Pulmonary vascular input impedance in the newborn and infant pig

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SUMMARY The input impedance of the main pulmonary artery in 26 pigs aged from 1 h to 2 weeks has been calculated from measurements of pressure and flow. From these data we have derived estimates of the hydraulic power output of the right heart.

The impedance spectra were similar in form to those in many other studies and were consistent with the presence of a single reflection site within the lung. The frequency of the (single) minimum decreased steadily with increasing age as did the corresponding zero crossing point on the phase curve. From estimates of propagation velocity the position of this "reflection site" was found to coincide with the position of the lung periphery in each age group.

An overall fall in characteristic impedance with increasing age was found to be due to the increasing diameter of the pulmonary artery rather than to changes in its elasticity.

The total power output/body weight of the right heart fell from 10.4 to 4.8 mW·kg⁻¹ from birth to 4 weeks of age. During this period the ratio of pulsatile to steady power fell from 0.5 to 0.31. We conclude that this fall is related to a reduction in the effective reflection of pressure and flow waves within the lung due to increasing attenuation and possibly to a reduction in the magnitude of the lumped reflection coefficient itself.

In young children with congenital heart disease the normal structural development of the lung is often seriously disturbed by pulmonary hypertension or by a reduction in blood flow. Such changes would be expected to effect the visco-elastic properties of these vessels and, in consequence, both pulsatile and steady power dissipation. Given the impossibility of doing invasive studies on normal infants, the present observations on normal newborn pigs are seen as a necessary step to an improved understanding of the mechanical behaviour of the structurally abnormal human pulmonary circulation.

In the normal pulmonary circulation abrupt changes in pressure and flow occur at birth,¹ and these functional changes are associated with structural changes in the peripheral pulmonary arteries. Pulmonary arterial smooth muscle mass² and medial thickness relative to vessel radius are reduced,³ while the size and number of intra-acinar vessels recruited increases rapidly.³ ⁴ During the first 2 weeks of life the functional stiffness (pressure strain elastic modulus) of the elastic and large muscular intra-pulmonary arteries changes little in spite of an increase in structural stiffness.²

In order to study further the relationship between pulmonary vascular morphology, elasticity and function we have carried out measurements of pressure and flow in the main pulmonary artery of pigs aged less than 1 h to 2 weeks. These data were used to calculate the hydraulic input impedance of the pulmonary vascular bed and to estimate the mean and pulsatile power supplied to the lung.

Methods and animals

Three large white sows provided the 26 piglets used in the study. The piglets remained with their mother and littermates until needed. At least four animals were studied during the first hour of life and at intervals during the first 2 weeks (table 1). Each age group included animals from all litters, all were healthy, had a normal birth weight and none were runts (table 1). In addition measurements were made on one animal aged 4 weeks in order to assess the frequency response and accuracy of the pressure measuring system (see below).

