Distribution of fetal cardiac output: importance of pacemaker location

PAUL T. PITLICK, STANLEY E. KIRKPATRICK, AND WILLIAM F. FRIEDMAN
Division of Pediatric Cardiology, University of California, San Diego 92103, and
School of Medicine, La Jolla, California 92037

Pitlick, Paul T., Stanley E. Kirkpatrick, and William F. Friedman. Distribution of fetal cardiac output: importance of pacemaker location. Am. J. Physiol. 231(1): 204-208. 1976. — Important questions exist about the relative roles of changes in heart rate versus extent of myocardial shortening in regulating fetal cardiac output, because increases in heart rate created by left atrial pacing have been shown to increase right ventricular output and decrease left ventricular output. Since the pacemaker site could importantly influence foramen ovale flow and, hence, each ventricle's output, changes in individual ventricular outputs were examined when both the right and left atria were paced at a rate of 270 beats/min in five acute and in eight chronically instrumented fetal lamb studies. With pacing of either atrium, total cardiac output was unchanged compared to control values. However, the right ventricle contributed more to total cardiac output with left atrial pacing (73% acute, 65% chronic) than with right atrial pacing (51% acute, 57% chronic). Convert changes were observed in left ventricular contribution to total cardiac output with left atrial pacing (27% acute, 33% chronic) as compared to right atrial pacing (49% acute, 43% chronic). Thus the disparity that exists normally in the contributions of the right and left atria to total cardiac output is accentuated with left atrial pacing and minimized with right atrial pacing. Pressure measurements demonstrated changes in the atrial pressure relations that would be expected to alter flow across the foramen ovale depending on the chamber initially activated. Previous experimental differences can, therefore, be attributed to changes in the magnitude of shunting across the foramen ovale and depend on pacemaker location.

IT HAS BEEN SUGGESTED that heart rate is the primary regulator of fetal cardiac output (12-14). Rudolph and Heymann and their associates have shown that right ventricular output increases substantially as increases in heart rate were produced by left atrial pacing (14). Studies from our laboratory have shown a reduction in left ventricular output associated with left atrial pacing (6, 7, 11) over a comparable range of heart rates. Since the above analyses of individual ventricular outputs show opposite directional changes with alterations in heart rate, it was considered necessary to examine more closely the experimental methods employed with respect to the site of pacing and the fact that the foramen ovale provides an interatrial communication in the normal fetus. Although the techniques for measuring cardiac output differed in the studies cited above (flowmeter (12, 14) vs. indicator dilution (6, 11)), simultaneous measurements of right and left ventricular output and of total cardiac output with selective pacing of each atrium have not been reported. Accordingly, the present investigation was designed to examine the latter interactions and the results form the basis of this report.

MATERIALS AND METHODS

The general techniques of fetal instrumentation have been described in detail previously (1, 2, 5). Nine mixed-western breed, pregnant ewes with gestational ages of 110–140 days (term = 147 days) were sedated with intramuscular meperidine (150 mg), chlorpromazine (37.5 mg), and atropine (0.5 mg). The maternal popliteal artery and vein were cannulated with polyvinyl catheters (0.038 inch ID) which were burrowed subcutaneously and exteriorized on the ewe's left flank. Spinal anesthesia was then induced with 4 ml 1% tetracaine, and the ewe was given 250 mg pentobarbital intravenously to maintain sedation. After hysterotomy the fetal head was exposed and catheters placed in the ascending aorta via the left external carotid artery and into the right atrium via the left external jugular vein under local anesthesia with 1 ml 1% lidocaine. The fetal head was replaced and after subcutaneous infiltration of 2 ml 1% lidocaine over the left fourth rib of the fetus, a thoracotomy was performed. Polyvinyl catheters were placed directly into the main pulmonary artery and into the left atrium, and bipolar pacing wires sutured to both the right and left atrial appendages.

Five fetuses were studied acutely; the four remaining fetuses were returned to the uterus after their catheters and wires were exteriorized. A full 2-wk recovery period was allowed before any studies were performed in the latter group, and a total of eight chronic studies were performed.

