A comparison of pressure-volume relations of the fetal, newborn, and adult heart

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Romero, Tomas, James Covell, and William F. Friedman. A comparison of pressure-volume relations of the fetal, newborn, and adult heart. Am. J. Physiol. 222(5): 1285-1290. 1972.—A marked paucity of information exists concerning the physiological characteristics of the developing heart. The purpose of the present investigation was to analyze and compare the compliance of the right and left ventricles in hearts obtained from 8 fetal and 9 newborn lambs and 10 adult sheep. Moreover, to assess the influence of filling of the contralateral chamber on distensibility, the distensibility of each ventricle was determined both with the opposite ventricle empty and at various fixed pressures. Using various models of left and right ventricular geometry, the pressure-volume data were converted to units of wall tension and percentage change in internal radius, allowing a direct comparison of all of the age groups studied. In addition, the concentrations of ventricular hydroxyproline were determined to evaluate the contribution of connective tissue to compliance at each age level. The major findings of the present study indicate that the pressure-volume and wall tension-radius relations of both the left and right ventricles are comparable in the fetal lamb close to term. In the newborn period, the right ventricle has compliance characteristics similar to the right ventricle of the fetus. The adult right ventricle is significantly more compliant than both the fetus and newborn. In the early postnatal period, the left ventricle alters its pressure-volume and stress-strain characteristics and assumes an intermediate position between fetus and adult. At all ages the right ventricle is more compliant than the left ventricle. When one evaluates the influence of filling one ventricle on reducing the distensibility of the opposite ventricle, the most profound effect is observed in the fetus, followed by the newborn, and then the adult.

Growth and maturation; cardiovascular dynamics; myocardium; compliance; hydroxyproline; connective tissue

An understanding of the changes in cardiovascular structure and function that accompany growth is a prerequisite to a proper comprehension of the clinical consequences of congenital heart lesions throughout life (4, 19). In this regard, any existing age-related differences in the force required to distend the ventricular chambers must be considered in assessing and comparing the responses of the premature, newborn, and adult hearts to normal or disease-induced alterations in ventricular volume. Although changes in ventricular volume are associated with many cardiovascular malformations and accompany corrective or palliative cardiac operations, a marked paucity of information exists concerning the basic physical properties of the myocardium in the fetus and newborn. Accordingly, the purpose of the present investigation was to analyze and compare the compliance or distensibility of the right and left ventricles in hearts obtained from fetal and newborn lambs and adult sheep. Moreover, in order to assess the influence of filling of the contralateral chamber on compliance, the distensibility of each ventricle was determined both with the opposite ventricle empty and at several fixed pressures. Using various models of left and right ventricular geometry, the pressure-volume data were converted to units of wall tension and percentage change in internal radius, allowing a direct comparison of all of the age groups studied. In addition, the concentrations of ventricular hydroxyproline were determined to evaluate the contribution of connective tissue to compliance at each age level.

Various aspects of these investigations have appeared previously in preliminary form (5, 6, 17).

MATERIAL AND METHODS

Whole hearts were excised rapidly from 14 adult sheep (1-3 years old) and 14 newborn lambs (12 ± 4 ± 3 days old) after pentobarbital anesthesia (15 mg/kg iv). The group of newborns ranged in age from 1 to 25 days and included 7 lambs less than 10 days of age. Adult and newborn animals were ventilated artificially with a Harvard positive-pressure respirator. Pregnancies were confirmed radiographically in ewes with known breeding dates. The hearts of 19 fetal lambs (138 ± 3 days gestational age, term = 147 days) were removed rapidly after hysterotomy under spinal anesthesia (4 ml of 1% lidocaine).

All hearts were rinsed and suspended in saline at a constant temperature of 32 C. The coronary arteries were ligated immediately beyond the coronary ostia, and each A-V groove was clamped to prevent ventriculocardiac regurgitation. Grooved steel plugs incorporating three metallic cannulas were tied into the aortic annulus and into the pulmonary annulus. One cannula was connected to a pressure transducer (Statham model P23 Db), another to a spring-loaded manual syringe, and the third cannula was connected to a vertical tubing utilized to regulate intracavitary pressure.

