Influence of Sympathetic Nerve Stimulation on Ventricular Function in the Newborn Lamb

By S. Evans Downing, Norman S. Talner, Alexander G. M. Campbell, Katherine H. Halloran, and Howard B. Wax

ABSTRACT
Cardiac responses to supramaximal electrical stimulation of postganglionic sympathetic nerve fibers were studied in 17 lambs, 10 hours to 3 days of age. In all lambs left ventricular contractility increased within 3 seconds and was unaltered by atropine, ganglionic blockade, or nerve sectioning proximal to the stimulating electrodes but was abolished by beta-receptor blockade. The responses were repeatedly demonstrated in two lambs subjected to bilateral adrenalectomy. Acidemia (pH 6.9) produced by lactic acid infusion failed to diminish the inotropic responses. Intravenous or left atrial injections of tyramine produced chronotropic and inotropic responses comparable to sympathetic nerve stimulation. Glucagon, 50 to 200 μg/kg, failed to elicit cardiac responses in lambs from 1 to 60 days of age. It is concluded that sympathetic neural mechanisms may strongly influence myocardial contractility in the newborn lamb and that these responses are independent of adrenal medullary release of catecholamines. These findings further suggest that the lamb possesses a myocardial adenyl cyclase system that responds only to catecholamines and may be blocked with propranolol.

ADDITIONAL KEY WORDS
propranolol glucagon adrenalectomy tyramine beta-receptor system

Previous studies from this laboratory have shown that chronotropic and inotropic responses may be reflexly elicited in lambs as early as the first day of life (1). Recent biochemical and histologic studies of myocardial sympathetic innervation in the newborn rabbit (2) and in the lamb (3) have suggested that cardiac sympathetic innervation is incomplete, and that catecholamine stores and enzyme systems are continuing to undergo developmental changes during the first several days of life. These findings introduce the possibility that alterations of sympathetic impulse traffic to the myocardium may have less influence on cardiac function in the newborn than in older animals. In addition, the observation that myocardial tissue from the newborn possesses an enhanced sensitivity to the administration of norepinephrine (2) suggested the possibility that circulating catecholamines released from the adrenal medulla or other sources might be the predominant mechanism for effecting chronotropic and inotropic changes in the newborn.

The present studies were designed to assess the effects of postganglionic sympathetic nerve stimulation upon cardiac frequency and contractility in the newborn lamb. Experiments were arranged to determine if age-related differences were demonstrable and if removal of adrenal tissue modified the responses. To identify possible developmental changes in the beta-receptor system, glucagon, which is known to increase cardiac contractility, presumably by stimulation of adenyl cyclase activity in the cat and other species (4), was studied in the newborn lamb and...
compared with responses from similar adult cat preparations.

**Methods**

Inotropic and chronotropic responses to neural stimulation were studied in 17 lambs varying in age from approximately 10 hours to 3 days. In addition, four lambs 1 to 5 days of age, two lambs approximately 2 months old and two adult cats were used for selective studies. All animals were anesthetized with pentobarbital, 15 to 25 mg/kg, and given heparin, 5 to 10 mg/kg.

Left ventricular performance was measured using a preparation similar in principle to that previously described (1). The trachea was intubated and the chest opened in the midline. Ventilation was maintained with a Harvard pump. The descending thoracic aorta was cannulated, and left ventricular output (minus coronary flow) was measured with a Statham cannulating type of electromagnetic flow transducer and a Medicon K-2000 flowmeter (Fig. 1). Aortic flow was passed through a Sams heat exchanger and returned to the descending aorta. The brachiocephalic artery was ligated near its origin and cannulated distally with a branch from the aortic loop. Arterial pressure was controlled with an adjustable constant-pressure reservoir. Cardiac output could be augmented by a pump-operated arteriovenous shunt (Fig. 1). Pressures were measured within the aortic arch and left ventricular chamber with Sanborn transducers. The maximal rate of rise of left ventricular pressure (dP/dt max) was computed by an RC differentiating circuit with a time constant of 0.268 msec. Blood temperature was continuously measured with a Yellow-Springs probe and telethermometer and maintained at 38 ± 1°C.

Arterial pH, Po2, and Pco2 were continuously measured with a Jewett flow-through electrode assembly and were frequently checked with an Instrumentation Laboratories blood gas analyzer and pH system.