In accord with our previous results (5), fetal arterial pH, P02, Pco2, and hematocrits were monitored during all studies, and averaged 7.35 ± 0.1, 24.8 ± 1.5, 50.6 ± 1.6, and 37.2 ± 1.6, respectively. During acute studies intravascular pressures were obtained using Statham P-23dB strain-gauge transducers and recorded on a Cleveite-Brush multichannel oscillograph and on magnetic tape. In all studies, the indocyanine green dye technique was employed to measure cardiac outputs (4,
Cardio-green dye was injected (0.5 ml in a concentration of 1.25 mg/ml) into the right atrium while blood for sampling was withdrawn simultaneously from the fetal ascending aorta and main pulmonary artery. Catheter volumes were 1.1 ml, and sampling rate was 8 ml/min from each great vessel. The total sampling period averaged 40 s and, therefore, approximately 12 ml were removed for each study. Sampled blood was reinjected and indicator was then injected into the left atrium with simultaneous sampling from the great arteries. These paired studies were done in the basal state, again when the right atrium was paced at 270 stimuli/min, and a 3rd time when the left atrium was paced at the latter rate. Ventricular outputs were calculated from the areas under the appearance curves on a standard program employing a PACE-EAI analog-digital computer.

The conventional application of indicator-dilution techniques to determine cardiac output assumes that intercirculatory shunting does not occur. When a shunt is present, it is necessary to alter the Stewart-Hamilton equation. In the fetal lamb shunting may occur at the level of both the foramen ovale and the ductus arteriosus. With injection of indicator into one atrium some dye may traverse the foramen ovale and appear upon sampling from the contralateral great artery. While the precise amount of dye entering the contralateral side may not be quantified after a single injection into one atrium and examining appearance curves, it is possible to quantify ventricular outputs by analyzing appearance curves after separate injections of indicator into each atria. For example, with an injection of dye (D) into the left atrium, an amount (dL) may be shunted from left to right across the foramen ovale. Thus LVO = (dL/A1) and RVO = (dL/P2), where A1 and P2 are the areas under the aortic and pulmonary artery appearance curves, respectively. Since left and right ventricular outputs are maintained constant during steady-state conditions, the above expressions give rise to the following equations:

\[ LVO = \frac{(P_2 - P_1)}{(A_1 - A_2)} D, \]

\[ RVO = \frac{(A_1 - A_2)}{D}. \]

The significance of results was calculated on a standard program using the Student paired- \( t \) test.

**RESULTS**

Values for gestational age, weight (in the acute animals), heart rate, and individual ventricular outputs are shown in Table 1. The average gestational age for the acute group was 130 days, and for the chronically instrumented animals it was 127 days.

**Atrial pressures.** The atrial pressure relationships at rest and during selective atrial pacing are shown in Fig. 1 as the difference in real time between right and left atrial pressure (ARA - LA). Excursions above zero of the ARA - LA tracing indicate that right atrial pressure is greater than left atrial pressure; conversely, when the tracing falls below the zero line, left atrial pressure is greater than right atrial pressure. Under basal conditions right atrial pressure exceeds left atrial pressure for almost all of the cardiac cycle (Fig. 1, top). Pacing the right atrium maintains the normal atrial pressure difference (Fig. 1, middle). In contrast, when initial activation of left atrium occurs as a result of pacing from that site, the pressure-difference curve is substantially more negative, indicating higher left atrial pressure for more of the cardiac cycle (Fig. 1, bottom).

