Pulmonary blood flow distribution is impaired in two distinctly different forms of pulmonary hypertension

Pulmonary arterial hypertension (PAH) is a common adverse complication associated with several cardiopulmonary pathologies, and has a bleak long-term prognosis. The underlying mechanisms governing the pathogenesis of PAH remain poorly understood, which is partly due to the varying etiologies for PAH, such as that caused by monocrotaline (MCT) and chronic hypoxia (CH) [2,5]. Indeed, the literature seems to suggest that both the cellular signal pathways that are involved in the pathogenesis of these forms of PAH, and the resultant morphological changes in the pulmonary vasculature, may differ between CH and MCT [1,2,5]. Whether these cellular and morphological differences between MCT and CH ultimately culminate in differing patterns of pulmonary blood flow distribution is not currently known. Yet, it is these changes in blood flow distribution, regardless of etiology, which are responsible for the adverse increase in pulmonary arterial pressure (PAP). In this study, we aimed to assess the changes in pulmonary blood flow distribution following MCT-induced PAH, and compare it with CH-induced PAH. We utilized SR microangiography, which has enhanced sensitivity to contrast material and superior visualization of pulmonary vessels compared to more conventional angiography methods. The results from this study will help to ascertain whether the nature of change in pulmonary blood flow distribution in two distinctly different models of PAH is etiology-dependant.

All experiments were performed at beamline **BL28B2**. We used control rats and rats with PAH, which was induced by either (i) injecting monocrotaline (60 mg/kg, sc.) three weeks prior to experimentation or, (ii) exposing rats to chronic hypoxia (10% O_2) for 4 weeks [3]. On the day of experimentation, rats were anesthetized and surgically prepared for pulmonary microangiography as previously described [4]. Angiogram images of the pulmonary microcirculation were recorded during air-breathing (baseline) and following the 4 min of acute hypoxia (8% O_2); before and after sympathetic beta-adrenoreceptor blockade (propranolol, 2 mg/kg i.v.).

Using SR, we could clearly visualize pulmonary vessels, ranging from the main axial artery (~1200 μm) to the 4th generation of branching (> 80 μm), in the left lung of control rats as well as rats with PAH, induced with either MCT or CH (Fig. 1). Importantly we observed that rats with PAH, regardless of etiology, had significantly fewer perfused vessel branches of the 4th generation compared to normal-rats (Fig. 2). This reduction in parallel blood flow in the hypertensive lung is the leading causal factor for the increase in pulmonary vascular resistance and, consequently, pulmonary arterial pressure.

Interestingly, the magnitude of acute hypoxic pulmonary vasoconstriction (HPV) was not modified by either form of PAH. Beta-adrenoreceptor blockade (propranolol) accentuated the magnitude of HPV in

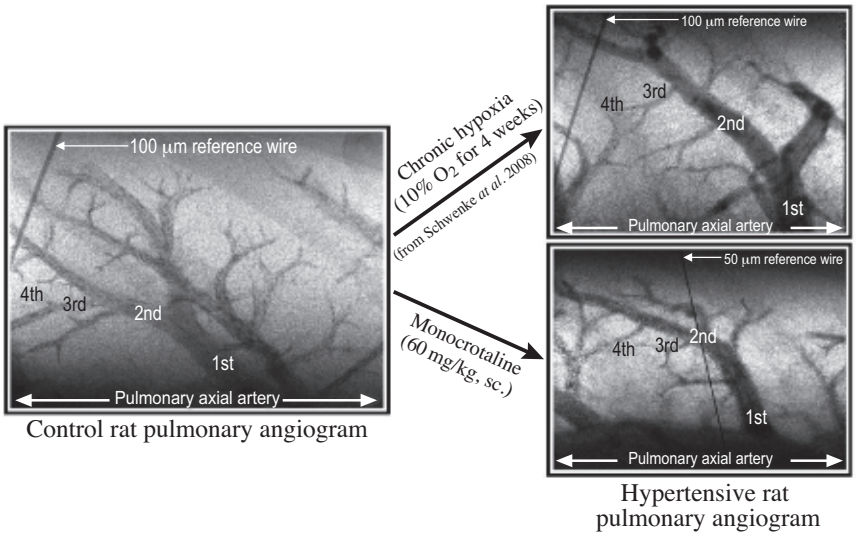

Fig. 1. Typical microangiogram images showing the first 4 branching generations of small pulmonary arteries in control rats (n = 7) and rats with PAH, induced with either chronic hypoxia (n = 5; TOP) or monocrotaline (n = 7; BOTTOM).

both control-rats and PAH-rats, particularly in the 300-500 μm sized vessels. However, in only those PAH-rats that were exposed to CH, did beta-blockade also accentuate the HPV in 100-200 μm vessels (Fig. 3).