Cardiac frequency was maintained constant when desired by electrical pacing of the left atrium. All pressures as well as cardiac output and ventricular dP/dt were recorded on a Sanborn 358 direct-writing recorder. The ductus arteriosus was ligated, and the extracorporeal tubing and reservoir were primed with freshly drawn, heparinized (5 mg/100 ml) sheep blood.

The left inferior sympathetic nerve trunk, which originates from the region of the third to fifth thoracic ganglia, was identified as it crossed the hemiazygos vein (5). The nerve trunk was cleared, placed on stainless steel stimulating electrodes, and bathed in mineral oil. Stimulation was achieved with a Grass S4 square-wave impulse generator. Supramaximal stimulation was obtained in most experiments utilizing a frequency of 15/sec, 5 msec duration, and 15 v. Responses were studied before and after proximal nerve sectioning, administration of tetraethylammonium chloride (TEAC), 100 mg, and propranolol, 0.25 mg/kg.

Responses were studied in two lambs, 2 and 3 days of age, subjected to bilateral adrenalectomy. Adrenal tissue was identified histologically. These findings were compared with two lambs who had sham operations, with removal of perinephric fat.

Glucagon (Eli Lilly Laboratories) was given to lambs in amounts of 25 to 200 μg/kg, infused intravenously for 1 to 2 minutes. In adult cats, glucagon was administered in the same manner in amounts of 25 to 50 μg/kg. Tyramine hydrochloride, 50 to 200 μg/kg, was given intravenously or injected into the left atrium.

Glucagon (Eli Lilly Laboratories) was kindly supplied by Ayerst Laboratories.
CARDIAC RESPONSES TO SYMPATHETIC STIMULATION

The data were analyzed by comparing the relationship of stroke volume, mean ejection rate, and $\frac{dP}{dt}$ max to the left ventricular end-diastolic pressure before, during, and after neural stimulation. Measurements were obtained under conditions of constant mean aortic pressure and heart rate, and either with constant cardiac output or during incremental increases of cardiac output from which ventricular function curves were drawn (1).

Results

INOTROPIC AND CHRONOTROPIC RESPONSES TO POSTGANGLIONIC CARDIAC SYMPATHETIC NERVE STIMULATION

All lambs had reversible increases of left ventricular contractility during nerve stimulation. This was manifested by increased mean ejection rate and $\frac{dP}{dt}$ max and usually a fall of end-diastolic pressure when the cardiac output, aortic pressure, and heart rate were maintained constant (Table 1). An example from a representative experiment is shown by the traces in Figure 2. Shortly after the initiation of nerve stimulation (first arrow, left panel) the onset of a response was discernible. Within 20 seconds a steady state had been achieved in which the end-diastolic pressure had fallen from 8 to 6 cm H$_2$O, and there was substantial widening of the diastolic interval. The duration of ejection had shortened from 165 to 120 msec, and the $\frac{dP}{dt}$ max had increased from 2,700 to 4,500 mm Hg/sec. When stimulation was stopped, these changes promptly began to reverse, and within approximately 3 minutes had returned to control values (Fig. 2, right panel). In all experiments, the responses appeared within 2 to 4 seconds of the onset of stimulation and began to diminish 3 to 5 seconds after interrupting stimulation.

Ventricular function curves were obtained during sustained nerve stimulation in a lamb approximately 10 hours of age. The results are illustrated in Figure 3. A control ventricular function curve was drawn (169).$^\dagger$

TABLE 1

Left Ventricular Responses to Sympathetic Nerve Stimulation with Stroke Volume, Heart Rate, and Aortic Pressure Held Constant

<table>
<thead>
<tr>
<th>Lamb no.</th>
<th>Age (days)</th>
<th>Mean ejection rate (ml/systolic sec)</th>
<th>$\frac{dP}{dt}$ max (mm Hg/sec)</th>
<th>pH</th>
<th>PO$_2$</th>
<th>PCO$_2$</th>
<th>No. of responses</th>
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<td>Control</td>
<td>During stimulation</td>
<td>Control</td>
<td>During stimulation</td>
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| Mean     | 19          | 28          | 2760   | 4270   | 7.40 | 130 | 23 | (169)$^\dagger$ |
| SD       | 5.5         | 7.7          | 1030 | 1420 | 0.07 | 49  | 6.35 |
| SE       | 1.3         | 1.9          | 250  | 345   | 0.02 | 12  | 1.59 |
| $P$      | < 0.001     | < 0.001      |