Key words: vascular impedance; lung, pig; power.
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Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Number in group</th>
<th>Age range (h)</th>
<th>Body weight (kg)</th>
<th>Heart rate (Hz)</th>
<th>Po (kPa)</th>
<th>Qo (ml min⁻¹)</th>
<th>Zo (Nm⁻² x s⁻¹)</th>
<th>Zc (Nm⁻² x s⁻¹)</th>
<th>Zc (CALC) (Nm⁻² x s⁻¹)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h</td>
<td>4</td>
<td>0.5–2 h</td>
<td>1.45±0.14</td>
<td>2.1±0.02</td>
<td>3.23±0.05</td>
<td>213±4</td>
<td>9.09±0.78</td>
<td>1.90±0.31</td>
<td>2.3</td>
</tr>
<tr>
<td>12 h</td>
<td>4</td>
<td>10–14 h</td>
<td>1.56±0.06</td>
<td>3.0±0.01</td>
<td>4.08±0.04</td>
<td>266±7</td>
<td>9.2±0.68</td>
<td>2.10±0.18</td>
<td>1.6</td>
</tr>
<tr>
<td>24 h</td>
<td>4</td>
<td>20–25 h</td>
<td>1.46±0.05</td>
<td>2.54±0.01</td>
<td>2.54±0.02</td>
<td>147±1</td>
<td>10.4±0.51</td>
<td>3.02±0.33</td>
<td>1.5</td>
</tr>
<tr>
<td>48 h</td>
<td>6</td>
<td>44–54 h</td>
<td>1.80±0.14</td>
<td>2.36±0.02</td>
<td>2.67±0.03</td>
<td>265±4</td>
<td>6.04±0.20</td>
<td>1.83±0.19</td>
<td>1.4</td>
</tr>
<tr>
<td>1 w</td>
<td>4</td>
<td>6–8 d</td>
<td>2.43±0.28</td>
<td>1.92±0.01</td>
<td>2.42±0.05</td>
<td>223±6</td>
<td>4.49±0.34</td>
<td>0.73±0.05</td>
<td>0.76</td>
</tr>
<tr>
<td>2 w</td>
<td>4</td>
<td>12–14 d</td>
<td>5.15±0.36</td>
<td>2.15±0.01</td>
<td>2.21±0.02</td>
<td>505±10</td>
<td>2.62±0.13</td>
<td>0.69±0.03</td>
<td>0.59</td>
</tr>
<tr>
<td>4 w+1</td>
<td>1</td>
<td>9 d</td>
<td>10.8</td>
<td>1.46±0.002</td>
<td>2.54±0.008</td>
<td>919±5</td>
<td>1.66±0.02</td>
<td>0.36±0.02</td>
<td>D</td>
</tr>
</tbody>
</table>

Mean values and ± standard error of the mean (where appropriate)

*Age units: h = hours; d = days; w = weeks

**Conversion factor: CGS units = SI units x 10⁻²

***Values calculated from elasticity data (Ref 5)

Each animal was anaesthetised with nitrous oxide in oxygen, intubated, and maintained on the same mixture using a positive pressure ventilator. Through a left thoracotomy the left lung was displaced and the main pulmonary trunk was exposed. A 19 gauge needle 1 cm long connected to a modified, saline-filled syringe (fig 1), was passed through the wall of the pulmonary trunk and the syringe clamped to the operating table. Intra-arterial pressure was measured through this assembly using a catheter tipped manometer (Gaetec 16CT). Clotting of the needle was minimised by pre-soaking the system in heparinised saline and flushing it with the same solution before each pressure run. An electromagnetic flow probe (Carolina Medical Instruments) was positioned distal and as closely as possible to the pressure needle. In all experiments the distance between the needle and the proximal edge of the flow probe was less than 5 mm. The diameter of the flow probe was chosen so that it minimised the constriction of the vessel while maintaining contact with the wall throughout the cardiac cycle. In the group of animals aged 1 week pacing leads were attached to the right atrial appendage.

The effect of inflation on blood pressure and flow in the lung is complex and depends upon the way in which the lung is inflated.** 8–11 We avoided this problem by stopping the respiration for about 6 s during each sampling period and did not observe any systematic changes in pressure or flow waveforms during this period.

The pulmonary arterial pressure and flow signals and the ECG signal were displayed on a monitor and stored on magnetic tape for analysis on an Apple II computer at a sample rate of 200Hz. Impedance spectra were calculated from the Fourier series of the pressure and flow signals. Fourier coefficients were expressed as mean values of at least 10 consecutive heart beats during which the R-R interval varied by less than 1 sample interval (5 ms). The findings were similar in animals of the same age and therefore the data from all animals of the same age were pooled and mean values of the Fourier coefficients were calculated. Harmonics of pressure and flow which were less than 2% in amplitude relative to the fundamental were excluded from the impedance calculation. Characteristic impedance was defined as the mean of all coefficients with a frequency greater than 8 Hz. **

Throughout each experiment the animals appeared healthy, body temperature was maintained and the systemic arterial blood gases, haematocrit and blood sugar were checked at half-hourly intervals. Blood gases remained normal (mean pH 7.38 ± 0.13 SD; mean pCO₂ 39.2 ± 3.1 mmHg SD, systemic arterial oxygen tension 219 ± 24 mmHg. The blood sugar was
always greater than 45 mg dl\(^{-1}\) and the haematocrit greater than 35, normal for pigs of this age. All animals were killed under anaesthesia at the end of each experiment.