Pressure-volume determinations were begun within 15 min of cardiectomy. The pressure signals and volume increments were inscribed on a Clevite-Brush recorder, model 260. During continuous monitoring of intraventricular pressure, intracavitary ventricular volume changes were determined by a zero-positioning method. The pressure transducer and a spring-loaded syringe were alternately connected to the ventricle, and the intraventricular pressure was increased by increments of approximately 10 mm Hg until the ventricle was empty and at various fixed pressures. Using various models of left and right ventricular geometry, the pressure-volume data were converted to units of wall tension and percentage change in internal radius, allowing a direct comparison of all of the age groups studied. In addition, the concentrations of ventricular hydroxyproline were determined to evaluate the contribution of connective tissue to compliance at each age level.

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were accomplished by infusing or withdrawing preset increments of saline at 32°C at fixed intervals: 2 ml for the adult heart and 0.2 ml for the newborn and fetal hearts. The initial pressure-volume relationship for each ventricle was determined with the opposite ventricle empty. Zero pressure was defined arbitrarily as the intracavitary pressure existing at zero volume, and the absence of a leak in the system was verified by measured withdrawal of the total amount of infused fluid after each experimental run. To avoid overdistension of the ventricles, the volume infusion was stopped arbitrarily at an intracavitary pressure of 30 mm Hg.

Following the inscription of pressure-volume relations with the opposite ventricle empty, each ventricular chamber was kept at a constant pressure of 5 or 15 mm Hg by saline infusions and adjustment of the height of the vertical siphon tube in order to study the influence of different ventricular filling pressures (5 and 15 mm Hg) on the pressure-volume relations of the opposite ventricle. A final pressure-volume relation was determined for each ventricle with the contralateral chamber empty. All final measurements were within 10% of those obtained at the beginning of the experiment.

Cardiac dimensions were determined with the heart at the zero-pressure point. The wall thickness was measured at the anterolateral aspect of the wall in both ventricles, 3 cm below the A-V groove in the adult, 1 cm in the newborn and fetus. These values were not used to calculate ventricular wall tension (vide infra). The RV and LV long axes were the longest distances measured between the apex and base.

The RV and LV circumferences were measured at the level of the tricuspid and mitral orifices, respectively. Circumference/axis ratios were employed as indicators of ventricular shape.

Connective Tissue Comparison

Hearts were removed from a separate group of eight fetal lambs and eight adult sheep whose ages matched those employed in the pressure-volume experiments. Samples of interventricular septum were dissected free of epicardium and endocardium, minced, blotted, and weighed. Water content was determined by drying to constant weight (24 hr at 100°C in vacuo over P₂O₅). Dry samples, weighing between 5 and 10 mg, were assayed for hydroxyproline by the method of Prockop and Udenfriend (16), and the concentration of hydroxyproline was expressed in micrograms per milligram of either dry or wet weight.

Stress-Strain Calculations

A) Left ventricle. Left ventricular wall tension was calculated using two different spherical and one ellipsoidal geometrical model (1, 3, 7, 8, 20, 22, 23). For all calculations, left ventricular mass corresponded to the left ventricular free wall and septum, and its homogeneous distribution was assumed. Wall thickness was calculated by subtracting the internal radius (Rᵢ) derived at any given volume from the external radius (Rₑ).

The following equations for tension (g/cm²) were employed:

\[
\text{Sphere 2: } \frac{PR \cdot R₁^3}{R₀^2 - Rᵢ^3} \quad (2)
\]

\[
\text{Ellipsoid: } \frac{PR \cdot R₁ - 2Rᵢ^3}{L^2} \quad (3)
\]

where PR = pressure (g/cm²), Rᵢ = internal radius (cm), Rₑ = external radius (cm), L = wall thickness (cm), L = longitudinal axis (cm).

The relationships between the tension-radius curves of the fetal, newborn, and adult groups were not dependent on the geometrical model utilized for calculating left ventricular wall tension. Thus, only data derived from employing equation 1 (T = PR·Rᵢ²/2h) will be presented in this report.

B) Right ventricle. Right ventricular wall tension was calculated employing equation 3 above. Rᵢ was calculated by assuming that right ventricular internal volume was represented by a hemiellipsoid, and right ventricular free wall mass was distributed homogeneously about the curved surface. Right ventricular wall thickness was calculated in the manner described above for the left ventricle.

