The relationship between heart rate and stroke volume in determining cardiac output has been investigated in adult animals and man (2, 3, 11, 12, 16, 17). It has been found that tachycardia or bradycardia are, in general, accompanied by reciprocal changes in stroke volume so that the cardiac output is not altered. Only during severe bradycardia or tachycardia is the stroke volume unable to compensate for heart rate changes and then the cardiac output may fall. The compensatory limits have been identified for the dog and man (3, 13, 14).

In the fetus, the hemodynamic impact of heart rate changes, particularly of bradycardia, has not been completely investigated. Indirect evidence derived from the studies of Downing (6) and his associates seems to suggest that the heart of the newborn lamb obeys the Frank-Starling Law.

The object of the present studies is: a) to investigate the relationship between heart rate and stroke volume, and b) to assess the influence of heart rate changes on systemic and pulmonary hemodynamics. Since in the fetus the heart rate decreases in response to a great number of physiologic stimuli and pathological stresses, emphasis was placed on the hemodynamic effects of bradycardia.

MATERIALS AND METHODS

In 9 near-term pregnant ewes of mixed breed, spinal anesthesia was induced using 4 mg of tetraacaine hydrochloride (Pontocaine) via an indwelling polyethylene catheter. Supplemental doses of lidocaine hydrochloride (Xylocaine) were given as required. This form of anesthesia was selected so that the fetal neural response would not be affected. A dog was then placed on her left side on an operating table and under hexylcaine hydrochloride (Cyclaine) local anesthesia the right jugular vein and carotid artery were cannulated with polyethylene catheters, the carotid catheter serving for monitoring maternal arterial pressure. A tracheostomy was performed and the ewe's respiration was assisted with a Bird respirator, using compressed air or 95% O₂ mixtures with 5% CO₂ added. Through a lower-ventral midline incision, the pregnant horn of the uterus was partially exteriorized and marsupialized to the anterior abdominal wall of the ewe to prevent evisceration. The fetus was then delivered through a hysterotomy and a saline-filled glove placed over the fetal head to prevent respirations. The fetal abdominal wall of the fetus was then marsupialized to the edges of the uterine incision to protect the umbilical circulation. Catheters were placed in the fetal abdominal aorta and inferior vena cava through the femoral artery and vein. The aortic catheter served for monitoring fetal arterial pressure, and the venous catheter for replacing fetal blood collected for respiratory gas analysis with maternal blood. A left thoracotomy was performed through the fourth intercostal space and the pericardium opened, care was taken to preserve the left vagus and phrenic nerves. The ascending aorta, main pulmonary artery, and ductus arteriosus were then isolated by blunt and sharp dissection and were fitted with balanced-field electromagnetic flow transducers.

Through a midline incision in the fetal neck, the left and right vagus nerves were separated from the carotid sheath for a distance of about 2 cm. The nerves were covered with a layer of mineral oil to prevent dehydration and to insulate the surrounding tissue. Fetal temperature was maintained by warm saline packs and a heat lamp. The details of these procedures have been previously reported (4, 5).

Maternal arterial and fetal arterial and pulmonary artery pressures were measured with Statham P-23 pressure strain gauges calibrated to a common zero base line. Phasic and integrated ascending aortic and ductus arteriosus blood flows were monitored with balanced-field electromagnetic flowmeters, the calibration characteristics of which have
been previously reported (18). Maternal and fetal blood pH, Po2, and PCO2 were analyzed by standard techniques (7). Heart rate was calculated from the frequency of arterial pulse waves. Left ventricular stroke volume was calculated as the dividend of the heart rate and the ascending aortic flow, which is the left ventricular output minus the coronary flow. Stroke volume was also randomly computed by planimetry of the area under the aortic phase-flow complex. Fetal effective cardiac output was calculated as the algebraic sum of the ascending aortic and ductus arteriosus flows.

A 30-min control period was allowed for pressures, flows, blood respiratory gases, and pH to stabilize; during this period, pressure and flow values were recorded every 3 min and blood gas and pH were analyzed at least twice. Thereafter, the previously isolated left and right vagus nerves were alternately ligated and divided. The effects of these procedures on heart rate, pressures, and flows were monitored continuously. The distal or caudal end of the vagus nerve were stimulated with a Grass model SS square-wave stimulator at voltages varying from a minimum of 10 μV to a maximum of 10 V. The duration of stimulus varied between 0.2 and 20 msec, with the majority occurring at 2 and 20 msec. The delay between stimuli was kept at 20 msec throughout the entire series. The majority of stimuli were therefore at a frequency between 25 and 45/set. Concomitant pressures, flows, blood gases, and pH values were analyzed by standard techniques (7).