**CALIBRATION AND ASSESSMENT OF PRESSURE AND FLOW MEASURING DEVICES**

The catheter tip manometer was calibrated against a mercury manometer before and after each experiment. During this interval the drift in zero level was, usually less than 2 mm mercury and no change in gain was detectable. The zero pressure calibration values were corrected to allow for the hydrostatic effect of the fluid column in the syringe. The three flow probes used in the study were calibrated in a pig aged 2 weeks by placing each probe in turn around the aorta at positions commensurate with their diameters. The animal was killed with an overdose of barbiturate and the blood was collected through a cannula tied into a common iliac artery. The ascending aorta was clamped, cannulated and connected to a reservoir positioned 1.3 m above the aorta. Blood was allowed to flow through the aorta and a measured amount was collected through the distal cannula during a known time interval. The flow rate calculated from these measurements was compared to that obtained from the flowmeter using the manufacturers calibration figures. The agreement was within 4% for the three probes. In all subsequent experiments the manufacturers figures for the electrical characteristics of the flowmeter (amplitude response: flat to 35 Hz; linear phase shift 2.16 degree Hz\(^{-1}\)) together with a correction for haematocrit were used to relate the flowmeter signal to absolute volume flow.

The frequency response of the pressure measuring system was tested in two ways. A latex tube filled with saline was connected at one end to a piston driven by a solenoid and was maintained at a pressure of 20 mmHg by a reservoir attached to the other end. The needle connected to the syringe was passed through the wall of the tube approximately 50 mm from the piston. The catheter tip manometer was passed down the tube through the reservoir and its tip was positioned close to the end of the needle. A pressure impulse was generated by energising the solenoid and the outputs from the two devices were Fourier analysed. The duration and amplitude of the impulse were such that frequencies of measurable amplitude up to at least 50 Hz were generated. When compared with the output of the catheter tip device in the tube the response of the needle syringe system was essentially flat up to 25 Hz with negligible phase-shift. Above this frequency the ratio of the harmonic modulus of the needle system to that of catheter tip manometer reached a maximum (2.0) at 35 Hz, while the phase lag increased to approximately 90 degrees at this frequency.

A similar comparison between the two methods of measuring pressure was performed in a living pig aged 4 weeks in which the pulmonary artery was considered to be sufficiently large to contain a catheter tip manometer without its disturbing the flow. This was passed through the right ventricle into the pulmonary artery. The syringe needle was passed through the wall of the vessel and the tip of the catheter tip device was positioned close to, but not touching the end of the needle. The Fourier series of the outputs from both devices were compared and the needle system was found to reproduce the signal from the intra arterial manometer with no loss of amplitude and negligible phase-shift up to a frequency of 25 Hz. The same animal was also fitted with a flow probe and a second catheter tip manometer, and both impedance and propagation velocity were determined.

**Results**

The mean pulmonary arterial pressure in animals aged 24 h was lower than in the younger animals and showed a further reduction by 2 weeks of age (table 1). Pulmonary blood flow did not show a consistent change with age during the first week of life. However, the values of pulmonary arterial pressure and of flow with respect to weight were similar to those previously reported in lightly anaesthetised spontaneously breathing pigs of less than 1 week of age. The zero frequency impedance modulus (Zo) changed little between birth and 24 h and then decreased progressively with age (table 1). The modulus of the characteristic impedance (Zc) decreased consistently after 48 h of age.

