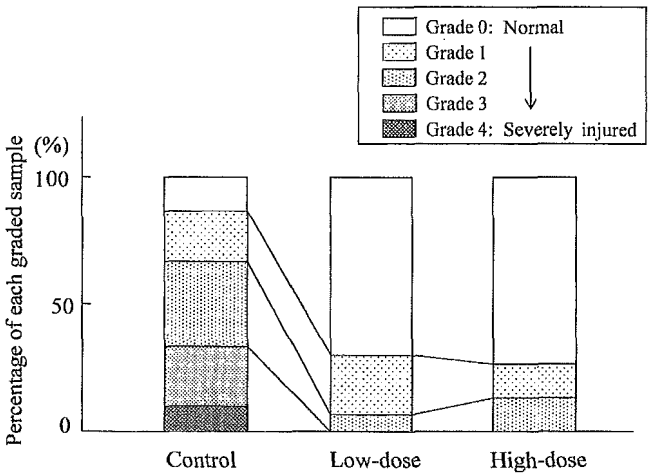

Fig. 4. Severity of mucosal injury during acute hypoxia. The degree of mucosal injury was graded on a scale of 0–5, with 0 considered normal and 5 representing severe cell disruption. Data are expressed as percentage of 27–28 fields. Control = normal saline; low-dose = 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ olprinone infusion; high-dose = 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ olprinone infusion. Chi-square test showed significant difference between control and two olprinone groups.

of activated leukocytes is considered a cause of exaggerated ischemia under inflammatory conditions.[2,23] Previous studies showed that hypoxia increased "vascular permeability" through the reduction of cyclic 3',5' adenine monophosphate (cAMP) levels in endothelial cells.[24] If such mechanism also works in "mucosal permeability" of the gut, olprinone, a phosphodiesterase III inhibitor, may antagonize hypoxia-induced alterations of cAMP contents through its original action to elevate intracellular cAMP, subsequently preserving cellular barrier function.[20,25] Further investigation is now under way to address whether involvements of inflammatory cells and intramucosal cAMP levels could be modulated by olprinone infusion in this model.

Because of its microcirculatory properties and redistribution of blood flow under insult, the gut mucosal layer is considered vulnerable to any type of reduction in oxygen delivery, such as ischemic, anemic, or hypoxic hypoxia.[26] Among them, hemorrhagic shock causing both ischemic and anemic hypoxia has been well investigated to elucidate the pathophysiology of bacterial translocation.[18,27] In this experiment, we applied hypoxic hypoxia to examine alterations of gut mucosal integrity under noninflammatory impacts and found that structural changes in gut mucosa caused by acute progressive hypoxia were ameliorated with olprinone infusion. Although the current study was not aimed at clarifying the presence of bacteria in mesenteric lymph nodes or portal blood by cultures, such findings as the alterations in pHi, portal endotoxin level, and mucosal structures indicated a possibility that olprinone infusion minimized the risk of bacterial translocation.

There are several limitations to the interpretation of the data reported. First, it could be argued that our study protocol was able to mirror the clinical situation. To mimic the clinical situation, we first determined the dose of olprinone infusion to augment CI to approximately 20% in rabbits. Then, we confirmed that one third of such an olprinone dose did not increase CI at normoxia. Even at a low-dose infusion, however, olprinone infusion attenuated hypoxia-induced myocardial suppression and subsequent hypoperfusion of the splanchnic area observed in the control group, indicating that characteristic profiles of olprinone, *i.e.*, the redistribution of blood flow to splanchnic circulation, was preserved without apparent augmentation of systemic blood flow. On the other hand, acute progressive hypoxia in this study might be too severe to mimic the clinical situation, according to high lethality in the control group. Second, some may argue that other pharmacologic interventions to augment CI show protective roles for splanchnic organs and an outcome that are similar to that of olprinone. In this experimental setting, we found no changes in pHi and mucosal structures between the low- and high-dose olprinone groups, although both $spDO_2$ and $spVO_2$ in the high-dose group were significantly greater than in the low-dose group at severe hypoxia. Previous studies demonstrated that dopamine infusion caused an imbalance between oxygen demand and supply in the splanchnic region because of flow redistribution away from the gut mucosa.[3,4] Also, we previously showed that epidural anesthesia protected gut integrity and minimized translocation of endotoxin under similar experimental conditions compared with dobutamine infusion alone,[6] indicating that augmentation of CI is not a key component for protection of intramucosal integrity of the gut under our protocol. Rather, olprinone possibly augments mucosal microcirculation by modulating distribution of blood flow within the gut. Finally, we applied air tonometry to obviate the confounding factors of saline tonometry, such as long equilibration period, temperature correction, and bias produced by the type of blood gas analyzers.[16,28] Although the values of pHi remain controversial,[29] tissue hypoxia of the gut in the current study design was caused by arterial hypoxemia, indicating that $PrCO_2$ should be similar to $Paco_2$ because of prompt removal of anabolically generated carbon dioxide from the tissues under high-flow dysoxic conditions.[17]

In conclusion, olprinone infusion preserves redistribution of blood flow to the splanchnic area and slows the progression of gut mucosal injury during acute hypoxia through both flow-dependent and -independent mechanisms. This property of olprinone may serve to prevent translocation of endotoxin, indicating a possibility that olprinone protects the host under insult.

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