Methods of Comparison

In order to compare directly the distensibility of the fetal, newborn, and adult right and left ventricles, all of different sizes and weights, the changes in wall tension were analyzed as a function of the percentage change in Rᵢ. The control value for Rᵢ corresponded to the calculated Rᵢ at a wall tension of 5 g/cm².

In order to calculate ventricular compliance, the pressure-volume and tension-radius data of each chamber, with zero volume and pressure in the opposite ventricle, were fitted to an exponential relationship in every experiment by the method of least squares approximation (21). The pressure-volume and tension-radius relations were defined as P = a + b·e⁻ⁿ and T = a + b·e⁻ⁿ, respectively, when P = pressure (mm/Hg), T = tension (g/cm²), V = volume (ml), Rᵢ = internal radius, and a, b, c are constants.

It is apparent from these equations that the slope of either the pressure-volume or tension-radius curves at any level of pressure or tension depends primarily on the magnitude of the constant c.

RESULTS

Anatomic Findings

Cardiac chamber weights and dimensions are summarized in Table 1 and related to body weight in Fig. 1. There were no significant differences between the weights of the free walls of either ventricle in the fetus or between the thickness of the fetal and the newborn right ventricles. Figure 1 demonstrates that relative to body weight there is a disproportionate growth of the left ventricle in the postnatal period. Moreover, total heart weight constituted a significantly greater percentage of body weight in both the fetus (0.60%) and newborn (0.73%) when compared to the adult (0.49%, P < 0.001). Although the absolute weights of both ventricles increased postnatally, the newborn right ventricle was only 29.7% heavier than the fetal right ventricle, whereas the left ventricular free wall almost
TABLE 1. Cardiac chamber weights and dimensions

<table>
<thead>
<tr>
<th></th>
<th>Fetus (8)</th>
<th>Newborn (9)</th>
<th>Adult (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>138 ± 3 days</td>
<td>11.9 ± 4 days</td>
<td>1.7 ± 0.5 years</td>
</tr>
<tr>
<td>Body wt, kg</td>
<td>3.9 ± 0.2*</td>
<td>5.27 ± 0.5*</td>
<td>50.4 ± 3.3*</td>
</tr>
<tr>
<td>Heart wt, g</td>
<td>23.3 ± 1.4</td>
<td>38.1 ± 3.4</td>
<td>251.1 ± 16.7</td>
</tr>
<tr>
<td>LV wt + septum, g</td>
<td>12.6 ± 0.3</td>
<td>21.8 ± 2.8</td>
<td>146.9 ± 9.7</td>
</tr>
<tr>
<td>LV wt free wall, g</td>
<td>8.0 ± 0.6</td>
<td>11.7 ± 1.9</td>
<td>100.3 ± 6.4</td>
</tr>
<tr>
<td>RV wt free wall, g</td>
<td>NS</td>
<td>9.6 ± 0.7</td>
<td>55.2 ± 3.5</td>
</tr>
<tr>
<td>LV wall thickness, mm</td>
<td>NS</td>
<td>8.0 ± 0.4</td>
<td>15.9 ± 0.7</td>
</tr>
<tr>
<td>RV wall thickness, mm</td>
<td>P &lt; 0.05</td>
<td>4.8 ± 0.2</td>
<td>6.95 ± 0.6</td>
</tr>
<tr>
<td>LV long axis, cm</td>
<td>7.4 ± 0.4</td>
<td>4.5 ± 0.2</td>
<td>8.19 ± 0.3</td>
</tr>
<tr>
<td>RV long axis, cm</td>
<td>3.8 ± 0.2</td>
<td>3.6 ± 0.1</td>
<td>7.16 ± 0.2</td>
</tr>
<tr>
<td>LV circumf, cm</td>
<td>4.86 ± 0.26</td>
<td>3.75 ± 0.17</td>
<td>10.53 ± 0.44</td>
</tr>
<tr>
<td>RV circumf</td>
<td>4.41 ± 0.26</td>
<td>4.23 ± 0.18</td>
<td>10.36 ± 0.47</td>
</tr>
<tr>
<td>LV long axis</td>
<td>1.27 ± 0.07</td>
<td>1.31 ± 0.10</td>
<td>1.31 ± 0.00</td>
</tr>
<tr>
<td>RV long axis</td>
<td>1.09 ± 0.06</td>
<td>NS</td>
<td>1.19 ± 0.08</td>
</tr>
</tbody>
</table>

* Values are averages ± se.

