PERSPECTIVES | The Pathophysiology of COVID-19 and SARS-CoV-2 Infection

Urgent reconsideration of lung edema as a preventable outcome in COVID-19: inhibition of TRPV4 represents a promising and feasible approach

Wolfgang M. Kuebler,1 Sven-Eric Jordt,2 and Wolfgang B. Liedtke2,3,4

1Institute of Physiology, Charité Medical University of Berlin, Berlin, Germany; 2Department of Anesthesiology, Duke University, Durham, North Carolina; 3Department of Neurology, Duke University, Durham, North Carolina; and 4Department of Neurobiology, Duke University, Durham, North Carolina

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Kuebler WM, Jordt SE, Liedtke WB. Urgent reconsideration of lung edema as a preventable outcome in COVID-19: inhibition of TRPV4 represents a promising and feasible approach. Am J Physiol Lung Cell Mol Physiol 318: L1239–L1243, 2020. First published May 13, 2020; doi:10.1152/ajplung.00161.2020.—Lethality of coronavirus disease (COVID-19) during the 2020 pandemic, currently still in the exponentially accelerating phase in most countries, is critically driven by disruption of the alveo-capillary barrier of the lung, leading to lung edema as a direct consequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We argue for inhibition of the transient receptor potential vanilloid 4 (TRPV4) calcium-permeable ion channel as a strategy to address this issue, based on the rationale that TRPV4 inhibition is protective in various preclinical models of lung edema and that TRPV4 hyperactivation potently damages the alveo-capillary barrier, with lethal outcome. We believe that TRPV4 inhibition has a powerful prospect at protecting this vital barrier in COVID-19 patients, even to rescue a damaged barrier. A clinical trial using a selective TRPV4 inhibitor demonstrated a benign safety profile in healthy volunteers and in patients suffering from cardiogenic lung edema. We argue for expedient clinical testing of this inhibitor in COVID-19 patients with respiratory malfunction and at risk for lung edema. Perplexingly, among the currently pursued therapeutic strategies against COVID-19, none is designed to directly protect the alveo-capillary barrier. Successful protection of the alveo-capillary barrier will not only reduce COVID-19 lethality but will also preempt a distressing healthcare scenario with insufficient capacity to provide ventilator-assisted respiration.

COVID-19; pulmonary edema; SARS-CoV-2; TRPV4; TRPV4 inhibitor

INTRODUCTION

At this point (April, 2020), true lethality of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections is unknown because the accurate number of infected individuals remains underdetermined (46). Any effective reduction in lethality of severe coronavirus disease (COVID-19) is urgently needed on a global scale. In particular, interventions to reduce the numbers of patients requiring assisted ventilation is critical because their numbers threaten to exceed the available ventilator capacity, a potentially catastrophic perspective (3, 51).

Here we propose the calcium-permeable transient receptor potential vanilloid 4 (TRPV4) ion channel as an underappreciated yet promising target for protecting the alveolo-capillary barrier of the lung in severe COVID-19 (Fig. 1). Clinically feasible inhibition of TRPV4 should be seriously and urgently considered as a rapidly implementable new treatment for this purpose.

THE CASE FOR INHIBITING TRPV4 IS BASED ON THE FOLLOWING 3 LINES OF EVIDENCE

1) Fortunately, the majority of patients infected with SARS-CoV-2 are not becoming critically ill. However, once SARS-CoV-2 infection progresses to the stage of pneumonia, then alveo-capillary barrier failure and ensuing formation of pulmonary edema become key pathogenic drivers toward critically ill SARS. This clinical stage shows characteristic symptoms of the acute respiratory distress syndrome (ARDS). This clinical path of SARS transitioning to critically ill SARS via alveo-capillary barrier failure is a shared hallmark of diseases caused by SARS-CoV-1, SARS-Middle East respiratory syndrome (MERS), and SARS-CoV-2 (7, 14, 22, 24, 25, 41). Recent findings in COVID-19 underscore the relevance for considering endothelial protective therapies: presence of SARS-CoV-2 in vascular endothelia, an inflammatory and pyroptotic response to it, and development of microthrombi in lungs and other organs of severely ill COVID-19 patients (4, 13, 42). Also, of note, ARDS is not a homogenous pathophysiologic entity in COVID-19. It can be based on viral injury to the air exchange apparatus of the lung, it can be immunologically mediated, and it can be combined.

