Pulmonary blood pressure can be increased on the precapillary side of the lung in PH Groups 1 (pulmonary arterial hypertension [PAH]), 3 (PH due to lung diseases and/or hypoxia), 4 (chronic thromboembolic pulmonary hypertension [CTEPH]), and 5 (PH with unclear multifactorial mechanisms); postcapillary hypertension corresponds to Group 2 (PH due to left heart disease) (Simonneau et al. 2013; Galiè et al. 2009). In patients, PH can be diagnosed and quantified by right heart catheterization, which also discriminates between post- and precapillary PH. Secondary to the increased PA blood pressure, exercise capacity in patients with PH is significantly decreased, and due to the pressure overload of the right heart induced by increased pulmonary vascular resistance (PVR), morphological changes of the right heart occur that may lead to right heart failure.

Effective animal models and corresponding readout parameters are essential to test PH drugs in the preclinical setting. Exercise capacity, accurate hemodynamic measurements, and advanced imaging tools are necessary to correctly categorize, quantify, and monitor disease progression and regression of PH in animal models. Exercise capacity can be assessed using treadmill testing. However, there are multiple determinants of maximal exercise capacity, including right and left ventricular function, pulmonary function, skeletal muscle function, and activity of the peripheral and central nervous systems. A complete hemodynamic assessment is needed to fully understand PH animal models, including PVR measurement and left and right heart catheterization to exclude PH Group 2. In rodent and other animal models used to study PH, the normal PA pressure is the same as that in healthy humans. However, in rats and mice the heart rate is 5–10 times faster than in humans. Pulmonary hemodynamics are optimally measured in lightly anesthetized, closed-chested animals. Although cannulating the PA is faster and requires less expertise in the open-chest preparation, opening the thorax falsely reduces cardiac output, heart rate, and PA pressures (particularly end-diastolic pressures). Imaging and even longitudinal imaging of the heart to follow morphological and functional changes in animal models can be performed with the same modalities used routinely in clinics, such as ultrasound imaging, magnetic resonance imaging (MRI), or computed tomography (CT). In addition, after dissection of the animal at the end of the study, the right and left ventricle weight can be measured to determine the hypertrophy of the right heart (Ryan et al. 2009).

Recently, the soluble guanylate cyclase (sGC) stimulator riociguat has been approved to treat PH Groups 1 (PAH) and 3 (CTEPH), thereby providing a novel approach for the treatment of different forms of PH (Ghofrani et al. 2013a,b). An important part of the development program for riociguat included a broad in vitro and in vivo pharmacologic characterization of this new pharmacologic principle; sGC stimulation was performed, including hemodynamic studies in different animal models, long-term studies in experimental cardiovascular diseases models, and studies in the target indication PH. sGC stimulators have shown beneficial effects in animal models with different underlying pathologies of acute and chronic PH. Improvements in clinically relevant parameters such as decreased pulmonary blood pressure as well as remodeling of the heart and vessels have been demonstrated. These animal models include ischemia-reperfusion injury-induced