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REPLY: We would like to thank Wang et al. (3) for their interest in and comment on our article. Since the first report of ketamine cystitis by Shahani et al. (2) 10 years ago, the mechanism of this new urinary dysfunction is still a mystery. Ketamine is accumulated in urine, and urothelial ulceration is commonly observed in severe ketamine cystitis patients, which might be the major reason for the hypothesis that ketamine disrupts urothelial barrier function and causes ketamine cystitis. Several recent articles also indicate a detrimental effect of ketamine on urothelial cells (1).

Urothelial cells form the tightest barrier in our body, which allows the bladder to temporarily store urine toxins. Recent research also indicates that the superficial cells of the urothelium are mechanosensory and undergo dramatic membrane trafficking in response to urine filling and emptying. Our key finding is that we observed voiding dysfunction by voiding spot assay and cystometrogram, but the barrier function is intact. We used a ketamine dosage that was sufficient to induce voiding dysfunction, but no urothelial abnormality could be detected, which indicates that ketamine-induced voiding dysfunction precedes the emergence of barrier dysfunction. We do agree with the comment that the urothelial barrier likely plays some role in the pathogenesis of ketamine cystitis, allowing urine to leak into the bladder interstitial spaces and aggravate the cystitis and voiding dysfunction. We tend to believe that this disrupted barrier is not due to direct toxicity, but is more likely a secondary effect of ketamine, affecting perhaps mechanosensory function and membrane trafficking. We also should bear in mind that there are extensive pathological changes in the other bladder tissues of ketamine cystitis patients, including neuronal and myogenic. It is also worth noting that not all patients have disrupted barrier function. We therefore strongly believe that ketamine might disrupt some yet unknown cellular pathways which causes extensive pathological changes in the bladder and also other organs. Understanding these ketamine-affected signal pathways will be critical for the treatment of ketamine cystitis.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS
W.Y. edited and revised manuscript; W.Y. approved final version of manuscript.

REFERENCES

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