2) TRPV4 channels are multimodally activated calcium-permeable cation channels that have been identified as important regulators of alveo-capillary barrier integrity, with expression in all relevant cell types of the alveo-capillary unit, namely alveolar type I and type II cells as well as alveolar capillary endothelial cells (1, 15, 31, 47, 48). Additionally, TRPV4 is expressed in and regulates the activation of innate immune cells such as alveolar macrophages and neutrophil granulocytes, which contribute to alveo-capillary barrier disruption via the release of proteases, cytokines, and reactive oxygen species (2, 11, 19, 20, 32, 35, 37, 48, 50). The critical role of TRPV4 in alveo-capillary barrier integrity was first documented in 2006 in a study demonstrating that selective TRPV4 activation results in rapid loss of alveo-capillary barrier function and subsequent formation of alveolar edema (1) (also see Fig. 2). Since then, the particular role of TRPV4 in alveo-capillary barrier regulation has been corroborated and extended in a series of preclinical studies showing protective effects of TRPV4 inhibition in models of pulmonary
edema following, e.g., mechanical overventilation, acid aspiration, or chlorine inhalation (2, 19, 20, 28, 31, 48). It was also demonstrated that TRPV4 regulates alveolo-capillary barrier integrity in a human lung-on-a-chip model (23). In several preclinical studies, including one in primates, selective TRPV4 inhibitors were shown to prevent or attenuate cardiogenic lung edema following acute left ventricular failure (40). On the other hand, a nanomolar potency TRPV4 selective activator caused lethality in several experimental animal species upon systemic injection by causing endothelial barrier failure with subsequent acute circulatory collapse and pulmonary edema (45). Recently, a gene-therapeutic approach was employed to suppress TRPV4 function via a coexpressed protein, the CD98 high-homology domain (26). Using adeno-associated virus (AAV) gene therapy vectors for transduction of human lung cells, this approach proved effective to attenuate alveolo-capillary barrier failure in a lung-on-a-chip model. Finally, exosomes derived from human adipocytes have been found to protect mice against ventilator-induced lung injury via inhibition of TRPV4-mediated calcium influx (49). Taken together, there is ample evidence for a protective effect of TRPV4 inhibition on alveolo-capillary barrier function, and different pharmacological and genetic approaches have been developed for effective targeting of TRPV4.

3) Inhibition of TRPV4 in COVID-19 patients is clinically feasible with inhibitor compounds available for clinical testing and implementation now. One particular inhibitor, GSK2798745, has been tested in phase I trials in human healthy volunteers, as
well as in patients with cardiogenic lung edema and chronic cough, and was found to be safe in all cohorts (5, 8, 9, 17, 39).

Importantly, compared with classic ARDS, which develops acutely and as such does not allow for preventive measures, COVID-19 is characterized by a gradual onset of symptoms that progress in a slow crescendo from flu-like symptoms to pneumonia and, ultimately, respiratory failure (51). As such, the COVID-19 scenario is ideally suited for adjunctive therapies such as inhibition of TRPV4. A TRPV4 inhibitor can be introduced into patients early after the onset of respiratory symptoms before their progression to a SARS-like clinical picture with the aim to stabilize the alveo-capillary barrier before its failure. Early protection of the alveo-capillary barrier before overt alveolar flooding may prove to be particularly lifesaving in regions where the needed medical infrastructure (number of ventilator beds, operated by competent intensive care teams) is insufficient against the number of patients in need with critically ill SARS. As such, TRPV4 inhibition appears as an attractive and feasible strategy to alleviate the global burden of deaths from COVID-19, which otherwise could rapidly become highly challenging. With development of COVID-19 countermeasures focusing on antivirals, vaccines, and protease-inhibitory and immunomodulatory drugs, treatment with a TRPV4 inhibitor for endothelial protection and protection of the lung’s barrier has an encouraging outlook to achieve additive or even synergistic effects (6, 10, 21, 27, 30, 43). There is also discussion about COVID-19 late sequelae of development of pulmonary fibrosis, which is suggested to depend on TRPV4 gain-of-function in pulmonary fibroblasts (18, 34). Thus, protecting the alveo-capillary barrier with a selective TRPV4 inhibitor would also be beneficial for addressing possible pulmonary fibrosis as a late consequence of COVID-19.

