Robert P. Dickson, M.D.
*Department of Internal Medicine*
*University of Michigan Medical School*
*Ann Arbor, Michigan*

*Department of Microbiology and Immunology*
*University of Michigan Medical School*
*Ann Arbor, Michigan*

and

*Michigan Center for Integrative Research in Critical Care*
*Ann Arbor, Michigan*

ORCID IDs: 0000-0003-1363-1525 (J.M.B.); 0000-0002-6875-4277 (R.P.D.).

### References

1. Gleeson K, Eggli DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. *Chest* 1997;111:1266–1272.
2. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. *Am J Med* 1978;64:564–568.
3. Dickson RP, Erb-Downward JR, Freeman CM, McCloskey L, Falkowski NR, Huffnagle GB, *et al*. Bacterial topography of the healthy human lower respiratory tract. *mBio* 2017;8:e02287-16.
4. Dickson RP, Erb-Downward JR, Falkowski NR, Hunter EM, Ashley SL, Huffnagle GB. The lung microbiota of healthy mice are highly variable, cluster by environment, and reflect variation in baseline lung innate immunity. *Am J Respir Crit Care Med* 2018;198: 497–508.
5. Segal LN, Alekseyenko AV, Clemente JC, Kulkarni R, Wu B, Gao Z, *et al*. Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation. *Microbiome* 2013;1:19. [Published erratum appears in *Microbiome* 2:21.]
6. Segal LN, Clemente JC, Tsay JC, Koralov SB, Keller BC, Wu BG, *et al*. Enrichment of the lung microbiome with oral taxa is associated with lung inflammation of a Th17 phenotype. *Nat Microbiol* 2016;1: 16031.
7. Wu BG, Sulaiman I, Tsay J-CJ, Perez L, Franca B, Li Y, *et al*. Episodic aspiration with oral commensals induces a MyD88-dependent, pulmonary T-helper cell type 17 response that mitigates susceptibility to *Streptococcus pneumoniae*. *Am J Respir Crit Care Med* 2021;203:1099–1111.
8. Lloyd CM, Marsland BJ. Lung homeostasis: influence of age, microbes, and the immune system. *Immunity* 2017;46:549–561.
9. Shenoy AT, Wasserman GA, Arafa EI, Wooten AK, Smith NMS, Martin IMC, *et al*. Lung $CD4^+$ resident memory T cells remodel epithelial responses to accelerate neutrophil recruitment during pneumonia. *Mucosal Immunol* 2020;13:334–343.
10. Gauguet S, D'Ortona S, Ahnger-Pier K, Duan B, Surana NK, Lu R, *et al*. Intestinal microbiota of mice influences resistance to Staphylococcus aureus pneumonia. *Infect Immun* 2015;83:4003–4014.
11. Noverr MC, Noggle RM, Toews GB, Huffnagle GB. Role of antibiotics and fungal microbiota in driving pulmonary allergic responses. *Infect Immun* 2004;72:4996–5003.
12. Mac Aogáin M, Tiew PY, Lim AYH, Low TB, Tan GL, Hassan T, *et al*. Distinct "Immunoallertypes" of disease and high frequencies of sensitization in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2019;199:842–853.
13. Di Guardo G, Agrimi U, Morelli L, Cardeti G, Terracciano G, Kennedy S. Post mortem investigations on cetaceans found stranded on the coasts of Italy between 1990 and 1993. *Vet Rec* 1995;136:439–442.
14. Venn-Watson S, Daniels R, Smith C. Thirty year retrospective evaluation of pneumonia in a bottlenose dolphin Tursiops truncatus population. *Dis Aquat Organ* 2012;99:237–242.





# Mitigating Viral Dispersion during Respiratory Support Procedures in the ICU

Over the past year, the world has been in the grip of a pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The coronavirus is causing an ever-increasing number of infections globally and to date is responsible for infection in more than 124 million individuals and more than 2.73 million deaths. SARS-CoV-2 infection can cause serious hypoxemia that requires hospitalization in approximately 20% of infected individuals. Depending on the severity of their illness, 10–25% of hospitalized patients need ICU admission and ventilator assistance.