The impedance spectra for the various age groups were similar in form (fig 2a). At all ages the modulus fell with increasing frequency, reached a minimum below 10 Hz and was followed by an increase towards a constant value. In none of the spectra was an obvious maximum observed. The impedance spectra were higher in animals aged 12 and 24 h than in those aged less than 1 h, but became lower by 48 h. During this period the frequency at which the minimum occurred fell from 10 to 4 Hz.

In animals of all age groups, at low frequencies the flow wave preceded the pressure wave resulting in negative values of the impedance phase (fig 2b). At frequencies between 4 and 10 Hz the phase became positive and, for all ages except 24 h remained positive and close to zero. The mean impedance spectrum obtained from animals aged 1 week in which the natural heart rate was increased by pacing was coincident with that obtained under control conditions, showing that the form of the spectrum was independent of the frequency in these experiments, as has previously been established.
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Discussion

The major technical problem in these experiments was the measurement of pressure in the small pulmonary arteries of the younger animals. A catheter tip manometer placed through the pulmonary valve could not be used since the diameter of the catheter was approximately 50% of the diameter of the pulmonary trunk and so would have disturbed right ventricular outflow and the form of the pressure and flow waves. Puncturing the pulmonary trunk and using a needle-syringe technique introduced the possibility of resonance occurring in the syringe. In vitro, and in vivo studies on a relatively large 4 week old pig showed that resonance did occur in the syringe at around 35 Hz but that the system faithfully reproduced

FIG 2 Variation of pulmonary vascular input impedance with frequency. (a) Modulus (b) Phase
the pressure wave given by the intra-arterial catheter. Because the pulmonary trunk was short we could not measure propagation velocity and so did not correct the impedance phase values for this effect. However in all experiments the flow probe was approximately 5 mm distal to the needle of the pressure system. Assuming a propagation velocity of the order of 2m.s⁻¹ we would imply that the measured flow wave would lag the measured pressure wave by an amount dependent on the frequency. The lag would be expected to reveal itself as a small linear increase in phase with increase in frequency (gradient 0.9 degree.Hz⁻¹). In practice, the spectra showed no such linear phase shift.

**IMPEDEANCE STUDIES**

The form of the impedance spectra in the present study are similar to those previously reported in several different animal species although we are unaware of any similar study on pigs. It is consistent with the presence of a single effective site of reflection, which probably results from the combined effect of numerous reflections distributed throughout the lung. The minimum and at which the phase crosses the zero line is different animal species although we are unaware of any simikar study on pigs.

In the present study the propagation velocity was measured directly in a 4 week old animal from the phase lag between two manometers positioned in the pulmonary artery 20 mm apart. The mean value calculated from the 10 harmonics above the fourth was 1.9 ± 0.03 (SEM) ms (cf 1.75 ms in man; 2.75 ms in the dog). In the same animal the propagation velocity (c) was also derived from the value of the characteristic impedance (Zc) measured at the same time using the expression:

\[ c = \frac{A.Zc}{\rho} \]  

(1)

where \( \rho \) is the density of blood (assumed to be 1.06 × 10³ kg.m⁻³) and \( A \) is the cross sectional area of the lumen. This expression gave a value of 2.03 ms. Since the directly measured and derived values were similar, we have used equation (1) to calculate the propagation velocities of the other groups of animals and hence to estimate the position of the reflection site from the relation \( c = fA \) (where \( f \) = frequency and \( A \) = wavelength).

Table 2 shows that the distance between the measurement and reflection sites increases as the animals grow.

In a different series of animals (unpublished data) the length of the right lower lobe pulmonary artery was determined by a radiographic technique. These figures (table 2) are similar in magnitude to the distance between the measurement and reflection site calculated from the data in this study and strongly suggest that the main contribution to the lumped reflection is from the periphery. Changes in the magnitude of the reflection coefficient with age could not be determined using the present experimental technique.

