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| 学位論文の題名 | Macitentan reverses early obstructive pulmonary vasculopathy in rats: Early intervention in overcoming the survivin-mediated resistance to apoptosis<br>（マシテンタンはサバイビンを介した細胞死抵抗性を低下させてラットの早期肺血管閉塞病変をリバースさせる）<br><br>American Journal of Physiology - Lung Cellular and Molecular Physiology<br>DOI: 10.1152/ajplung.00129.2014 |
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**Background:** It remains unknown whether current disease-targeting therapy can histologically reverse obstructive pulmonary vasculopathy and how the timing of the therapy influences the antiremodeling effects of the compound. **Objective:** We test the hypothesis that a novel endothelin receptor antagonist macitentan reverses the early and/or late stages of occlusive pulmonary vascular disease (PVD) in rats.

**Methods:** Rats with pulmonary arterial hypertension (PAH), which were produced by combined exposure to a vascular endothelial growth factor receptor inhibitor Sugen 5416 and hypobaric hypoxia for 3 wk, were assigned to receive macitentan or vehicle during 3–5 wk (early study) or during 5–8 wk (late study) after Sugen injection.

**Results:** Compared with vehicle-treated PAH rats and PAH rats evaluated before treatment initiation, the macitentan-treated rats showed decreases in the proportion of occlusive lesions in the early study, a finding consistent with the reversal of right ventricular systolic pressure and indexes of right ventricular hypertrophy and medial wall thickness. Macitentan ameliorated but did not reverse the proportion of occlusive lesions in the late study. Although macitentan decreased the proportion of Ki67+ lesions in both studies, macitentan increased the proportion of cleaved caspase 3+ lesions and suppressed an antiapoptotic molecule survivin expression in the early study but not in the late study.

**Conclusion:** macitentan reversed early but not late obstructive PVD in rats. This reversal was associated with the suppression of survivin-related resistance to apoptosis and proliferation of cells in PVD.