CGRP. This potential anti-inflammatory effect of lung denervation might contradict the authors' model, unless there is crosstalk between vagal parasympathetic and sensory neuroimmune modulation.

Neurogenic inflammation is a key process in many inflammatory conditions and its modulation or blockade offers several treatment

options. In this respect, surgical joint denervation is a well-recognized technique that improves osteoarthritic pain and synovial inflammation in the hand, where joints are densely innervated^{4,5}. Nevertheless, in the more complex scenario of a denervated lung, the hypothetical equilibrium between vagal parasympathetic and sensory neuroimmune modulation should be taken into account, and further research is needed to comprehend the precise physiopathology and the role of both types of fibre in neurogenic lung inflammation. Vagal, sympathetic and sensory neurectomy following lung denervation could exacerbate COVID-19-associated inflammation through neuroimmune modulation but in theory could also exert anti-inflammatory effects secondary to disruption of inflammatory neuropeptide release⁶.

Reply to: Neuroimmune interactions and COVID-19 in lung transplant recipients


Francesco De Virgiliis and Simone Di Giovanni 

We would like to thank Joan Arenas-Prat for his correspondence on our Perspective (Lung innervation in the eye of a cytokine storm: neuroimmune interactions and COVID-19. *Nat. Rev. Neurol.* **16**, 645–652 (2020))¹, which raises some interesting issues (Neuroimmune interactions and COVID-19 in lung transplant recipients. *Nat. Rev. Neurol.* <https://doi.org/10.1038/s41582-021-00484-x> (2021))².

In our Perspective, we proposed a novel therapeutic approach to COVID-19 based on a model of neuroimmune interaction in the lungs, in which we suggest that lung inflammation is modulated by lung-innervating nerve fibres. This model implies that targeted modulation of lung innervation, especially vagal fibres, which account for the majority of lung innervation, could help resolve life-threatening lung inflammatory reactions in pathological situations such as COVID-19.

In summary, if denervation exerts anti-inflammatory effects in the joints, could it have similar effects in the lungs?

There is a reply to this letter by De Virgiliis, F. & Di Giovanni, S. *Nat. Rev. Neurol.* <https://doi.org/10.1038/s41582-021-00485-w> (2021).

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<https://doi.org/10.1038/s41582-021-00484-x>

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Competing interests

The author declares no competing interests.



innervation, which might result in an anti-inflammatory outcome. In addition, he mentions studies in patients who underwent surgical joint denervation, which showed that loss of sensory inputs at the joint relieved osteoarthritic pain and synovial inflammation^{4,5}. On the basis of these data, the author suggests that sensory denervation could have similar effects in the lungs, which might be at odds with our model whereby vagus innervation is proposed to have a net anti-inflammatory function.

Although we agree with the author that crosstalk between vagal parasympathetic and sensory neuroimmune modulation will be taking place, the net pro-inflammatory or anti-inflammatory outcome is likely to be tissue-specific and will depend on the inflammatory stimulus. The data from Saez-Giménez B. et al.³ provide exciting clinical evidence in support of our model, as acute lung denervation due to transplant surgery

was associated with adverse outcomes from COVID-19. Indeed, in line with our proposed model, these data suggest that lack of lung innervation could worsen SARS-CoV-2 infection outcomes, mirroring the poor COVID-19 prognosis observed in elderly individuals⁶, in whom the vagal tone is reduced.

Although these data do not systematically prove our model, they strengthen the idea that the activity of vagal fibres innervating the lungs could be manipulated to prevent maladaptive inflammation in patients affected by COVID-19, and possibly by other respiratory viruses.

Lastly and most importantly, these findings strongly advocate the urgent need for systematic studies to shed light on fibre-specific tissue innervation and its interaction with the immune system in tissue-specific pathophysiological inflammatory conditions, including but not limited to COVID-19.

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<https://doi.org/10.1038/s41582-021-00485-w>

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Competing interests

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