A novel right-heart catheterization technique for in vivo measurement of vascular responses in lungs of intact mice

HUNTER C. CHAMPION, DOUGLAS J. VILLNAVE, ALLEN TOWER, PHILIP J. KADOWITZ, AND ALBERT L. HYMAN
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Champion, Hunter C., Douglas J. Villnave, Allen Tower, Philip J. Kadowitz, and Albert L. Hyman. A novel right-heart catheterization technique for in vivo measurement of vascular responses in lungs of intact mice. Am. J. Physiol. Heart Circ. Physiol. 278: H8–H15, 2000.—The present study employed a new right-heart catheterization technique to measure pulmonary arterial pressure, pulmonary arterial wedge pressure, and pulmonary vascular resistance in anesthetized intact-chest, spontaneously breathing mice. Under fluoroscopic guidance, a specially designed catheter was inserted via the right jugular vein and advanced to the main pulmonary artery. Cardiac output was determined by the thermodilution technique, and measured parameters were stable for periods of ≤3 h. Pressure-flow curves in vivo were curvilinear, with mean pulmonary arterial pressure increasing more rapidly at low pulmonary blood flows of 5–10 ml/min and less rapidly at higher blood flow rates. The pressure-flow relationship was shifted to the left by the nitric oxide synthase inhibitor nitro-L-arginine methyl ester (L-NAME) at higher blood flow levels, whereas the cyclooxygenase inhibitor sodium meclofenamate was without effect. The increase in pulmonary arterial pressure in response to acute hypoxia (fractional inspired O2 10%) was augmented by L-NAME but unaltered by sodium meclofenamate. The present results demonstrate that the right-heart catheterization technique can be used to measure pulmonary vascular pressures and responses in the mouse. This is, to our knowledge, the first report of a right-heart catheterization technique to measure pulmonary vascular pressures and responses in the intact-chest, spontaneously breathing mouse and should prove useful for the investigation of pulmonary vascular responses in transgenic mice.

cardiac output; pulmonary vascular bed; mouse; vascular resistance; pressure-flow relationship; acute hypoxia; nitric oxide

THE ABILITY TO PRODUCE targeted gene mutations in the mouse represents a powerful tool for studying physiological and pathophysiological roles of receptors and gene products in the intact mammal (17, 21, 24). New mouse models are being developed using gene knockout and gene overexpression strategies to investigate the functional role of overexpression or deletion of gene products to determine their role in physiological regulation (17, 21, 24). Although a great deal of information has been obtained using molecular techniques, it is clear that in vitro and in vivo studies of the phenotypes are required for a full understanding of the physiological significance of genetic alterations (5, 6, 14, 17, 21, 24). Moreover, it is becoming increasingly clear that many of the newly developed strains of mice exhibit unexpected phenotypes that have been discovered only after in-depth studies (5, 6, 14, 17, 21, 24, 36).

Cardiovascular studies have been carried out in mice through the miniaturization of catheter-transducer systems and have yielded information on systemic arterial pressure, heart rate, cardiac output, and left ventricular (LV) function in both conscious and anesthetized animals (5, 6, 13, 14, 17, 21, 24, 30, 31, 36). Pulmonary arterial pressure has been reported recently using an open-chest mouse model with direct puncture and catheter placement (33, 36). It has recently been suggested, however, that a closed-chest model may prove more useful in the determination of cardiovascular parameters because heart rate, LV systolic pressure, and maximal rise and fall in LV pressure were significantly higher in closed-chest mice compared with values in open-chest animals (14).

In addition to the measurement of pulmonary arterial pressure, cardiac output has been evaluated in a number of studies in mice (5, 6, 13, 14, 30, 31, 35). Techniques used to determine cardiac output include the use of radiolabeled microspheres, echocardiography, blood conductivity, and Doppler ultrasound techniques (5, 6, 13, 14, 30, 31, 35). Although measurements were obtained on a consistent basis with each technique, the cardiac output values ranged from 12.6 ± 7 ml/min in one study (5) to 25 ± 1 ml/min in another (6).

Thermodilution is an indicator dilution technique that is employed for clinical and laboratory measurement of cardiac output in humans and in large and small animals such as the dog, cat, and rat (8, 16, 20). Although this technique has been modified for use in the mouse, there is no full report in the literature, to our knowledge, to date of the use of the thermodilution technique to assess cardiac output in the mouse.

