

## **RESULTS**

### ***Time Course of RV Systolic Pressure by Two Dimensional Echocardiography***

In the parasternal short axis view on echocardiography, the ratio of the short diameter to the long diameter of LV in the end-systolic phase was calculated, and we evaluated the change of RV systolic pressure using this ratio as an index of the degree of PH (37, 38). Changes in this ratio are shown in Fig. 2. The ratio in Control healthy group did not change on Day 7, 14, and 19 from baseline (Day 1) value (Fig. 2). The ratio in PH group was markedly decreased on Day 14, and the ratio was progressively decreased on Day 19 (Fig. 2). On Day 19, the decrease in the ratio in PH+TA group and PH+BPS group was inhibited to a similar extent (Fig. 2). The decrease in the ratio in PH+TA+BPS group was markedly inhibited compared to that in PH+TA group and PH+BPS group (Fig. 2).

### ***Hemodynamic Measurements***

Systemic systolic blood pressure was as follows; Control healthy group:  $117\pm 5$  mmHg, PH group:  $95\pm 3$  mmHg, PH+TA group:  $105\pm 3$  mmHg, PH+BPS group:  $105\pm 4$  mmHg, and PH+TA+BPS group:  $104\pm 4$  mmHg. It was significantly lower in PH groups with or without treatments compared with Control healthy group; however it did not differ among 4 PH groups. As an index of PH, we measured RV systolic pressure and calculated the ratio of RV systolic pressure to systemic systolic blood pressure ( $P_p/P_s$ ), and they are shown in Fig. 3. RV systolic pressure and  $P_p/P_s$  were much greater in PH group than in Control healthy group (Fig. 3). They were comparably lower in PH+TA group and PH+BPS group than in PH group (Fig. 3). These indices were lowest in PH+TA+BPS group among PH rats with treatments (Fig. 3).

### ***Weight Measurements***

Before injection of MCT or saline, there was no difference between in the body weight (BW) of each group: Control healthy group,  $133\pm 2$  g; PH group,  $131\pm 3$  g; PH+TA group,  $133\pm 3$  g; PH+BPS group,  $135\pm 3$  g; and PH+TA+BPS group,  $131\pm 2$  g. On Day 19, the BW of each group

was as follows: Control healthy group,  $277\pm 5$  g; PH group,  $245\pm 5$  g; PH+TA group,  $246\pm 7$  g; PH+BPS group,  $240\pm 3$  g; and PH+TA+BPS group,  $236\pm 7$  g. On Day 19, it was significantly lower in PH group with or without treatments compared with Control healthy group; however, it did not differ among 4 PH groups. The ratios of RV wet weight to BW and of RV wet weight to LV wet weight were markedly higher in PH group than in Control healthy group (Fig. 4). They were comparably lower in PH+TA group and PH+BPS group (Fig. 4). These indices were lowest in PH+TA+BPS group among PH rats with treatments (Fig. 4).

#### ***Expression of $\alpha$ - and $\beta$ -Myosin Heavy Chain (MHC) mRNA in RV***

We used the ratio of the expression of  $\beta$ -MHC mRNA to  $\alpha$ -MHC mRNA as a molecular marker for ventricular hypertrophy. The ratio of the expression of  $\beta$ -MHC mRNA to  $\alpha$ -MHC mRNA in RV was markedly higher in PH group (Fig. 5). The increase was comparably depressed in PH+TA group and PH+BPS group (Fig. 5); furthermore, the ratio was almost normalized in PH+TA+BPS group (Fig. 5).

#### ***Histology of Lungs***

The medial wall thickness of the pulmonary artery was evaluated by the ratio of medial wall thickness to external diameter, and the results are shown in Figs. 6 and 7. The medial wall thickness in PH group was about 1.4-fold greater than in Control healthy group (Figs. 6 and 7). The ratio tended to be lower in PH+TA group or PH+BPS group compared to PH group (vehicle treatment), however, it showed no statistical significance among PH group, PH+TA group, and PH+BPS group (Fig. 7). On the other hand, the ratio showed the lowest value in PH+TA+BPS group among PH rats of 3 treatment groups and the statistical significance was observed between PH group and PH+TA+BPS group (Figs. 6 and 7).