**Table 1. Individual values—acute and chronic studies**

<table>
<thead>
<tr>
<th>Animal No</th>
<th>Days Post-operative</th>
<th>Weight, kg</th>
<th>Gestational Age, days</th>
<th>Basal Heart Rate, beats/min</th>
<th>Control</th>
<th>Cardiac Outputs, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RV</td>
<td>LV</td>
<td>Total</td>
</tr>
<tr>
<td>1</td>
<td>Acute</td>
<td>1.2</td>
<td>110</td>
<td>160</td>
<td>450</td>
<td>480</td>
</tr>
<tr>
<td>2</td>
<td>Acute</td>
<td>3.2</td>
<td>130</td>
<td>144</td>
<td>900</td>
<td>450</td>
</tr>
<tr>
<td>3</td>
<td>Acute</td>
<td>3.4</td>
<td>130</td>
<td>192</td>
<td>760</td>
<td>510</td>
</tr>
<tr>
<td>4</td>
<td>Acute</td>
<td>4.0</td>
<td>140</td>
<td>210</td>
<td>1,040</td>
<td>560</td>
</tr>
<tr>
<td>5</td>
<td>Acute</td>
<td>3.4</td>
<td>192</td>
<td>810</td>
<td>630</td>
<td>1,440</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>Acute</td>
<td>3.2 ± .5</td>
<td>180 ± 12</td>
<td>790 ± 98</td>
<td>530 ± 31</td>
<td>1,320 ± 111</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>120</td>
<td>210</td>
<td>980</td>
<td>360</td>
<td>1,340</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>127</td>
<td>190</td>
<td>1,360</td>
<td>750</td>
<td>2,110</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>130</td>
<td>140</td>
<td>940</td>
<td>460</td>
<td>1,400</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>121</td>
<td>230</td>
<td>680</td>
<td>520</td>
<td>1,200</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>127</td>
<td>140</td>
<td>480</td>
<td>310</td>
<td>790</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>131</td>
<td>155</td>
<td>1,210</td>
<td>540</td>
<td>1,750</td>
</tr>
<tr>
<td>12</td>
<td>21</td>
<td>130</td>
<td>195</td>
<td>1,070</td>
<td>880</td>
<td>1,950</td>
</tr>
<tr>
<td>13</td>
<td>25</td>
<td>134</td>
<td>165</td>
<td>600</td>
<td>440</td>
<td>1,040</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>Chronic</td>
<td>127 ± 2</td>
<td>178 ± 12</td>
<td>920 ± 108</td>
<td>530 ± 68</td>
<td>1,450 ± 161</td>
</tr>
</tbody>
</table>

RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium.
Ventricular outputs. Average values of total and individual ventricular outputs at rest and with selective atrial pacing are presented in Table 1 and Fig. 2 and percent changes in distribution are illustrated in Fig. 3. In the acutely instrumented animals, control values normalized for body weight were 275 ml/min per kg for right ventricular output and 200 ml/min per kg for left ventricular output. These are similar to values reported previously from other laboratories with respect both to absolute values and the percentage contribution of each ventricle to total output (12, 13). At naturally occurring heart rates right ventricular output was greater than left ventricular output in both the acute experiments and in the chronically instrumented animals, although this difference was somewhat more pronounced in the chronic group. Left ventricular output was similar for both acute and chronic animals in the basal state.

As a final validity check for the determination of cardiac output by our method, average right ventricular outputs in our chronically instrumented animals were compared to outputs previously obtained by electromagnetic flow probes at 123 days' gestation (12, 13). Values were essentially identical both under basal conditions and when the left atrium was paced at 270 beats/min.

In the above comparisons two parameters were varied: heart rate was changed from basal to 270 beat/min, and, in addition, the focus for cardiac contraction was changed from the sinus node to an external electrical value. Conversely, with left atrial pacing, the output of the left ventricle fell 47% (P < .01), while no change was observed in right ventricular output (P < .06) compared to control.

In the chronically instrumented animals pacing of either atrium did not significantly alter total cardiac output (P < 0.08). However, with right atrial pacing the output of the left ventricle rose substantially (23%, P < 0.006), while right ventricular output was unchanged (P < 0.63) compared to control. Conversely, with left atrial pacing, right ventricular output rose 12% (P < 0.07), while left ventricular output was unchanged (P < 0.54) compared to control.