In the animals aged 1 week the spectrum was unaltered by pacing at 2.5 Hz and 3.5 Hz. In a number of studies it has been assumed that the apparent lack of interdependence between heart rate and the form of the impedance spectrum implies that the pulmonary vasculature behaves as a linear system. More recently this assumption has been questioned (at least with regard to the systemic circulation) since pacing may alter vascular smooth muscle tone. However Noble has shown that intra-coronary injections of calcium ion or catecholamine which introduce high frequency components into the ejected flow wave while having no effect on the vasculature do not alter the form of the impedance spectrum. It is probable that the behaviour of the pulmonary vasculature, like that of most other biological systems, is not strictly linear. Nevertheless, estimations of vascular impedance provide a useful measure of the relationship between vascular pressure and flow on the one hand; and structure and elasticity on the other.

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**Table 2**

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>( f_{\text{min}} ) (Hz)</th>
<th>( A ) (mm²)*</th>
<th>c (ms⁻¹)</th>
<th>( \lambda/4 ) (mm)**</th>
<th>l (mm)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>10.6</td>
<td>1.90</td>
<td>60</td>
<td>68-73</td>
</tr>
<tr>
<td>12 h</td>
<td>10</td>
<td>15.0</td>
<td>2.97</td>
<td>74</td>
<td>66-75</td>
</tr>
<tr>
<td>24 h</td>
<td>11</td>
<td>16.2</td>
<td>4.58</td>
<td>104</td>
<td>76-81</td>
</tr>
<tr>
<td>48 h</td>
<td>10</td>
<td>18.2</td>
<td>3.14</td>
<td>78</td>
<td>84-88</td>
</tr>
<tr>
<td>1 w</td>
<td>7</td>
<td>31.6</td>
<td>2.18</td>
<td>84</td>
<td>86-94</td>
</tr>
<tr>
<td>2 w</td>
<td>5</td>
<td>41.0</td>
<td>2.67</td>
<td>133</td>
<td>84-98</td>
</tr>
<tr>
<td>4 w</td>
<td>4</td>
<td>65.4</td>
<td>2.22</td>
<td>139</td>
<td>118-125</td>
</tr>
</tbody>
</table>

*Values of cross sectional area at working pressure of each age group obtained from a previous study (5)

**Quarter wavelength position corresponding to impedance minimum at a frequency of \( f_{\text{min}} \)

†Radiographic length of right lower lobe pulmonary artery (unpublished data, a different series of animals).
POWER INPUT TO THE LUNG

The power output of the right heart was estimated according to the principles outlined by Milnor et al.\textsuperscript{20}

Since the measurement site was close to the lung, we have made no correction for power dissipated along the pulmonary trunk\textsuperscript{23} and have assumed that the power output from the right heart is equal to the power input to the lung. Its variation with age is shown in table 3. There was considerable scatter in the results, as shown by the magnitude of the standard errors. Since kinetic energy work rate is proportional to flow squared; and potential energy, to the cube of flow, small errors in the measurement of flow will produce comparatively large changes in the calculated power values.

The total power output of the right heart per unit body weight fell by a factor of two between birth and 2 weeks. Our estimates of the total power output per unit weight of the older animals are of the same order of magnitude as those found in the adult pig (7.7 mW·kg\textsuperscript{-1} \textsuperscript{20}, 4.4 mW·kg\textsuperscript{-1} \textsuperscript{10}, 5.7 mW·kg\textsuperscript{-1} \textsuperscript{22}).

The ratio of the pulsatile to steady power input also decreased with age, a change which may be related to the amount of energy reflected from the lung periphery. The magnitude of any reflected wave will depend on the degree of attenuation, and if the major reflection site is at the periphery, attenuation will be related to pathway length. The distance over which a wave travels from the heart to the reflection site and back is 60 mm in the newborn pig and 240 mm at 4 weeks (table 2). Assuming an average attenuation coefficient of 1% per cm at a frequency of 10 Hz\textsuperscript{23} the attenuation will account for only a 6% drop in amplitude in newborns, while in the older animals the reduction will be of the order of 22%. Recruitment of small intracapillary arteries soon after birth\textsuperscript{3} may also contribute to wave attenuation in the very young animal. The greater amount of vascular smooth muscle in the peripheral arteries of the newborn may increase vessel tone and so increase the magnitude of any reflections seen in the main pulmonary artery. In adult dogs the influence of wave reflection on the form of input impedance spectrum is small.\textsuperscript{24} We conclude that the reduction with age in the pulsatile power output of the right heart relative to its steady counterpart is due to a decrease in effective wave reflection dependent on an increase in attenuation and possibly on the magnitude of the reflection coefficient itself.