$dP/\text{dt max} = \text{maximal rate of rise of left ventricular pressure.} \ast \text{With bilateral adrenalectomy.} \dagger \text{Total number of positive responses.}$

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FIGURE 2
Original traces showing hemodynamic responses to cardiac sympathetic nerve stimulation.
CO = cardiac output; AP = aortic pressure; LVEDP = left ventricular end-diastolic pressure;
LVP = left ventricular pressure; LV dP/dt = rate of change of left ventricular pressure
(mm Hg/sec); ECG = electrocardiogram. First arrow, stimulation begun. Second arrow, stimulation stopped. Fast chart speed = 100 mm/sec; slow chart speed = 0.25 mm/sec. Black line top of right panel = 100 mm. See text for further description.

function curve was obtained, and the relationship of stroke volume, mean ejection rate, and dP/dt max to left ventricular end-diastolic pressure was plotted (open circles). In addition, the relationship of ejection time to stroke volume was plotted. Nerve stimulation was then begun and continued for approximately 5 minutes. A second ventricular function curve was obtained during this period (solid circles). The stroke volume and, to a greater extent, the mean ejection rate curves were shifted to the left. The dP/dt max was approximately 50% greater over the entire end-diastolic pressure range. As would be expected, the ejection time increased with increasing stroke volume. During neural stimulation the ejection time for any given stroke volume was substantially shortened. These findings were repeated during four periods of sustained stimulation and were compared with seven control curves. Evidence for diminished responsiveness with repeated sustained stimulation was not found.

In none of the experiments, regardless of the age of the lamb, was there evidence for failure or fatigue of the response to neural stimulation unless gross cardiac failure developed after many hours of experimentation. The stability and reproducibility of these responses are shown by the data from a lamb approximately 10 hours of age (Fig. 4). These responses were obtained over a period of 1 hour and 40 minutes of data gathering, following which the experiment was terminated. There was no evidence for diminished responsiveness with time.

To assess the relative magnitude of the response to neural stimulation, comparison was made with steady-state responses to infusion of various amounts of norepineph-
CARDIAC RESPONSES TO SYMPATHETIC STIMULATION

LAMB #21  AGE - 10 HRS  AP 50  HR 235

To be continued...
Top: Hemodynamic responses to cardiac sympathetic nerve stimulation before beta-receptor blockade. Left panel = control. Middle panel = during stimulation. Right panel = control. Chart speed = 100 mm/sec. Symbols same as in Figure 2. Bottom: Responses to neural stimulation (middle) completely abolished by prior administration of propranolol (0.25 mg/kg). Black line in middle panel = 100 mm.

traces shown in Figure 6. Before propranolol administration (Fig. 6, top) and during constant cardiac output, aortic pressure and heart rate, neural stimulation produced a
marked reduction of end-diastolic pressure, shortening of the duration of ejection, and an increase of dP/dt from approximately 3,000 to 4,500 mm Hg/sec (middle panel). With cessation of neural stimulation these changes reversed (right panel). Following beta-receptor blockade with propranolol, 0.25 mg/kg, the response to sympathetic nerve stimulation was completely abolished (Fig. 6, bottom, middle panel).

Although all of the lambs studied showed positive inotropic responses to electrical stimulation of the left inferior cardiac sympathetic nerve, increases of heart rate were demonstrated in 10 animals, and 7 showed no rate changes during stimulation. A likely explanation for this is that the distribution of nerve fibers did not include the sinoatrial node in all preparations. When chronotropic responses were observed they were usually large. In the 10 responsive animals the mean initial heart rate was 195 (± 7.1 se) and increased to 254 (± 15.3 se) during nerve stimulation. With cessation of nerve stimulation the rate returned to 192 (± 7.6 se). These changes were highly significant (P < 0.01). The presence or magnitude of the chronotropic responses was unrelated to age.