Numbers in parentheses indicate number of observations.

FIG. 1. Relations between heart weight, chamber weight, and body weight in fetal and newborn lamb and adult sheep. Columns represent average values (±SEM). Significantly higher newborn heart wt/body wt ratio (P < 0.001) results from a higher LV wt/body wt ratio (P < 0.001) than either fetus or adult. For both fetus and newborn, RV wt/body wt ratio was higher than adult (P < 0.001). Thus, fetus has a greater heart wt/body wt ratio than adult (P < 0.001) because of a greater RV mass.

doubled in weight (+03.8%). The weight gain of the ventricular septum more closely paralleled that of the left ventricle (+54.3%). The wall thickness of both ventricles was comparable in the fetus. However, the postnatal changes in left ventricular wall thickness are considerable (+42.9%), while the thickness of the newborn right ventricle is little changed from that of the fetus (+9.1%).

Hydroxyproline is found only in collagen and forms a constant concentration of collagen (?). In order to evaluate the influence of collagen on ventricular distensibility, the concentration of hydroxyproline in fetal and adult ventricles was determined (Table 2). When compared to the adult, the fetal ventricle has a lower hydroxyproline concentration per gram of wet weight, but since the fetal myocardium contained a significantly higher water content (79 ± 0.9 % vs. 74.3 ± 0.5 %, respectively, P < 0.001), there were similar hydroxyproline concentrations when the data were expressed in terms of dry weight.

TABLE 2. Hydroxyproline concentrations and water content

<table>
<thead>
<tr>
<th></th>
<th>Fetus (8)</th>
<th>Newborn (9)</th>
<th>Adult (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Content (%)</td>
<td>79.7 ± 0.9*</td>
<td>0.427 ± 0.3</td>
<td>1.8 ± 0.08</td>
</tr>
<tr>
<td>HOP, µg/g wet wt</td>
<td>0.427 ± 0.3</td>
<td>0.731 ± 0.4</td>
<td>2.76 ± 0.2</td>
</tr>
<tr>
<td>HOP, µg/g dry wt</td>
<td>1.8 ± 0.08</td>
<td>1.05 ± 0.44</td>
<td>2.5 ± 0.41</td>
</tr>
</tbody>
</table>

* Values are averages ± se.

Numbers in parentheses indicate number of observations.

Pressure-Volume Relations

The average pressure-volume curve for each ventricle at each age is shown in Fig. 2. No significant differences existed in the pressure-volume relations of either ventricle in the fetus, whereas the relatively greater stiffness of the left ventricle compared to the right becomes apparent in the newborn period and is quite striking in the adult.

The influence of filling of either ventricle on the pressure-volume relationships of the opposite ventricle is illustrated in Fig. 3. Both right and left ventricular pressure-volume relationships were comparable with either 0 or 5 mm Hg pressure in the opposite ventricle. However, at any age, pressures of 15 mm Hg in either ventricle significantly decreased the volume necessary to achieve an intracavitary pressure of 5 mm Hg in the contralateral chamber. This
The results of the present study indicate that the pressure-volume and wall tension-radius relations of both the left and right ventricles are comparable in the fetal lamb close to term. In the newborn period the right ventricle has compliance characteristics similar to the right ventricle of the fetus, and the adult right ventricle is significantly more compliant than either the fetal or newborn right ventricle. In the early postnatal period, the left ventricle alters its pressure-volume and stress-strain characteristics and assumes an intermediate position between fetus and adult. At all ages, the right ventricle is more compliant than the left ventricle, the most profound effect is observed in the fetus, followed by the newborn and then the adult. This increased sensitivity of the fetal ventricle to filling of the contralateral ventricle may explain the ease with which the premature newborn exhibits systemic venous congestion in the presence of lesions primarily deranging left ventricular function or pressure.