In summary, we have utilized the resource of SR microangiography to show that the adverse changes in pulmonary blood flow distribution in the hypertensive lung are comparable between MCT and CH models. We also demonstrated that the acute HPV was not altered in both forms of PAH, although sympathetic modulation of pulmonary vasoreactivity becomes critically important in the CH-model, but not the MCT-model. Both models of PAH represent specific types of PAH typically observed in humans and, therefore, such differences between the two PAH models should be considered in future studies, especially those studies investigating potential therapeutic interventions for a specific form of PAH.

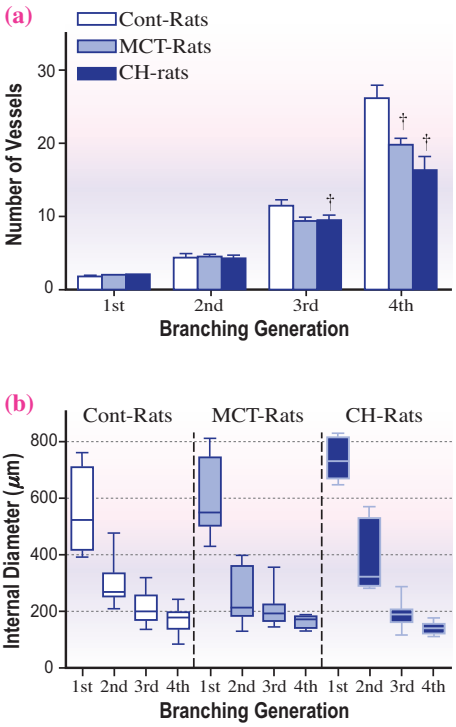

Fig. 2. **(a)** The distribution of blood flow through the pulmonary circulation was impaired in PAH, evident by a decrease in the number of perfused vessel, particularly those of the 3rd and 4th generation, in PAH rats compared to control rats († $P < 0.05$). There was no significant difference between MCT-rats (n = 7) and CH-rats (n = 5). **(b)** The range in vessel size for each branching generation did not change following the development of PAH.

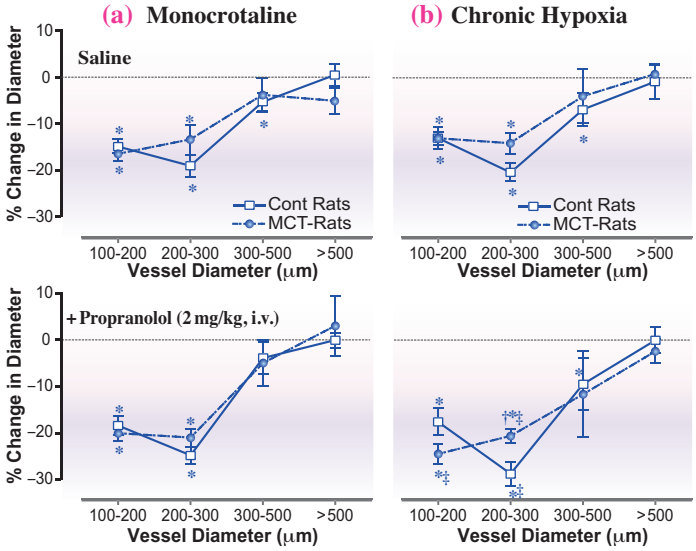

Fig. 3. The magnitude of vasoconstriction (% decrease in vessel diameter) during acute hypoxia in control-rats and rats with PAH induced either by (i) CH for 4 weeks, or (ii) a single injection of monocrotaline. Sympathetic β-adrenergic blockade was achieved using propranolol (2 mg/kg, i.v.). * Significant response to acute hypoxia ($P < 0.05$). † Significant difference between control-rats and CH-rats ($P < 0.05$). ‡ Significant effect by propranolol administration ($P < 0.05$).

Daryl O. Schwenke [a,*], Keiji Umetani [b] and Mikiyasu Shirai [c]

[a] Department of Physiology, University of Otago, New Zealand
[b] SPring-8 / JASRI
[c] Department of Cardiac Physiology, National Cerebral and Cardiovascular Research Institute, Japan

*E-mail: daryl.schwenke@stonebow.otago.ac.nz

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