Bosentan and Overcirculation-Induced Experimental Pulmonary Arterial Hypertension

To the Editor:

In the article by Rondelet et al., the authors report data obtained from a model of increased pulmonary blood flow induced by a left-to-right shunt after creation of an anastomosis between the left subclavian artery and the pulmonary artery (Blalock-Taussig shunt) in piglets aged 20±1 days and weighing 5.9±0.2 kg. After an observation period of 90±1 days, the animals underwent reinvention for hemodynamic evaluation.

With respect to the hemodynamic data as given in Table 2 of their paper, the mean systemic arterial pressure was reported to be 131 to 133 mm Hg in the 3 groups of farm piglets studied under general anesthesia. This implicates an unusually high systemic arterial pressure in their animals; other groups have reported the mean systemic arterial blood pressure to be ~87 mm Hg (range, 60 to 103 mm Hg, depending on the anesthetic regime used), which is similar to our own findings. Especially in the group treated with bosentan, a substance known to lower both pulmonary and systemic arterial blood pressure, one would expect a lower mean systemic blood pressure compared with a sham or placebo group. But this was not the case in the series of Rondelet and coworkers. Taking into account that the increase in pulmonary artery pressure achieved by the Blalock-Taussig anastomosis was small in relation to the high systemic arterial blood pressure achieved by the anastomosis, the model presented by Rondelet’s group reflects pulmonary vascular disease induced by high pulmonary blood flow without an important elevation in pulmonary artery pressure.

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Response

Ullmann and colleagues criticize our paper on overcirculation-induced pulmonary arterial hypertension in piglets on the basis of an excessively high systemic arterial pressure, an absence of significant systemic vasodilating effects of bosentan, and only a moderate increase in pulmonary artery pressure.

The porcine blood pressure has been reported variably in the literature, depending on strain, cardiac output, and anesthetic regimen. Many investigators also measured relatively high mean systemic arterial pressures, in the range of 111 to 135 mm Hg. It is likely that blood pressure is normally higher in pigs than in many other species, including humans.

The absence of a decrease in blood pressure under chronic bosentan therapy has also been noted in patients with pulmonary arterial hypertension, indicating a more important role for endothelin in abnormally increased pulmonary vascular resistance than in the maintenance of normal systemic hemodynamics. As for the pulmonary hemodynamic measurements, it must be emphasized that pulmonary artery pressure was measured after closure of the Blalock-Taussig anastomosis and control of venous return to correct for any flow-related component of induced pulmonary hypertension. Under these conditions, pulmonary vascular resistance increased by 57% as a result of an 80% increase in medial thickness of resistive arterioles. Mean pulmonary artery pressure increased to 33 mm Hg. This is admitted lower than in patients with pulmonary arterial hypertension, who present with mean pulmonary artery pressures of ~50 mm Hg. However, the change was highly significant and was compatible with relatively early stages of the disease, which is exactly what we wanted to study.

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