Various modalities are employed for the treatment of patients hospitalized with coronavirus disease (COVID-19), the disease caused by SARS-CoV-2. Besides antiviral drugs, immune-based therapy, monoclonal antibodies, and convalescent plasma, prone positioning and supplemental oxygen are essential adjunctive measures for relief of hypoxemia. An assortment of interfaces for delivery of supplemental oxygen, including nasal prongs, facemasks of various types, high-flow nasal oxygen (HFNO), or oxygen supplementation with noninvasive ventilation (NIV), are routinely used in critically ill patients.

Aerosols are generated during many respiratory support procedures. Among the aerosol-generating procedures (AGPs) identified by the CDC (1) and the World Health Organization (2) in the ICU, endotracheal intubation, open suctioning, tracheotomy, manual ventilation, and bronchoscopy stimulate coughing and deep respirations and could increase production of bioaerosols containing pathogens from infectious patients. Other AGPs disperse aerosols to the environment (e.g., oxygen administration with nasal prongs or facemasks, HFNO, and NIV) (3). The dispersion effects of the virus in ambient air rely on the amount of virus production, particle size of patient-generated droplets, and the speed and distance of transportation (3). Aerosols generated by these latter AGPs produce "fugitive emissions," comprising a mixture of aerosols generated by the device and bioaerosols from the patient. The role of fugitive emissions in enhancing the spread of viruses to bystanders or healthcare workers has been a matter for debate (4).

In this issue of the *Journal*, Avari and colleagues (pp. 1112–1118) used a mannequin that simulated the breathing pattern of spontaneously breathing patients with mild to moderate respiratory



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distress and exhaled a constant breath-to-breath viral load of a bacteriophage generated by a vibrating mesh nebulizer as a surrogate for SARS-CoV-2 (5). They simulated the clinical situation in a negative-pressure ICU room. Viral dispersion was quantitated at various locations in the room during invasive mechanical ventilation via a cuffed orotracheal tube and a filter placed at the expiratory port of the ventilator and was compared with noninvasive respiratory support using nasal prongs, HFNO, a nonrebreather face mask with N99 high-efficiency particulate air filter, helmet ventilation with positive end-expiratory pressure (PEEP) valve, and bilevel positive-pressure NIV (5). The lowest bacteriophage concentrations occurred during invasive mechanical ventilation, whereas the highest concentrations were recorded while using HFNO or nasal prongs. Moreover, viral concentrations were highest closer to the mouth and lower toward the foot end of the bed. The variability in bioaerosol dispersion led the investigators to conclude that the risk of transmitting infection, and appropriate infection control, differs among several respiratory procedures used in the ICU (5).

Ideally, Avari and coinvestigators would have reported on aerosol generation during intubation and extubation of the mannequin because a burst of aerosol generation during these procedures could pose a significant risk of spreading infection (6). Such a comparison would provide a balance of the risks associated with mechanical ventilation versus other noninvasive respiratory support procedures. However, such a study requires exploring aerosol generation during a whole range of clinical scenarios involving intubation and extubation of critically ill patients.

A major strength of Avari and colleagues' investigation was to use a bacteriophage to model viral exposure, unlike previous studies that used nonviral particles (References 17–21 in Reference 5). Viruses can spread in the hospital environment by airborne transmission. Tang and colleagues generated an aerosol of live attenuated influenza virus with a jet nebulizer from a mannequin, and when a home jet nebulizer and simple mask was used, they found viral contamination in the environment that decreased with increasing distance from the mouth (7). Lednicky and coworkers used a liquid sampling system placed 2–4.8 m away from a patient with COVID-19 and demonstrated live virions of SARS-CoV-2 in the hospital room even in the absence of AGPs (8). In hospital rooms with patients with COVID-19, SARS-CoV-2 contamination should be expected, especially in the ICU environment (9). Although live virions are present at low concentrations and only in a small percentage of air samples (9), it is essential to reduce exposure to the virus and protect healthcare workers.

