References

1. Filewod NC, Lee WL. Inflammation without vascular leakage: science fiction no longer? *Am J Respir Crit Care Med* 2019;200:1472–1476.
2. Wong HK, Cheung TT, Cheung BM. Adrenomedullin and cardiovascular diseases. *JRSM Cardiovasc Dis* 2012;1:1–7.
3. Voors AA, Kremer D, Geven C, Ter Maaten JM, Struck J, Bergmann A, *et al*. Adrenomedullin in heart failure: pathophysiology and therapeutic application. *Eur J Heart Fail* 2019;21:163–171.
4. Brusse-Keizer M, Zuur-Telgen M, van der Palen J, VanderValk P, Kerstjens H, Boersma W, *et al*. Adrenomedullin optimises mortality prediction in COPD patients. *Respir Med* 2015;109:734–742.
5. Singh JSS, Burrell LM, Cherif M, Squire IB, Clark AL, Lang CC. Sacubitril/valsartan: beyond natriuretic peptides. *Heart* 2017;103: 1569–1577.
6. Geven C, Blet A, Kox M, Hartmann O, Scigalla P, Zimmermann J, *et al*. A double-blind, placebo-controlled, randomised, multicentre, proof-of-concept and dose-finding phase II clinical trial to investigate the safety, tolerability and efficacy of adrecizumab in patients with septic shock and elevated adrenomedullin concentration (AdrenOSS-2). *BMJ Open* 2019;9:e024475.

Reply to Mehmood

From the Author:

I thank Dr. Mehmood for his comments. I agree that the pathological importance of vascular leakage extends far beyond sepsis and acute lung injury (acute respiratory distress syndrome) to include diverse syndromes such as heart failure (1, 2), renal failure (3), and connective tissue diseases (4). In my opinion, this reflects the fact that increased endothelial permeability is usually maladaptive, given the detrimental effects of tissue edema. Furthermore, severe vascular leakage may be difficult for the body to remediate, given the limited ability of the mature endothelium to proliferate (5).

As we enter the era of clinical trials for agents that stabilize the vascular barrier (6), it is important to remember that multiple cellular and molecular mechanisms exist for vascular leakage. These include endothelial apoptosis (7), pyroptosis (8), and remodelling of endothelial cell–cell junctions and the cellular cytoskeleton (9). The success of drugs aimed at reducing vascular leakage in clinical trials may therefore depend on the cause of the leakage and the mechanism of action of the drug. Nonetheless, given its ubiquity in clinical medicine, the prospect of either harnessing (10) or counteracting vascular leakage without impairing the immune response (11) is an intriguing prospect for clinicians. ■

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References

1. Thorneloe KS, Cheung M, Bao W, Alsaid H, Lenhard S, Jian MY, *et al*. An orally active TRPV4 channel blocker prevents and resolves pulmonary edema induced by heart failure. *Sci Transl Med* 2012;4: 159ra148.
2. Friedrich EE, Hong Z, Xiong S, Zhong M, Di A, Rehman J, *et al*. Endothelial cell Piezo1 mediates pressure-induced lung vascular hyperpermeability via disruption of adherens junctions. *Proc Natl Acad Sci USA* 2019;116:12980–12985.
3. McCurley A, Alimperti S, Campos-Bilderback SB, Sandoval RM, Calvino JE, Reynolds TL, *et al*. Inhibition of $\alpha v\beta 5$ integrin attenuates vascular permeability and protects against renal ischemia-reperfusion injury. *J Am Soc Nephrol* 2017;28:1741–1752.
4. Zhu W, London NR, Gibson CC, Davis CT, Tong Z, Sorensen LK, *et al*. Interleukin receptor activates a MYD88-ARNO-ARF6 cascade to disrupt vascular stability. *Nature* 2012;492:252–255.
5. Tannock IF, Hayashi S. The proliferation of capillary endothelial cells. *Cancer Res* 1972;32:77–82.
6. Geven C, Blet A, Kox M, Hartmann O, Scigalla P, Zimmermann J, *et al*. A double-blind, placebo-controlled, randomised, multicentre, proof-of-concept and dose-finding phase II clinical trial to investigate the safety, tolerability and efficacy of adrecizumab in patients with septic shock and elevated adrenomedullin concentration (AdrenOSS-2). *BMJ Open* 2019;9:e024475.
7. Sugiyama MG, Armstrong SM, Wang C, Hwang D, Leong-Poi H, Advani A, *et al*. The Tie2-agonist vasculotide rescues mice from influenza virus infection. *Sci Rep* 2015;5:11030.
8. Cheng KT, Xiong S, Ye Z, Hong Z, Di A, Tsang KM, *et al*. Caspase-11-mediated endothelial pyroptosis underlies endotoxemia-induced lung injury. *J Clin Invest* 2017;127:4124–4135.
9. Goldenberg NM, Steinberg BE, Slutsky AS, Lee WL. Broken barriers: a new take on sepsis pathogenesis. *Sci Transl Med* 2011;3:88ps25.
10. Sugiyama MG, Mintsopoulos V, Raheel H, Goldenberg NM, Batt JE, Brochard L, *et al*. Lung ultrasound and microbubbles enhance aminoglycoside efficacy and delivery to the lung in E*scherichia coli*-induced pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2018;198:404–408.
11. Filewod NC, Lee WL. Inflammation without vascular leakage: science fiction no longer? *Am J Respir Crit Care Med* 2019;200:1472–1476.

Importance of Occupational Exposure Data: A National Idiopathic Pulmonary Fibrosis Registry Perspective

To the Editor:

We read with interest the insightful opinion provided by Nett and colleagues regarding the importance of gathering