Although pulmonary arterial pressure has been measured in an open-chest mouse model (33, 36), little, if anything, is known about pulmonary arterial and wedge pressures and pulmonary vascular responses in intact-chest, spontaneously breathing anesthetized mice. The purpose of the present study, therefore, was
to develop a right-heart catheterization technique for the measurement of pulmonary vascular pressures as well as to measure cardiac output by the thermodilution technique. Moreover, the present study was undertaken to investigate the pulmonary arterial pressure-pulmonary blood flow relationship in the intact-chest mouse and to investigate the influence of nitric oxide release and cyclooxygenase product formation on the pressure-flow relationship and the pulmonary vascular response to acute hypoxia.

METHODS

Surgical procedures. The American Physiological Society's principles for research involving animals were followed. CD1 mice weighing 25–38 g were anesthetized with thiopental (85–95 µg/g ip) and ketamine (3 µg/g ip) and were placed on a thermoregulated surgical table. Supplemental doses of anesthetic were given as needed to maintain a uniform level of anesthesia. Body temperature was monitored with a rectal probe (Yellow Springs Instruments, Yellow Springs, OH) and was maintained at 37°C with a water-jacketed heating blanket except where otherwise noted. The trachea was cannulated (PE-90 tubing) to maintain a patent airway, and the animals breathed room air enriched with 95% O2-5% CO2 except in experiments in which the effects of acute ventilatory hypoxia were studied. A femoral artery was cannulated (PE-10 tubing was heated and gently pulled over a 0.010-in. coronary angioplasty guide wire) for the measurement of systemic arterial pressure. Systemic arterial pressure was measured with a Viggo-Spectramed transducer (Viggo Spectramed, Oxford, CA) attached to a polygraph (Grass Instruments model 7, Quincy, MA). Heart rate was electronically monitored from the systolic pressure pulses with a tachometer (Grass model 7P44A). The left jugular vein was cannulated (PE-10 tubing) for the administration of agonists and antagonists. These techniques have been described previously (9).

Technique for measuring pulmonary arterial pressure. The anesthetized mice were strapped in a supine position to a fluoroscopic table. A specially designed single-lumen catheter was constructed (Nu-Med, Hopkinton, NY). The catheter was 145 mm in length and 0.25 mm in outer diameter, with a specially curved tip to facilitate passage through the right heart, main pulmonary artery, and the left or right pulmonary artery. Before the catheter was introduced, the catheter curve was initially straightened with a 0.010-in. straight angioplasty guide wire to facilitate passage from the right jugular vein into the right atrium at the tricuspid valve under fluoroscopic guidance (Picker Surveyor, Cleveland, OH). As the straight wire was removed, the natural curve facilitated entry of the catheter into the right ventricle. A 0.010-in. soft-tip coronary artery angioplasty guide wire was then inserted, and the catheter was pushed over the guide wire into the main pulmonary artery under fluoroscopic guidance (Fig. 1). Pressure in the main pulmonary artery was measured with a pressure transducer (Schneider/Namic, Glenn Falls, NY), and mean pulmonary arterial pressure was derived electronically and recorded continuously. For the determination of pulmonary arterial wedge pressure, the catheter was advanced to the left or right pulmonary artery and wedged with continuous measurement of the pressure waveform.

Technique for measurement of cardiac output. Cardiac output was measured by the thermodilution technique. A known volume (20 µl plus catheter dead space) of 0.9% NaCl solution at 23°C was injected into the right atrium, and changes in blood temperature were measured in the root of the aorta. A cardiac output computer (Cardiotherm 500, Columbus Instruments, Columbus, OH) equipped with a small-animal interface was used. The thermistor microprobe (Fr-1; Columbus Instruments) was inserted into the right carotid artery and advanced to the aortic arch, where changes in aortic blood temperature were measured. A catheter placed in the right jugular vein was advanced to the right atrium or main pulmonary artery for rapid bolus injection of the saline injectate. The saline solution was injected with a constant-rate syringe (Hamilton, Reno, NV) to ensure rapid and repeatable injection of the saline indicator solution. Thermodilution curves were recorded on a chart recorder (Western Graphtec, Irvine, CA) (Fig. 2), and pulmonary and systemic arterial pressures were monitored continuously. Catheter placement was verified at postmortem examination. A similar method has been previously employed in the intact rat (8, 16).