Avari and colleagues reported that viral aerosol dispersion was reduced to levels comparable to those seen with invasive mechanical ventilation when a helmet device fitted with a PEEP valve was used (5). Likewise, in previous investigations it was reported that connecting a filter to an oxygen mask (e.g., HiOx Oxygen mask [Novus Medical Inc] or Respan's Tavish mask) reduced aerosol dispersion (10). In spontaneously breathing patients on HFNO, placing a surgical mask on the patient's face or using tissue to cover the mouth or nose could reduce the dispersion distance (11) or virus load (12). Adopting appropriate personal protective measures markedly reduces the risk of transmitting SARS-CoV-2 during AGPs (3, 13). In the initial phases of the pandemic, intubation and invasive mechanical ventilation was preferred over NIV and HFNO to diminish aerosol spread. However, with a better understanding of the transmission of SARS-CoV-2 (3), many centers have advocated a more conservative approach to oxygen supplementation in hypoxemic patients with COVID-19 that relies on initiating NIV or HFNO for critically ill patients in whom invasive mechanical ventilation is not essential (14, 15). The investigation by Avari and colleagues (5) highlights the need for further study of SARS-CoV-2 contamination in ICU environments. Furthermore, when NIV or HFNO are used in patients with COVID-19, it is all the more important to develop new methods and devices and promote other control measures that reduce the transmission of SARS-CoV-2 and mitigate the risk to healthcare workers in the ICU. ■

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Rajiv Dhand, M.D., F.R.S.M.
*Department of Medicine*
*University of Tennessee Graduate School of Medicine*
*Knoxville, Tennessee*

ORCID ID: 0000-0002-3621-2422 (R.D.).

## References

1. Centers for Disease Control and Prevention. Clinical questions about COVID-19: questions and answers. [accessed March 23, 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html.
2. World Health Organization. Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed. [accessed March 23 2021]. Available from: https://apps.who.int/iris/handle/10665/339151.
3. Dhand R, Li J. Coughs and sneezes: their role in transmission of respiratory viral infections, including SARS-CoV-2. *Am J Respir Crit Care Med* 2020;202:651–659.
4. Fink JB, Ehrmann S, Li J, Dailey P, McKiernan P, Darquenne C, *et al*. Reducing aerosol-related risk of transmission in the era of covid-19: an interim guidance endorsed by the International Society of Aerosols in Medicine. *J Aerosol Med Pulm Drug Deliv* 2020;33:300–304.
5. Avari H, Hiebert RJ, Ryzynski AA, Levy A, Nardi J, Kanji-Jaffer H, *et al*. Quantitative assessment of viral dispersion associated with respiratory support devices in a simulated critical care environment. *Am J Respir Crit Care Med* 2021;203:1112–1118.
6. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012;7:e35797.
7. Tang JW, Kalliomaki P, Varila TM, Waris M, Koskela H. Nebulisers as a potential source of airborne virus. *J Infect* 2020;81:647–679.
8. Lednicky JA, Lauzardo M, Fan ZH, Jutla A, Tilly TB, Gangwar M, *et al*. Viable SARS-CoV-2 in the air of a hospital room with COVID-19 patients. *Int J Infect Dis* 2020;100:476–482.
9. Birgand G, Peiffer-Smadja N, Fournier S, Kerneis S, Lescure FX, Lucet JC. Assessment of air contamination by SARS-CoV-2 in hospital settings. *JAMA Netw Open* 2020;3:e2033232.
10. Somogyi R, Vesely AE, Azami T, Preiss D, Fisher J, Correia J, *et al*. Dispersal of respiratory droplets with open vs closed oxygen delivery masks: implications for the transmission of severe acute respiratory syndrome. *Chest* 2004;125:1155–1157.

11. Hui DS, Chow BK, Chu L, Ng SS, Lee N, Gin T, *et al*. Exhaled air dispersion during coughing with and without wearing a surgical or N95 mask. *PLoS One* 2012;7:e50845.
12. Johnson DF, Druce JD, Birch C, Grayson ML. A quantitative assessment of the efficacy of surgical and N95 masks to filter influenza virus in patients with acute influenza infection. *Clin Infect Dis* 2009;49:275–277.
13. Liu M, Cheng SZ, Xu KW, Yang Y, Zhu QT, Zhang H, *et al*. Use of personal protective equipment against coronavirus disease 2019 by healthcare professionals in Wuhan, China: cross sectional study. *BMJ* 2020;369:m2195.
14. Tobin MJ. Basing respiratory management of COVID-19 on physiological principles. *Am J Respir Crit Care Med* 2020;201: 1319–1320.
15. Daniel P, Mecklenburg M, Massiah C, Joseph MA, Wilson C, Parmar P, *et al*. Non-invasive positive pressure ventilation versus endotracheal intubation in treatment of COVID-19 patients requiring ventilatory support. *Am J Emerg Med* 2021;43: 103–108.





