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COMMENT

Response to Michiel Alexander de Raaf et al.

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We sincerely appreciate your interest in and opinions about our article. Here is our reply.

Regarding your concerns about potential emphysema, we believe the histopathological assessments in our study (Fig. 2A from the original article which is commented), including hematoxylin and eosin staining, Masson's trichrome staining, Verhoeff-Van Gieson staining, and immunofluorescence staining for caspase-3, have provided convincing evidence that no significant emphysema was observed in either the Sugen-only rats or Sugen/hypoxia (SuHx) rats, even at 8 weeks, which is contrary to the results in some of the previous studies [1–3].

Regarding the occlusive intimal changes, Toba et al. previously showed significant pulmonary vascular luminal obstruction in SuHx-PH (pulmonary hypertension) rats [4]. Similarly, our data also indicated pulmonary vascular luminal obstruction, reflected by the scoring performed on Verhoeff-van Gieson-stained slides as follows: no evidence of neointimal formation (grade 0), partial luminal occlusion (<50%; grade 1), and severe luminal occlusion (>50%; grade 2) (Fig. 3A from our original article which is commented).

It is well known that the pulmonary arterial pressure (PAP) can be predicted and calculated based on the cardiac output (CO) and pulmonary vascular resistance (PVR) with the formula $PAP = CO \times PVR$. The intraluminal radius of pulmonary arterioles plays a decisive roles in PVR [5]. However, the number of vessels in the lung affects the cross-sectional area for blood circulation. A decreased number of vessels also leads to increased PVR. It has been reported that vascular endothelial growth factor (VEGF) and VEGF receptor 2 are critical factors affecting endothelial cell survival [6, 7] and angiogenesis [8, 9]. Therefore, Sugen may not only lead to pulmonary vascular occlusion but also induce damage and the loss of microvessels, which would mean that the degree of pulmonary vascular remodeling cannot fully explain the degree of right ventricle (RV) failure in the Sugen-only model. There is evidence that microvascular alterations occur in the RV [10, 11]. In the Sugen model, the RV microvasculature is dysfunctional and not comparable [12]. Therefore, the reduction in CO in Sugen-only rats to almost the same degree as that observed in SuHx rats was supposedly caused not only by the change in afterload but also by the direct toxic effect of Sugen.

The greatest significance of our study is that it provides more relevant models for studying the pathogenesis of pulmonary hypertension caused by endothelial dysfunction and pulmonary vascular remodeling with different severities.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The manuscript has been approved by all authors for publication. This study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University.

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