Generation of pulmonary arterial pressure-cardiac output plots. To study pulmonary arterial pressure-flow curves in the intact-chest mice, the mice were cooled or heated to temperatures ranging from 29°C to 41°C (as measured by the thermistor probe in the aortic arch), and cardiac output and pulmonary arterial pressure were evaluated. Pressure-flow relationships were derived by plotting pulmonary blood flow (cardiac output) against mean pulmonary arterial pressure (2).

Fig. 1. Radiograph of left anterior (A) and right anterior (B) oblique view with caudal rotation of right-heart catheterization procedure in intact-chest, spontaneously breathing anesthetized mouse with catheter and 0.010-in. guide wire in left pulmonary artery (LPA). SVC, superior vena cava; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle.
In the fourth set of experiments, the influences of the nitric oxide synthase inhibitor nitro-L-arginine methyl ester (L-NAME) and the cyclooxygenase inhibitor sodium medofenate on the pressure-flow relationship were investigated. Pressure-flow curves were evaluated before and after 20 min after administration of L-NAME (50 mg/kg iv) or sodium medofenate (2.5 mg/kg iv).

In the last set of experiments, the influence of acute hypoxia (10% O2-90% N2) on pulmonary arterial pressure was assessed. In these experiments the mice breathed 10% O2-90% N2 from a mask over the endotracheal tube for 3–5 min, and peak changes in mean pulmonary arterial pressure were measured. The influence of the nitric oxide synthase inhibitor L-NAME on the increase in pulmonary arterial pressure in response to acute ventilatory hypoxia was investigated.

Drugs. L-NAME, sodium medofenate, and bradykinin (Sigma Chemical, St. Louis, MO) were dissolved in 0.9% NaCl. Arachidonic acid (Sigma) was dissolved in 100% ethanol and diluted with 0.9% NaCl. The vehicles for the agonists used had little, if any, effect on baseline vascular pressures. The stock solutions were stored in a freezer in 1-ml opaque tubes, and working solutions were prepared daily and kept on crushed ice during the course of the experiment.

Statistics. The hemodynamic data are expressed as means ± SE and were analyzed using a one-way ANOVA with repeated measures and Scheffé’s F-test or a paired t-test. A P value of < 0.05 was used as the criterion for statistical significance.

RESULTS

Control measurements of systemic arterial pressure, heart rate, cardiac output, and pulmonary arterial and wedge pressures were obtained in 9–10 animals, and these data are summarized in Table 1. The tracing in Fig. 2 shows a thermodilution curve in intact-chest mice. Injection into the right atrium of 20 μl of 0.9% saline at 23°C induced a 0.4°C change in aortic temperature as detected by the thermistor probe positioned in the aortic arch (Fig. 2). The aortic blood temperature change, as measured by the thermistor catheter, was

Table 1. Control values in intact-chest, spontaneously breathing mice

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Value</th>
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<tbody>
<tr>
<td>Systolic pressure, mmHg</td>
<td>90 ± 9</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>82 ± 8</td>
</tr>
<tr>
<td>Mean systemic arterial pressure, mmHg</td>
<td>85 ± 8</td>
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<tr>
<td>Mean right atrial pressure, mmHg</td>
<td>417 ± 15</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>147 ± 0.5</td>
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<tr>
<td>Cardiac output, ml/min</td>
<td>10.4 ± 0.5</td>
</tr>
<tr>
<td>Total peripheral resistance, mmHg·ml⁻¹·min</td>
<td>8.6 ± 0.7</td>
</tr>
<tr>
<td>Right ventricular systolic pressure, mmHg</td>
<td>16.3</td>
</tr>
<tr>
<td>Right ventricular diastolic pressure, mmHg</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>Systolic pulmonary arterial pressure, mmHg</td>
<td>14.7 ± 0.8</td>
</tr>
<tr>
<td>Diastolic pulmonary arterial pressure, mmHg</td>
<td>9.4 ± 0.7</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, mmHg</td>
<td>12.8 ± 1.9</td>
</tr>
<tr>
<td>Mean pulmonary arterial wedge pressure, mmHg</td>
<td>4.8 ± 0.9</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, mmHg·ml⁻¹·min</td>
<td>0.79 ± 0.09</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 9–10 animals.
rapid in increase and decrease and did not exhibit a secondary plateau, suggesting that recirculation of the indicator was minimal (Fig. 2). The cardiac output for the curve in Fig. 2 was 10.2 ml/min, and the summary data for cardiac output are shown in Table 1. The effect of placement of the pulmonary arterial catheter on cardiac output was evaluated in intact-chest mice, and with the catheter in the pulmonary artery, was 10.0 ± 0.8 ml/min (n = 6), which is not significantly different compared with cardiac output in animals without pulmonary arterial catheter placement (P > 0.05). The influence of the passage of time on mean pulmonary arterial pressure and cardiac output was evaluated in intact-chest mice, and these data are summarized in Fig. 3. When compared at 30-min intervals over a 3-h time period, mean pulmonary arterial pressure and cardiac output values were stable (Fig. 3).

