Response to letter by Dr. M. S. A. Mohamed (Antagonizing reactive oxygen species during lung perfusion)

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TO THE EDITOR: We thank Dr. M. S. A. Mohamed for his insightful comments regarding our recent paper on endothelial mechanosignaling and its implications in lung transplant (1). We are glad that, as emphasized by our article, the author agrees that the use of KATP channel agonist(s) would be a good strategy to reduce oxidative damage during storage of lungs. Our suggested use of a KATP agonist (in this case cromakalim) in the (lung) graft preservation solution is based on our signaling studies showing that depolarization resulting from closure of this channel drives reactive oxygen species (ROS) production with ischemia (2, 3, 6).

Dr. Mohamed suggests another possibility. He raises the point that ischemia reperfusion (I/R) with lung transplant is akin to ischemic preconditioning, or IPC, which has widely been reported to be protective in several organs. The protection afforded by IPC arises, in part, from activation of KATP channels. Thus, based on the IPC model, use of a KATP agonist would be an obvious choice for reduction of oxidative damage. But although the protective effect of IPC or multiple short episodes (1–3 min) of ischemia followed by reperfusion are known in the central nervous and cardiac systems, there are relatively limited data related to the effects of IPC on lungs. Besides the storage of lungs and the standard EVLP (ex vivo lung perfusion) technique does not mimic an IPC maneuver per se (the ischemic times are considerably longer and range between 1–6 h and the reperfusion too is for longer periods). However, it is possible, as suggested by the author, that having short periods of ischemia, with a period of perfusion between them for EVLP, may reduce oxidative damage. The IPC effect with lung I/R has often been via systemic preconditioning by other remote organ ischemia (such as hind limb or heart) (4, 5). Thus further study of the role of IPC in lung I/R and on the EVLP maneuver is warranted.

As suggested by Dr. Mohamed, antagonizing ROS by addition of antioxidants to the lung preservation solution would (by blocking oxidative damage and the inflammation cascade) be a reasonable protective strategy. Thus the hydrogen gas therapy with EVLP may hold promise due to its antioxidant effects but this has been incompletely assessed till date. Alternatively, inhibiting the cascade that leads to ROS production with lung I/R rather than scavenging ROS after they are produced may be a better approach. This is partly because protective antioxidant therapy has had a mixed clinical response so far and because theoretically it is difficult for a ROS scavenger to compete with tissue components for reaction with ROS.

Of course, this is not to indicate that the addition of antioxidants either alone or in combination with KATP agonist(s) to the lung perfusate or storage solution would have no additional protective effect. Signaling upon transplant represents the amalgamation of several events. Besides I/R, immunological, inflammatory, and attendant innate immune responses also play a role in oxidative damage and the pathogenesis of graft dysfunction. Understanding these pathways and how they intersect can help identify agents that can attenuate the signaling events that drive this pathogenesis. In this direction, our article highlights how our understanding of the events in the pulmonary endothelial “mechanosignaling” cascade can translate into inclusion of agents in the preservation solution of lung grafts.

REFERENCES