RESULTS

The effects of preparatory surgery did not differ from those previously reported (4, 5, 7). Control maternal and fetal pressures, flows, blood gases, and pH values were within the normal established ranges observed in our laboratory (see Tables 1 and 2). The data in these tables also show that the blood respiratory gases and circulatory parameters approximated control values during nonbradycardic recovery periods for the duration of the experiment, indicating the stability of the preparation.

Effects of vagal section. Section of the right or the left vagus nerve had no significant effect on the fetal heart rate, arterial pressure, and ascending aortic, main pulmonary artery, and ductus arteriosus blood flows. Traction on either vagus nerve, however, tended to cause bradycardia. In view of this finding, traction of the nerve was avoided during electrical stimulations.

Effects of vagal stimulation. Fetal vagal stimulation caused two types of bradycardia. The first type was termed rhythmatic bradycardia and is defined as a decrease in heart rate with or without occasional extrasystole; a representative example is presented in Fig. 1. It can be seen that despite the marked decrease in heart rate, minimal changes occurred in arterial pressure and in the ascending aortic and ductus arteriosus flows.

The second type of bradycardia was arrhythmic and is defined as a decrease in heart rate with numerous irregularities; a typical example is presented in Fig. 2. It is clear that this type of bradycardia was accompanied by major decreases in vascular pressures and flows.

Because of the variability between the individual animals, the percent changes from prestimulus values of pressure and flows, the dependent variables, were calculated and plotted as a function of percent change of the heart rate, the independent variable. Data for the rhythmic and arrhythmic bradycardias are presented separately. Linear regression lines were constructed for each group using standard techniques (15), and the formula for the line and the correlation coefficient (r) shown.

Figure 3 presents the relationship between the changes in stroke volume and the heart rate. Rhythmic bradycardia occurred in the great majority of instances when the heart rate decreased between 1 and 30%. In these cases, an

| TABLE 1. Mean blood respiratory gas and pH values |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | C               | 30 min          | 60 min          | 90 min          |
| Po2, mm Hg     | 23 ± 1.7        | 24 ± 1.7        | 19 ± 1.5        | 21 ± 0.7        |
| PCO2, mm Hg     | 37 ± 1.9        | 36 ± 2.4        | 36 ± 2.7        | 39 ± 2.8        |
| pH              | 7.38 ± 0.01     | 7.41 ± 0.01     | 7.41 ± 0.03     | 7.37 ± 0.01     |

Values are means ± 1 se. Values represent the results of the abdominal aortic samples taken during the control period (C) and the sample closest to times 30, 60, and 90 min after the start of vagal stimulation.
verse relationship was observed between the heart rate and stroke volume ($r = -0.70$, Fig. 3).

Arrhythmic bradycardia invariably occurred when the heart had decreased by more than 20% of control. In these cases, there was also an increase in stroke volume, which in the great majority of instances, was proportionally less than the fall in the heart rate ($r = -0.92$, Fig. 3). Under these circumstances, hemodynamic alterations occurred that are described below. A test for the probability of a difference between the two regressions gave a value of $P < 0.02$.

Figure 4 illustrates a representative example of the increase in stroke volume that occurred during bradycardia. Planimetry of the area under the curve of the phasic-flow complexes of the ascending aorta and ductus arteriosus gave a mean stroke volume of 1.8 and 2.0 ml, respectively, in the control period. Vagal stimulation in this case caused a rhythmic bradycardia of 60% and the stroke volume increased to an average of 3.3 and 2.8 ml. During the recovery period the heart rate and stroke volume returned to control values.

Figure 5 presents the relationship between the fetal effective cardiac output (ascending aortic plus ductus arteriosus flows) and the heart rate. Regular rhythmic bradycardia was accompanied by minor changes in the cardiac output ($r = -0.85$). Arrhythmic bradycardia caused a major decrease in cardiac output ($r = -0.70$). The probability of a difference between the two regressions was less than 0.05 but greater than 0.02.