The influence of changes in body temperature on cardiac output was determined in mice heated or cooled to temperatures ranging from 29°C to 41°C (Fig. 4). As body temperature increased, cardiac output increased, and peak output in response to increased temperature was 24.4 ml/min at 41°C (Fig. 4). Pulmonary arterial wedge pressure was not altered by changes in blood temperature from 29°C to 41°C (data not shown). The relationship of pressure to blood flow was evaluated, showing that pulmonary arterial pressure increased as pulmonary blood flow was increased by the rise in body temperature (Fig. 4). Pulmonary arterial pressure increased more rapidly at flow rates of 5–8 ml/min and more slowly as higher pulmonary blood flow rates were reached (Fig. 4). Pressure-flow curves were reproducible when repeated 30 min after the control curve was obtained (data not shown). When cardiac output was reduced by balloon occlusion of the IVC, pulmonary arterial pressure decreased (Fig. 5). Compared with changes in pulmonary arterial pressure in response to the reduction in body temperature, the pressure-flow relationship under conditions of IVC occlusion and temperature change was similar (Fig. 5).

The influence of nitric oxide synthase inhibition on the pressure-flow relationship was studied by comparing pressure-flow curves before and after administration of L-NAME (50 mg/kg iv; Fig. 6). Administration of the nitric oxide synthase inhibitor under baseline conditions resulted in an increase in pulmonary arterial pressure (Fig. 6). The pressure-flow relationship at low flow rates was similar in control mice and in mice treated with L-NAME (Fig. 6). However, as pulmonary blood flow increased above a flow rate of ~9 ml/min, the pressure-flow curve in L-NAME-treated mice was significantly shifted to the left compared with the curve obtained under control conditions (Fig. 6). This dose of L-NAME significantly reduced pulmonary and systemic depressor responses to the endothelium-dependent va-
sodilator bradykinin (data not shown). In contrast to the effects of L-NAME, the inactive arginine analog D-NAME did not alter the pressure-flow curve in the pulmonary vascular bed (data not shown). In other experiments, the role of vasodilator prostaglandins in the curvilinear nature of the pressure-flow relationship was investigated and pressure-flow curves were compared before and beginning 20 min after administration of sodium meclofenamate (2.5 mg/kg iv; Fig. 6). The pressure-flow curve in mice after treatment with the cyclooxygenase inhibitor was similar to the control curve (Fig. 6). This dose of sodium meclofenamate reduced pulmonary and systemic depressor responses to the prostaglandin precursor arachidonic acid (data not shown).

The pulmonary vascular response to acute hypoxic exposure and the role of nitric oxide release on the response to hypoxia were investigated, and when mice were ventilated with the hypoxic gas mixture (10% O₂-90% N₂) for 3–5 min, pulmonary arterial pressure increased significantly (Fig. 7). After ventilation with the hypoxic gas mixture was discontinued, pulmonary arterial pressure returned to baseline value within 3–4 min. The influence of nitric oxide synthase inhibition on the increase in pulmonary arterial pressure in response to acute hypoxia was evaluated, and after administration of L-NAME (50 mg/kg iv), the pressor response to acute hypoxia was significantly greater than the response observed during the control period (Fig. 7). The role of vasodilator prostaglandins in modulating the increase in pulmonary arterial pressure in response to acute hypoxia was evaluated, and sodium meclofenamate did not alter the increase in pulmonary arterial pressure in response to acute hypoxia (data not shown).