# The Yin and Yang of the Renin–Angiotensin–Aldosterone System in Acute Kidney Injury

Despite intensive research, the pathophysiology of acute kidney injury (AKI) in critical illnesses remains poorly understood, as do the links between AKI and poor outcomes. Post–cardiac surgery AKI is not exempt. Multiple, heterogeneous mechanisms are likely in play. Hemodynamic factors, systemic inflammatory response, and cardiopulmonary bypass–induced hemolysis certainly contribute (1, 2). Other contributing factors remain unrecognized or underexplored, such as the complex role of the renin–angiotensin–aldosterone system (RAAS) (3).

In a fascinating study published in this issue of the *Journal*, Küllmar and colleagues (pp. 1119–1126) report the association between postoperative plasma renin level and the risk of developing AKI after cardiac surgery (4). Plasma renin levels measured 4 hours after cardiopulmonary bypass were strongly associated with AKI, whereas preoperative values were not. Patients with higher postoperative plasma renin levels and higher changes in plasma renin compared with preoperative values (Δ-renin) developed more AKI than patients with lower levels and smaller changes. Patients with AKI had a median (interquartile range) rise in plasma renin of 99.6 μU/ml (6.7, 318.0; $P < 0.001$). This Δ-renin was the strongest predictor of postoperative AKI in the study (area under the curve–receiver operating characteristic, 0.817) and superior to urinary AKI biomarkers DKK3 and [TIMP-2]* [IGFBP7].

The primary hypothesis of the authors is that an angiotensin II deficit occurs after cardiac surgery to explain these findings. In a feedback loop, renin is released in response to decreased activation of the AT1R (angiotensin II type 1 receptor) by angiotensin II (Figure 1, Scenario 1). This can be caused by either impaired generation of angiotensin II or AT1R blockade. Angiotensin II is produced when the endothelial membrane–bound enzyme ACE (angiotensin-converting enzyme) cleaves angiotensin I. Conditions associated with endothelial dysfunction, such as septic shock or cardiopulmonary bypass, can reduce ACE activity, decrease angiotensin II, and increase renin levels (5, 6). Decreased expression of AT1R was also reported in sepsis-associated AKI (7). This hypothesis is supported by several findings in Küllmar and colleagues, including higher and more prolonged vasopressor requirements, high Δ-renin levels, and higher renin over aldosterone ratio in patients with AKI. Of note, although patients treated with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB) had higher plasma renin levels and overall higher risk of AKI, no interaction was found between ACEi/ARB therapy and Δ-renin for predicting AKI.

An alternative hypothesis to that of Küllmar and colleagues is that significant activation of the RAAS occurs after cardiac surgery (with consequently high angiotensin II tone), triggering intrarenal vasoconstriction, decrease in renal blood flow, and regional inflammation (Figure 1, Scenario 2). Unfortunately, plasma angiotensin II levels were not available in the study, thus making it impossible to definitively distinguish the two possibilities. The alternate hypothesis is supported by lower blood pressures (a trigger for RAAS activation) in the group with AKI and supranormal plasma levels of both renin and aldosterone after surgery (8). Furthermore, there are many reports of decline in renal blood flow associated with elevated intrarenal vascular resistance and increased angiotensin II levels after cardiac surgery (9, 10). In this line, the use of intrarenal vasodilators has long been proposed to decrease the risk of post–cardiac surgery AKI.

## What Are the Implications of This Study?

This study clearly demonstrates that plasma renin elevation after cardiac surgery is associated with AKI risk and strongly implicates the RAAS. The RAAS clearly holds a pivotal pathophysiologic role in cardiovascular and renal diseases, including AKI (11). Elevated plasma renin is associated with poor outcomes both in chronic conditions such as heart failure and acute conditions such as vasodilatory shock. A *post hoc* analysis of the ATHOS-3 trial (angiotensin II versus placebo in catecholamine-resistant vasodilatory shock, defined as a need for norepinephrine >0.2 μg/kg/min) demonstrated that high plasma renin was associated with a risk of death and nonrecovery from AKI (6, 12). Angiotensin II has long been known as a mediator of renal injury in the subacute and chronic settings. Angiotensin II promotes



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