Hemodynamic effects of bradycardia in the fetal lamb

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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 tetracaine 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. The animal 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 served 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 ventral 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 S5 square-wave stimulator at voltages varying from a minimum of 100 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. Continuous flows and pressure recordings were taken during each stimulation period; blood gas and pH analysis were performed at frequent intervals. A suitable recovery period was allowed after each stimulation.

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 rhythmic bradycardia and is defined as a decrease in heart rate 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 int

<table>
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<th>TABLE 2. Mean values of representative cardiovascular parameters</th>
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<tr>
<td>Heart rate, beats/min</td>
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<td>Arterial pressure, mm Hg</td>
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<td>Ascending aortic flow, ml/min per kg</td>
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<td>Ductus arteriosus flow, ml/min per kg</td>
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<td>Effective cardiac output, ml/min per kg</td>
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<td>Systemic vascular resistance, mm Hg/ml/min</td>
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Values are means ± 1 SE. Values were taken during 30-min control period (C) and at 30, 60, and 90 min after the start of vagal stimulation during a nonbradycardic period (effective cardiac output = the ascending aortic + ductus arteriosus flows).

Exp. 92 Oct 23, 1970
Fetal Weight 2596 gm

![Fig. 1](http://ajplegacy.physiology.org/Downloadedfrom10.2203.2017/p.2342464)
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 main-
tains a normal rhythm. Under these circumstances, the fetal
ventricle is capable of increasing its volume and main-
taining 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 de-
celeration, 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 in-
creased, 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 be-
yond the maximally inhibitory interval an arrhythmia fre-
quently occurred.

In the present series no effort was made to control the
timing of the stimulus in relation to the cardiac cycle; there-
fore, 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 ventricu-
lar ejection force cannot be stated.

The absence of any significant alterations in the pulmo-
rary 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 transi-
tory 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 attri-
buted 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 parasym-
pathetic fibers, confirmed by an increase in heart rate. Stimu-
lation of both vagi in these animals, however, failed to illic-
it a tachycardia above the control rate. This finding would
suggest that either the sympathetic fibers are not present in

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 out-
put is not altered (3, 14). When the decrease or the increase
in heart rate exceeds these limits, the changes in stroke vol-
ume 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 main-
tains a normal rhythm. Under these circumstances, the fetal

![Figure 5](http://ajplegacy.physiology.org/)

**FIG. 5.** Linear regression relating percent change from control of
fetal effective cardiac output to percent change of heart rate during
(-----) rhythmic and (.....) arrhythmic bradycardia. \( r \) = formula of
line, \( r \) = correlation coefficient.

![Figure 6](http://ajplegacy.physiology.org/)

**FIG. 6.** Linear regressions relating percent change from control of
arterial pressure to percent change of heart rate during (-----)
rhythmic and (.....) arrhythmic bradycardia. Solid line (----) illus-
trates regression for combined group.

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

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the fetal vagus nerves or that the cardioaccelerator system
is already maximally saturated.

The authors acknowledge the technical assistance of David Hun-
tman, Helena Martinek, and Della Fuller.

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