In the above comparisons two parameters were varied: heart rate was changed from basal to 270 beat/min, and, in addition, the focus for cardiac contraction was changed from the sinus node to an external electrical...
atrial pacing and fetal cardiac output

stimulus. The data may, therefore, be analyzed more appropriately by comparing individual ventricular outputs when only one variable—the pacing site—is changed at a constant heart rate (Fig. 2). Thus, in both acute and chronic experiments, right ventricular output was significantly higher when the left atrium was paced, as compared to its output during right atrial pacing (∂ < 0.05). Conversely, left ventricular output was significantly higher when the right atrium was paced, as compared to its output during left atrial pacing (∂ < 0.009). The relative alterations in the distribution of ventricular output are illustrated in Fig. 3.

Discussion

The current studies were stimulated by the controversy that exists concerning the relative roles which heart rate and the Frank-Starling mechanism assume in the regulation of cardiac output in the fetal lamb. In previously reported studies (12, 13) it was stated that the Frank-Starling mechanism is of little importance in the fetal sheep, and that heart rate is the primary regulator of cardiac output. Evidence for this latter view emanated from chronically instrumented fetal lamb experiments in which intravascular volume infusions did not increase right ventricular output substantially (3, 8) and studies in which left atrial pacing significantly increased right ventricular output (12, 13). In the latter experiments (12, 13) right ventricular output was shown to increase progressively from low heart rates produced by vagal stimulation to higher rates produced by left atrial pacing until a decline occurred beyond heart rates of 300 beats/min. In contrast, we have shown that fetal left ventricular output decreases as a result of left atrial pacing at heart rates above basal levels (6). Moreover, evidence for the importance of the Frank-Starling mechanism in regulating fetal cardiac output was provided in studies from our laboratory demonstrating that in the chronically instrumented fetal lamb, large changes in beat-to-beat extent of left ventricular shortening occurred as a consequence of spontaneous and experimentally induced alterations in left ventricular end-diastolic diameter (7). Hence, we have maintained that the Frank-Starling mechanism is operative and effective in the fetal lamb, and is a major determinant of fetal cardiac output.

When analyzing the apparent differences induced by left atrial pacing upon fetal left and right ventricular outputs it was recognized that the site of atrial pacing could importantly alter the pattern of blood flow across the patent foramen ovale and thus alter the magnitude of either left or right ventricular filling. While the present study does not provide direct data supporting the importance of the Frank-Starling mechanism in the fetus, it does identify the necessity of considering the location of the atrial pacemaker site before drawing conclusions concerning the role of heart rate per se in regulating fetal cardiac output. Thus the present investigation demonstrated that total cardiac output was unchanged statistically from control values in both acute and chronic experiments with both left and right atrial pacing. Despite the fact that total cardiac output did not change significantly with selective atrial pacing, important changes occurred in the contribution of each individual ventricle to total cardiac output. Further, selective atrial pacing resulted in important differences in atrial pressure relations that were related not to heart rate, but rather to the location of the pacemaker site since output of either ventricle was reduced significantly when the ipsilateral atrium was paced, when compared to either ventricle's output with contralateral atrial pacing. This study suggests that the higher initial left atrial pressure during left atrial pacing diminishes the magnitude of normal right-to-left shunting across the foramen ovale, resulting in augmentation of right ventricular filling and a relative increase in right ventricular output. Conversely, right atrial pacing maintains the normal fetal right atrial pressure dominance, promotes right-to-left flow across the foramen ovale, and increases left ventricular filling and output. Although changing the artificial pacemaker site alters individual ventricular outputs, no important changes occur in total cardiac output. While the current findings allow a more comprehensive view of the problems associated with defining the relations between heart rate and fetal ventricular outputs, the question of the relative roles of the Frank-Starling mechanism and heart rate in regulating cardiac output in the fetus requires further study.

This investigation was supported by Public Health Service Grants HL 12373 and HL 08646.

P. T. Pillick was the recipient of a postdoctoral fellowship from the San Diego County Heart Association.

W. F. Friedman is the recipient of a Public Health Service Research Career Development Award HL 41737 from the National Heart and Lung Institute.

Address for reprints: W. F. Friedman, Dept. of Pediatrics, University Hospital, 225 West Dickinson Street, San Diego, Calif. 92103.

Received for publication 4 August 1975.

REFERENCES