A number of factors may be responsible for the distensibility differences observed between the young and old hearts. Well-known differences exist in various mammalian species in the mass relationships between the two ventricles.
TABLE 3. Exponential fit of grouped data

<table>
<thead>
<tr>
<th></th>
<th>Left ventricle</th>
<th>Right ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus (8)</td>
<td>( P = 2 + 2.4e^{0.3V} ) ( P &lt; 0.05 )</td>
<td>( P = 0.03 + 1.1e^{0.4V} ) ( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Newborn (9)</td>
<td>( P = 0.01 + 1.9e^{0.4V} ) ( P &lt; 0.001 )</td>
<td>( P = -0.18 + 1.2e^{0.4V} ) ( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Adult (10)</td>
<td>( P = 3.3 + 0.2e^{-0.3V} ) ( P &lt; 0.05 )</td>
<td>( P = 1.0 + 0.2e^{0.0V} )</td>
</tr>
</tbody>
</table>

**Tension-radius relations** \( T = a + be^{CRi} \)

- **Fetus (8)**: \( T = 1.4 + 0.00001e^{1.25Ri} \) \( P < 0.01 \)
- **Newborn (9)**: \( T = 2.7 + 0.00005e^{6RI} \) \( P < 0.001 \)
- **Adult (10)**: \( T = 3.5 + 0.00001e^{2RI} \) \( P < 0.001 \)

Numbers in parentheses indicate number of observations.

in the perinatal period when compared to the adult (11, 12). The perinatal change in right and left ventricular mass undoubtedly reflect the cardiocirculatory transition necessitated by the transfer from placental to pulmonary gas exchange and the accompanying changes in systemic and pulmonary venous return and vascular resistance (19). The cardiac chamber weights and dimensions obtained in the present study reveal a disproportionate rate of change of chamber size and wall thickness between the two ventricles after birth. Thus, in the newborn, the left ventricle gets larger and thicker walled faster than the right ventricle gets larger and thinner walled. Since the calculation of wall tension is inversely proportioned to wall thickness (1, 3, 9, 10), the rapidly thickening newborn left ventricle begins to approximate the adult left ventricle in its stress-strain relations, while the right ventricular wall thickness and stress-strain relations are still similar to those of the fetus.

We have found that compliance increases with advancing development in cardiac muscle isolated from the right ventricles of fetal lambs and adult sheep (5, 17). These findings parallel those obtained in the present study utilizing the whole heart. However, the isolated muscle differences cannot be accounted for by the alterations in the mass relationships between the ventricles, since the curves relating resting tension to muscle length are significantly steeper in the fetus and newborn, even when the tensions generated by the isolated muscles are corrected for muscle cross-sectional area. In this regard, we have observed major ultrastructural differences between fetal and adult myocardium that may help explain a reduced compliance in the young heart (6, 17). The diameter of the myofilaments is significantly less in
the fetal than the adult heart and, furthermore, it is evident that in the young hearts the proportion of noncontractile mass (nuclei, mitochondria, and surface membranes) to the number of myofilaments is significantly higher than in the adult. Thus, relatively increased amounts of noncontractile cellular elements, including surface membranes, may contribute to the age-related differences in ventricular distensibility (6).

There are several factors that may be excluded as accounting for the apparent stiffness of the fetal and newborn hearts. Experiments demonstrating changes in pressure-volume relations following coronary perfusion with collagenase (14) indicate that passive ventricular distensibility may be influenced by interstitial connective tissue. In the present study there were no significant differences in cardiac hydroxyproline concentration when the data were corrected for dry weight. However, when corrected for wet weight, there was significantly more hydroxyproline found in the fetal than the adult heart and, furthermore, it is evident that spherical shape would increase the calculated values of wall tension (18). Moreover, because the wall thickness of either ventricle in the adult is less relative to chamber weight when compared to the fetus or newborn, even greater differences would be observed than calculated by the present methods. It is known that clamping the mitral valve may alter the slope of a pressure-volume relationship (15). In the study by Powell et al. (15) the average increase in stiffness associated with clamping the mitral valve was 0.97 cm H2O/ml of infused volume. It is unlikely that our findings were influenced significantly by A-V valve clamping, since far greater age-related differences were observed than could be accounted for in the absence of clamping.

Since the elasticity of a biological structure is a history-dependent phenomenon (7), it is possible that our results might be different if our wall tension-radius calculations were based on different initial lengths. In order to examine this question, tension-radius relations were constructed from an initial length corresponding to the internal radius at an initial length corresponding to the internal radius at

REFERENCES