COMMENTARY AND CAVEATS

We argue for rapid consideration of TRPV4 inhibitory therapy that can be implemented essentially NOW for effective protection of the alveo-capillary barrier of COVID-19 patients.

Despite its clear promise, some potential restrictions and caveats should not go unmentioned. First, systemic inhibition of TRPV4 could prove problematic because of potential effects on hepatic function, a concern that is particularly relevant in the critically ill (38), yet a hepatoprotective role of TRPV4 inhibition has also been postulated in acetaminophen toxicity (12). Notably, phase I clinical trials using a selective TRPV4 inhibitor did not detect increased liver enzymes in healthy volunteers or patients with congestive heart failure (17). In regard to respiratory infections, recent studies report that TRPV4 inhibition may reduce bacterial clearance of *Pseudomonas aeruginosa* by macrophages (36). However, TRPV4 inhibition seems beneficial in lung infection with *Streptococcus pneumoniae*, the most frequent microbial cause of community-acquired pneumonia (29). Additionally, an earlier study documenting the role of TRPV4 in alveolar barrier integrity in vivo demonstrated that ventilator-induced lung injury depended on TRPV4 function in macrophages (19, 20).

Another caveat is that loss-of-function of *Trpv4* adversely affects hypoxic pulmonary vasoconstriction (16), which might be impaired already in perhaps some critically ill COVID-19 patients with severe hypoxemia (33). Inhibiting TRPV4 in these patients might worsen the hypoxemia and dysregulation further.

Although these potential caveats, rooted in preclinical studies with divergent results or in alternative explanations, need to be subjected to scrutiny in future studies, we believe that they are outweighed by the urgent need for alveo-capillary barrier-stabilizing drugs in the present COVID-19 pandemic.

Rapid clinical trials will be daunting but feasible, as the example of currently ongoing clinical trials with remdesivir in COVID-19 illustrates (44). We prefer a prospective double-blinded, placebo-controlled trial in early COVID-19 because of the rigor that such a trial will have. This will allow an outpatient setting with daily oral medication, with minimal patient contact, targeting a primary outcome of the patient needing assisted ventilation.

Taken together, we reiterate the global and urgent priority to reduce COVID-19-associated lethality and potentially disastrous burden on healthcare systems due to the need for ventilator-assisted respiration. We identify TRPV4 as a promising target to protect and rescue the integrity of the alveo-capillary barrier as an achievable milestone to avoid extremely unfortunate outcomes. Addressing this task under normal circumstances would perhaps take years. We do not have this time now and need to adapt regulatory schedules to our unprecedented current situation.

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**DISCLOSURES**

W. B. Liedtke cofounded TRPblue, a biotechnology start-up company that is aiming to commercialize TRPV4/TRPA1 dual-inhibitory compounds for treatment of chemotherapy-associated nerve pain and chronic allergic skin inflammation. Of note, none of TRPblue’s compounds would be suitable for the advocated approach because they await testing in humans and are intended for topical application to skin. S.-E. Jordt was supported by cooperative agreement U01ES015674 by the National Institutes of Health Countermeasures Against Chemical Threats (CounterACT) program to investigate the efficacy of TRPV4 inhibitors in models of chlorine inhalation injury. He received TRPV4 inhibitors from GlaxoSmithKline Pharmaceuticals for these studies. W. M. Kuebler does not have any conflicts of interest, financial or otherwise, to disclose.

**AUTHOR CONTRIBUTIONS**

W.M.K. and W.B.L. prepared figures; W.M.K., S.-E.J., and W.B.L. drafted manuscript; W.M.K. and W.B.L. edited and revised manuscript; W.M.K., S.-E.J., and W.B.L. approved final version of manuscript.

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