Executive Summary

Pulmonary hypertension refers to increased blood pressure in the pulmonary artery, vein and capillaries.

Most of the animal work being done is in the areas of pulmonary arterial hypertension, pulmonary venous hypertension and thrombotic/embolic pulmonary hypertension, in animal models, has long been hindered by the lack of a fast, portable, high-resolution, research and animal focused imaging system that can visualize cardiac function, structure and blood flow \textit{in vivo}, in real-time and most importantly, non-invasively.

Luckily, VisualSonics’ revolutionary Vevo® micro-ultrasound system satisfies all the above criteria, allowing researchers to collect a plethora of important data over the lifespan of animals, thereby significantly reducing the number of animals needed. Flow velocities, ejection fractions and cardiac output can be quantified within seconds, while software such as VevoStrain™ provides sophisticated analysis of speckle tracking and myocardial strain that are on the cutting edge of research.

Numerous satisfied Vevo customers from institutions such as Harvard, Johns Hopkins and Mouse Imaging Center (MICe) are publishing articles in leading journals such as Cell, Science, PNAS and Nature Medicine. This is a testament of the power and versatility of high-resolution ultrasound.
Background on Pulmonary Hypertension

Pulmonary hypertension refers to increased blood pressure in the pulmonary artery, vein and capillaries. Its causes can be classified according to 5 categories set by the World Health Organization:


2. Pulmonary venous hypertension: associated with left side valvular or myocardial diseases. Failure of the left heart to pump blood efficiently leads to pooling of blood in the lungs, causing pulmonary edema and pulmonary effusions.

3. Pulmonary hypertension associated with disorders of the respiratory system or hypoxemia: this category refers to diseases such as COPD that causes inadequate oxygenation of arterial blood as a result of lung disease, impaired control of breathing or high altitude.

4. Pulmonary hypertension caused by thrombotic or embolic diseases: this includes embolisms due to clots in pulmonary arteries or embolism of other matters such as tumors or parasites.

5. Pulmonary hypertension caused by diseases affecting the pulmonary vasculature: caused either by inflammatory processes or mechanical obstructions.

From the above list, most of the animal research done currently involves categories 1, 2 and 4. Coincidentally, it is also in these three categories that Vevo systems by VisualSonics can play a significant role in helping researchers streamline experiment design and data collection.
Animal Research in Pulmonary Hypertension and Examples of Micro-Ultrasound

Most research done in the area of pulmonary arterial hypertension is via mice and rat strains, with some work being done on piglets and calves. Of these, rats are most commonly used because of their ease of handling and large enough size to perform surgeries on. Similarly, rats are also often used to study left ventricular dysfunction.

The primary cause of death for patients with PAH is high right ventricular afterload leading ultimately to right heart failure and right ventricular function is the most important determinant of longevity. Because of this, much of the research being done on PAH involves determining ventricular thickness and pulmonary artery blood velocity. One recent example of this was when Bogarrd et al. used the Vevo 770 system to obtain two dimensional M-Mode and Doppler imaging from rats to determine RV inner diameter, free wall thickness, septal thickness in diastole and systole, pulmonary artery diameter and velocity time index.

An additional example of micro-ultrasound in pulmonary hypertension research is demonstrated by Summer et al. who used the Vevo 770 system to quantify left ventricular dimension, percent fractional shortening, left ventricular mass index, anterior wall thickness and posterior wall thickness. In addition, the peak velocity and acceleration of the pulmonary artery was measured by Pulsed-wave Doppler and the ratio of early to late filling wave was determined via transmitral Pulsed-wave Doppler velocity.

Recently, Toporsian et al. used the Vevo 770 to study mice heart and great vessels under the effects of increased endothelial oxidative stress. This was achieved through the Vevo’s ability to record the dynamic changes in chamber/lumen dimensions and RV stroke volume. In addition, the isovolumetric contraction, relaxation and ejection times were measured. By combining micro-ultrasound with micro-CT scanning of the mice lungs, the authors were able to further validate their results. This is a demonstration of the power and versatility of the Vevo system in combination with other imaging modalities to help researchers achieve their goals.

Figure 2: Flow in mouse pulmonary artery
Market Research and VisualSonics’ Value Proposition

Many of the animal models are used to determine therapeutic drug effects, which often lead to arterial and vasculature remodeling. Furthermore, as discussed earlier, measures of cardiac function and left and right ventricular parameters are also extremely important. Traditionally, these can only be determined via surgical catheters, dissection or MRI imaging. However, the first two methods are troublesome and often fatal, resulting in large numbers of animals required to obtain significant results. Furthermore, animals cannot be studied over long periods in order to observe vascular remodeling and hypertrophy over time. MRI, on the other hand, is expensive and not readily available to most researchers in the laboratory setting. With the Vevo, researchers now have access to a tool to visualize these animals in real-time and in vivo, with images approaching MRI quality.\(^6\) Below is a summary of the unique value proposition VisualSonics delivers to researchers with the Vevo micro-ultrasound systems:

1. Non-invasive, in vivo, real-time imaging, especially useful for imaging processes that happen over a period of time, such as wall hypertrophy and diseases associated with chronic and acute exacerbations, such as COPD.

2. High-resolution (30 µm) imaging to observe pulmonary arteries, veins and tricuspid valves in murine models.

3. Monitoring flow rates, ejection fractions, cardiac output in anesthetized or conscious animals.

4. Detecting flow velocity, direction and regurgitation with Color Doppler Mode.

5. 3D visualization of the heart.

6. Cutting edge analysis of longitudinal, circumferential and radial strain and strain rate, including velocity and displacement, on myocardial wall with VevoStrain based on speckle tracking.

7. Dedicated animal platform to monitor ECG, heart rate, body temperature and respiration rates.

![Figure 3: Doppler flow through tricuspid valve](image-url)
References