DISCUSSION

The present results show that a right-heart catheterization technique can be used to measure pulmonary arterial and wedge pressure and that the thermodilution technique can be used to measure cardiac output in the intact-chest, spontaneously breathing anesthetized mouse. Moreover, the results of the present study indicate that the pressure-flow relationship in the pulmonary vascular bed is curvilinear and that the inhibition of nitric oxide synthase, but not cyclooxygenase, shifts the pressure-flow relationship to the left at higher flow rates. These results also demonstrate that acute hypoxia increases pulmonary arterial pressure and that the response is augmented by the inhibition of nitric oxide synthase, but not by inhibition of cyclooxygenase.

The effect of the targeted disruption of the endothelial nitric oxide synthase (eNOS) gene (NOS3) on the pulmonary vascular bed has been studied in the mouse. A similar open-chest technique was used in mice deficient in atrial natriuretic peptide receptor A, in which the pulmonary hypertension in response to chronic hypoxia was augmented (36). In previous studies in open-chest animals, baseline mean pulmonary arterial pressure in wild-type mice ranged from 16.4 ± 0.6 (33) to 20.3 ± 0.5 mmHg (36). It has been suggested that a closed-chest preparation may have advantages during the study of cardiovascular function because LV pres-
sure and the rate of pressure development can be altered by opening of the chest and the use of positive-pressure ventilation (24). For this reason, a right-heart catheterization technique was developed to study pulmonary vascular pressures and responses in the closed-chest, spontaneously breathing mouse. With the use of this technique under fluoroscopic guidance, a specially designed catheter was inserted into the right jugular vein and advanced into the main pulmonary artery. Baseline mean pulmonary arterial pressure in the strain of mice used in the present study was 12.8 ± 1.9 mmHg. The reason for differences in results between the present study and previous studies in open-chest mice is uncertain but may be related to the experimental procedure or strain of mice used. However, the role of strain differences in the assessment of pulmonary arterial pressure cannot be accounted for by the present data and must be investigated in future studies. Pulmonary arterial pressure was stable over a 3-h time period, and the present experiments indicate that an index of left atrial pressure can be obtained by advancing the pulmonary artery catheter into the wedge position. With the measurement of these parameters and cardiac output, pulmonary vascular resistance can be calculated.

Cardiac output has been determined in mice using a variety of techniques (5, 6, 13, 14, 30, 31, 35). In these studies, the range of values varied from 12.6 ± 7 to 25 ± 1 ml/min (5, 6). The thermodilution technique has been modified for use in small animals, and the present study, to our knowledge, is the first evaluation of this technique in the mouse. The present results from the use of the thermodilution technique show that cardiac output averaged 10.4 ± 0.5 ml/min and was stable during the course of the experiment. Moreover, these data suggest that cardiac output in the mouse is similar or somewhat greater than values in the rat, cat, dog, or human when cardiac output is expressed in milliliters per gram of body weight (15, 16, 20).

The present experiments describe the shape of pressure-flow curves in the pulmonary vascular bed of intact-chest, spontaneously breathing mice. Beginning at low blood flow (5 ml/min), mean pulmonary arterial pressure increased as flow rates increased to 24 ml/min with a steeper slope at flows of 5–10 ml/min in the mice. Moreover, as flow increased from ~10 ml/min to 24 ml/min, pulmonary arterial pressure increased more slowly as pulmonary blood flow was increased. Similar pressure-flow relationships have been described in the intact dog and rat, and the modulation of pulmonary arterial pressure as blood flow increases may serve as a protective mechanism to decrease the tendency for pulmonary edema formation when cardiac output is increased in physiological states, such as with exercise (15, 16). As blood flow increases, a more gradual rise in pulmonary arterial pressure has generally been attributed to distension of perfused vessels and recruitment of previously nonperfused vessels (15, 22, 29).