The relationship between induced alterations in heart rate and the fetal mean arterial pressure is shown in Fig. 6. Rhythmic bradycardia was followed by a minor decrease in arterial pressure; with a 50% reduction in heart rate, the arterial pressure fell by about 15% ($r = -0.75$). Arrhythmic bradycardia caused, in general, a much more marked decrease in arterial pressure, but the severity of the hypotension did not seem to be directly related to the degree of bradycardia ($r = -0.18$). Statistical analysis failed to demonstrate significant difference between the two regressions ($P < 0.1$). The two groups were therefore combined into a single regression that has a correlation coefficient of 0.75 (Fig. 6).
A relationship exists when the heart rate decreases and lambs with intact umbilical circulations show that a similar fall.

The fetal heart often became less and less responsive to repeated stimulation; not infrequently, during stimulation, the heart rate decreased but then “escaped” and returned to control values despite the persistence of the stimulus.

There was no correlation between the frequency and intensity of the stimulus and the fetal cardiovascular effects. The fetal heart often became less and less responsive to repeated stimulation; not infrequently, during stimulation, the heart rate decreased but then “escaped” and returned to control values despite the persistence of the stimulus.

**DISCUSSION**

Data gathered by various investigators have shown that in the adult dog a decrease in heart rate to about 60 beats/min or an increase to about 180 beats/min is accompanied by a reciprocal change in stroke volume so that the cardiac output is not altered (3, 14). When the decrease or the increase in heart rate exceeds these limits, the changes in stroke volume are insufficient to compensate and the cardiac output falls.

The present data obtained from unanesthetized fetal lambs with intact umbilical circulations show that a similar relationship exists when the heart rate decreases and maintains a normal rhythm. Under these circumstances, the fetal ventricle is capable of increasing its volume and maintaining a normal ejection force; hence the increment in stroke volume is sufficient to compensate for the decrease in heart rate. These findings suggest that during cardiac deceleration, the fetal heart seems to obey the Frank-Starling Law. This is in agreement with the findings of Downing and his co-workers in the sheep newborn heart (6), and with Andersson in isolated human fetal hearts (1).

Although in our experimental preparation we did not monitor ECG because of technical difficulties, the studies of Levy and his co-workers (8–10) on the relationship of the interval between P waves and the cardiac cycle in the adult dog could be used to explain the occurrence of bradycardia with or without arrhythmia. These authors have reported that as the number of vagal stimuli per cardiac cycle is increased, the P-P interval is prolonged. They also noted that the proximity of the stimulus to the P wave was related to the P-P interval. Stimuli delivered at increasing interval up to 0.22 sec after the P waves were increasingly inhibitory, while stimuli beyond that time produced progressively smaller P-P intervals. In addition, they noted that as the intervals between the P wave and the stimulus increased beyond the maximally inhibitory interval an arrhythmia frequently occurred.

In the present series no effort was made to control the timing of the stimulus in relation to the cardiac cycle; therefore, the possibility that the arrhythmia might have been related to the stimulus and P waves cannot be ruled out. However, because the vagal stimulation was administered at a rapid rate (25–45 pulses/sec), to a heart beating at least 3 times/sec, the appearance of an arrhythmia could be due to a random occurrence.

But whatever the mechanisms of arrhythmia, it is clear that the stroke volume, despite its increase, is unable to compensate for the fall in heart rate. Whether this inability is due to impairment in ventricular filling or in the ventricular ejection force cannot be stated.

The absence of any significant alterations in the pulmonary and systemic vascular pressures, and in the blood flows of the pulmonary artery, aorta and ductus arteriosus can be ascribed to the compensatory effects of the stroke volume during rhythmic bradycardia. Likewise, the lack of any effect on blood respiratory gases and pH indicates that transitory bradycardia may not be as detrimental to the fetus as has been believed in the past.

On the other hand, when arrhythmia occurs, even transitory bradycardia may affect fetal hemodynamics and may represent a danger to fetal survival.

In the present study, the heart very often “escaped” from the influence of vagal stimulation. Such a phenomenon, which has been observed in adult animals, has been attributed to the development of refractoriness in the cardiac muscle to neural stimuli. Whether this mechanism is the same in the fetus cannot be stated.

It has been suggested that in the sheep the vagus nerves contain sympathetic cardioaccelerator fibers. To test this hypothesis, atropine was given intravenously to some fetuses in doses sufficient to block the cardiac parasympathetic fibers, confirmed by an increase in heart rate. Stimulation of both vagi in these animals, however, failed to illicit a tachycardia above the control rate. This finding would suggest that either the sympathetic fibers are not present in
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The fetal vagus nerves or that the cardioaccelerator system is already maximally saturated.

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