

## Evaluation of pulmonary arterial hypertension: invasive or noninvasive?

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In medical research animal models have demonstrated their value in elucidating (1) mechanisms of disease, (2) factors implicated in morbidity and mortality of the disease, and (3) new therapeutic avenues to treat the disease. For acute as well as chronic diseases, models for translational medicine have been developed and applied with great benefit. The use of experimental animals should comply with both the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals in which researchers demonstrate that they have carefully considered the three R's of animal testing alternatives: (1) Reduction of the numbers of animals used, (2) Refinement of techniques and procedures to reduce pain and distress, and (3) Replacement of animals by other models than living animals. Particularly the condition to reduce the number of animals necessary to test a hypothesis is difficult to meet, but the use of animal models and techniques that allow longitudinal measurements from the same animals may lead to a wealth of data from a limited number of animals. In translational research of cardiovascular disease the use of echocardiography allows longitudinal studies of natural history and therapeutic success.

In the current issue of the *International Journal of Cardiovascular Imaging*, Koskenvuo and coworkers [1] used echocardiography in a rat model of monocrotaline-induced pulmonary arterial hypertension (PAH). The authors evaluated whether invasive measurements of blood pressures, vascular resistances, right ventricular (RV) wall thickness and RV cavity size could be replaced accurately by corresponding echocardiographic measurements. The authors succeeded to acquire echocardiographic images that produced parameters of PAH with low (<10%) intra-observer and low inter-observer variability, except for tissue Doppler derived isovolumetric relaxation time of the RV (IVRT') having an interobserver variability of 22.2%. Regarding diagnostic performance of echocardiographic parameters to detect PAH, i.e. a mean pulmonary arterial pressure >25 mmHg, the authors found a sensitivity of 86.4%, a specificity of 97.6%, a positive predictive value of 92.3%, and a negative predictive value of 93.8%. At day 21, noninvasive assessment of PAH demonstrated large differences between invasively measured systolic PAP and echocardiographically assessed systolic PAP ( $39.5 \pm 15.5$  and  $66.4 \pm 18.8$  mmHg, respectively) and between invasively measured total pulmonary vascular resistance (TPVR) and echocardiographically assessed TPVR ( $3.5 \pm 2.3$  and  $7.7 \pm 2.8 \cdot 10^4 \text{ dyn.s.cm}^{-5}$ ). The authors held these large differences responsible to the absence of significant tricuspid valve regurgitation (TR) jet in several rats with developing PAH. This seems a very likely explanation as at day 35 both

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Editorial Comment onto the article of Koskenvuo et al.  
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invasively measured systolic PAP and TPVR approached echocardiographically assessed systolic PAP and TPVR much better. Of note, TPVR has not previously been studied in rodents using echocardiography. It was concluded that the use of non-invasive parameters may replace invasive measurements in detecting successful disease induction and to complement invasive data in the evaluation of PAH severity in a rat model.

The difficulty of performing invasive measurements in animals with advanced PAH is an important limitation of all invasive parameters and underscores the importance of innovative noninvasive measurements. The highly vulnerable status of the RV and more generally of the heart in rats with severe PAH often hampers extensive characterization of RV function with the pressure-conductance catheter as we have experienced ourselves [2–4]. As a result, echocardiography may have a specific new role in evaluating PAH. The main disadvantage of electrocardiographic assessment of PAH is to accurately assess the functional characteristics of RV. In the present study, in 13 out of 75 (17%) studies no adequate echocardiographic RV measurements could be performed. Generally, assessment of the RV is cumbersome by echocardiography due to limited acoustic window and the abnormal shape of the RV [5–16]. These limitations might be to a certain extent overcome by using transesophageal or 3D-echocardiography [17–21], but magnetic resonance imaging often provides a better visualization of the RV, allowing improved quantification [22–33].

In the current study [1], however, it was clearly shown that employment of echocardiography in animals allows assessment of in vivo RV function without additional harm to the animals. In addition, echocardiography enabled longitudinal measurements thereby lowering the number of animals included in the study. Knowledge and experience in echocardiography of small rodents, so elegantly shown by the authors, is hard to acquire but this is certainly the way to go in future translational research of chronic cardiovascular diseases.

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