The increase in mean pulmonary arterial pressure in response to L-NAME under baseline conditions suggests that in the physiological range of flow, nitric oxide plays a significant role in maintaining the low basal tone in the pulmonary vascular bed. When blood flow was reduced to <9 ml/min, there was no significant difference between control pressure-flow curves and curves obtained after administration of L-NAME. These data may be interpreted to suggest that when blood flow is low, nitric oxide does not play a measurable role in regulating pulmonary vascular tone. Moreover, because the pressure-flow curve was shifted to the left after administration of L-NAME compared with the curve obtained under control conditions, these data may suggest that nitric oxide plays a more important role in maintaining the curvilinear nature of the pressure-flow relationship at higher flow rates. It is possible that increased shear at higher flow rates may account for the apparent increased role of nitric oxide under these conditions, similar to results in the intact-chest rat (16). In addition, although the pressor response to L-NAME was greater at higher than at lower flow rates, the comparison of responses to L-NAME at different levels of baseline pressure and tone may be difficult. These data are consistent with results in the pulmonary vascular bed of the intact-chest rat (16). However,
the effects of L-NAME on the pulmonary vascular bed may be mediated by mechanisms that are not related to inhibition of nitric oxide production and require studies in eNOS-deficient mice (3).

The results with the cyclooxygenase inhibitor suggest that cyclooxygenase products probably do not contribute to the hyperbolic shape of the pressure-flow curve, because pretreatment with medofenamate did not alter the pressure-flow relationship. Similar results have been reported in the isolated rat lung under conditions of constant pulmonary pressure gradient and in the intact-chest rat under conditions of controlled blood flow (7, 16).

It is possible that the reduction in body temperature increased blood viscosity, resulting in increased pressure at any given flow rate (28). An increase in blood viscosity has been shown to alter pulmonary arterial pressure under conditions of hypothermia (28), although in this study changes in viscosity were observed at temperatures <29°C. In the present study, pulmonary blood flow (cardiac output) was reduced by cooling the body to as low as 29°C as well as by occlusion of the IVC using a balloon catheter. The results of these experiments with both temperature-induced and mechanically induced reduction of cardiac output demonstrate that the pressure-flow relationship with flow rates ranging from 5 to 10 ml/min were similar. Although a role for viscosity cannot be ruled out, these data suggest that the reduction in pulmonary blood flow caused by decreasing body temperature is likely not caused by increased viscosity of the blood. The results with IVC occlusion in the present study are consistent with observations in the intact-chest conscious dog (23, 25).

It has been reported that nitric oxide plays an important role in modulating the pulmonary pressor response to hypoxia and that inhibition of nitric oxide synthase augments the pressor response to chronic and acute hypoxia (1, 4, 19, 26, 27, 32). It has been shown recently that eNOS-deficient mice have an increased pulmonary pressor response to chronic and intermediate hypoxia (10, 34). In addition, in vivo gene transfer of nitric oxide synthase to the pulmonary vascular bed of the rat decreased the pressor response to hypoxia (18). The present results are consistent with previous studies showing that the pulmonary pressor response to acute hypoxia is augmented by a nitric oxide synthase inhibitor. It has been reported that cyclooxygenase products play a role in modulating the pulmonary pressor response to hypoxia in the dog and guinea pig (11, 12). However, inhibition of the cyclooxygenase pathway did not alter the increase in pulmonary arterial pressure in response to acute hypoxia in the mice, suggesting that the release of vasoconstrictor prostanoids does not play a role in modulating the pulmonary vascular response to hypoxia. The reasons for differences in the present study and previous reports in the guinea pig and dog are uncertain but may reflect differences in species or the experimental procedure employed.

In summary, the results of the present study demonstrate that a right-heart catheterization technique can be employed to measure pulmonary arterial and wedge pressure and that the thermodilution technique can be used to measure cardiac output in the intact-chest, spontaneously breathing mouse. The parameters measured were stable, and the pressure-flow relationship in the pulmonary vascular bed of the mice was curvilinear. Nitric oxide release appears to play a role in regulating pulmonary vascular tone under conditions of increased flow and in modulating the pressor response to hypoxia. In contrast, it appears that nitric oxide plays a less important role under low-blood-flow conditions. The results of the present study suggest that the release of cyclooxygenase products is not important in modulating the pressure-flow relationship or the pressor response to hypoxia. This is, to our knowledge, the first report of the use of a right-heart catheterization technique to measure pulmonary vascular pressures and responses in the intact-chest, spontaneously breathing mouse and should prove useful for the study of phenotype changes in the pulmonary circulation of transgenic mice.

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