A detailed study of the relationship between age, vaso-activity and pulmonary vascular impedance should provide some explanation for the change in pulsatile/steady power ratio during early life.

Smooth muscle activity and attenuation controls the values of low frequency impedance and peripheral resistance, and may also affect the magnitude of the characteristic impedance, although this depends mainly on the elasticity and diameter of the larger proximal vessels.\textsuperscript{22-27} The findings in the present and in a previous study taken in conjunction, suggest that the fall in characteristic impedance with increasing age is due primarily to the increasing size of the pulmonary arteries rather than to the change in their elasticities. In the previous study\textsuperscript{5} we measured the static elasticity of the pulmonary artery in infant pigs and found that, in spite of a marked increase in the structural stiffness during early life the pressure-strain elastic modulus of each age group measured at its in vivo working mean pressure changed little during this period.

Using the expression:

\[ Z_c = \frac{(p\cdot Ep/2)\cdot 1/A}{2} \] (2)

and the Ep values from the previous study, the calculated value of Zc falls from 2.3 to 0.59 × 10\textsuperscript{6} Nm\textsuperscript{-2} s (table 1). Both estimated and calculated values of Zc fall with age and at most ages the values are similar. Given these observations, the variation with age appears to be determined primarily by changes in cross sectional area of the pulmonary arteries.

In conclusion, in the pig at birth the pulmonary arteries are of relatively small diameter but show a comparatively high distensibility even at a high pulmonary arterial pressure. During the first 2 weeks

\begin{table}
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Study (mW)</th>
<th>Pulsatile (mW)</th>
<th>Total power input</th>
<th>Pulsatile/ steady power input</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KE*</td>
<td>PF†</td>
<td>KE</td>
<td>PF</td>
</tr>
<tr>
<td>1 h</td>
<td>1.11±0.53</td>
<td>9.00±2.1</td>
<td>1.66±0.39</td>
<td>3.35±0.77</td>
</tr>
<tr>
<td>12 h</td>
<td>3.12±1.01</td>
<td>15.8±2.4</td>
<td>5.63±1.5</td>
<td>4.97±1.8</td>
</tr>
<tr>
<td>24 h</td>
<td>1.10±0.02</td>
<td>7.12±1.3</td>
<td>0.56±0.14</td>
<td>4.80±1.7</td>
</tr>
<tr>
<td>48 h</td>
<td>0.83±0.20</td>
<td>14.7±2.9</td>
<td>4.71±0.69</td>
<td>6.09±1.3</td>
</tr>
<tr>
<td>1 w</td>
<td>0.33±0.06</td>
<td>11.4±2.2</td>
<td>1.97±0.12</td>
<td>3.43±0.12</td>
</tr>
<tr>
<td>2 w</td>
<td>0.42±0.12</td>
<td>19.8±5.7</td>
<td>3.41±0.34</td>
<td>4.46±1.6</td>
</tr>
<tr>
<td>4 w</td>
<td>0.75</td>
<td>39.1</td>
<td>5.94</td>
<td>7.39</td>
</tr>
</tbody>
</table>

*Power due to kinetic energy of blood
†Pressure/flow power

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of life both arterial diameter and structural stiffness increase but functional distensibility is unchanged at the new lower pressure and the right ventricular power output/kg is halved. The ratio of pulsatile to steady power input to the lung decreased from 0.5 to 0.39 between the first hour and 2 weeks of life, a change which probably due to increased attenuation of the reflected wave with increasing pathway length. A reduction in the magnitude of the reflection coefficient due to an increase in size and reduction in muscularity component.

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References

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