INOTROPIC RESPONSES TO CARDIAC SYMPATHETIC NERVE STIMULATION FOLLOWING ADRENALECTOMY

To assess the influence of adrenal medullary release of catecholamines upon the responses observed with cardiac sympathetic nerve stimulation, two lambs, 2 and 3 days of age were subjected to bilateral adrenalectomy. The responses were compared with two animals subjected to sham operation in which perirenal fat was removed. The results of those two groups compared with animals not subjected to adrenalectomy are shown in Figure 7. Although the average magnitude of the responses in the adrenalectomized animals may have been somewhat less than those with intact adrenals, they were not less than the responses to animals subjected to sham operation. Furthermore, the responses could be repeatedly elicited during eight tests in one animal and ten in the other. There was no evidence for loss of responsiveness with repeated stimulation.
Adrenergic responses to sympathetic nerve stimulation during progressively more severe lactic acidemia, and with correction of arterial pH (THAM). Other symbols same as in Figure 5. Stroke volume (SV) was held nearly constant, with a variation of ±0.24 ml. Lactic acidemia failed to diminish the positive inotropic responses.

EFFECTS OF METABOLIC ACIDEMIA ON INOTROPIC RESPONSES TO CARDIAC SYMPATHETIC NERVE STIMULATION

To evaluate the suggestion that metabolic acidemia may diminish beta-receptor responsiveness to norepinephrine, and therefore possibly interfere with neurotransmitter mechanisms, neural stimulation was carried out in two lambs, during metabolic acidemia produced with lactic acid, and following correction of arterial pH with tromethamine. The results from one of these animals is shown in Figure 8. With aortic pressure, heart rate, and cardiac output held essentially constant, neural stimulation (solid circles) produced a large increase of dP/dt max and mean ejection rate and a reduction of end-diastolic pressure. Lactic acid administration was then initiated and continued until the pH reached 6.91. Repeated tests during the development of progressive acidemia showed no diminution in the magnitude of the responses. With the administration of tromethamine the arterial pH was corrected back to 7.34. This caused no important change in the responses. Similar observations were made in a second lamb.

CARDIAC RESPONSES TO GLUCAGON AND TYRAMINE

Cardiac responses to glucagon and tyramine administration were compared with those to cardiac sympathetic nerve stimulation in six lambs, four of which were aged 1 to 5 days and two 45 and 60 days. Responses to glucagon were also studied in two adult cats. Although all of the lambs showed the expected inotropic responses to nerve stimulation, none of them manifested a significant positive chronotropic or inotropic response to glucagon administration in amounts varying from 25 to 200 µg/kg. However, systemic vasodilatation was manifested by an increased systemic blood flow for a given arterial pressure. Contrastingly, both adult cats demonstrated large chronotropic and inotropic responses to glucagon, 25 µg/kg. Although glucagon failed to produce responses in the lamb, tyramine, 50 to 200 µg/kg, given...
intravenously or injected into the left atrium, produced chronotropic and inotropic responses comparable to those seen with neural stimulation.

The results from an experiment with a 4-day-old lamb are illustrated in Figure 9. Cardiac sympathetic nerve stimulation produced a large inotropic response and a modest increase of heart rate. Glucagon, 100 mg/kg, produced no change of heart rate, mean ejection rate, dP/dt, or end-diastolic pressure. Tyramine, 125 μg/kg, produced a very large increase of heart rate, mean ejection rate and dP/dt, and reduction of the end-diastolic pressure. Approximately 12 minutes later, when the tyramine response had dissipated, the response to sympathetic nerve stimulation was again tested. This did not differ significantly from the initial response to nerve stimulation.

Discussion

The positive inotropic and chronotropic responses to supramaximal cardiac sympathetic nerve stimulation in the newborn lamb do not differ from those observed in the adult of many species. Responses were elicited in all preparations, and included an increase in dP/dt max, a decrease in the duration of left ventricular ejection, an increase in the diastolic interval, and usually a fall in left ventricular end-diastolic pressure. These were obtained under conditions of constant heart rate and controlled aortic pressure and are indicative of a modification of myocardial force-velocity relations (6). When stimulation was less than supramaximal, the magnitude of the response varied directly with the frequency and strength of stimulation (3 cps to 15 cps, 5 to 15 v). The increase in ventricular contractility following sympathetic stimulation was rapid in onset (3 seconds), persisted throughout the stimulation, and returned to control conditions within 1 to 3 minutes. Bilateral adrenalectomy and ganglionic blockade did not modify the responses, but they were completely abolished by beta-receptor blockade with propranolol. These data thus show a sympathetic nerve supply to the myocardium which, when activated by electrical stimulation, can increase cardiac contractility.

The chronotropic responses to left sympathetic nerve stimulation were less consistent than the inotropic responses. As changes of heart rate primarily reflect sympathetic stimulation of the sinoatrial node, it is likely that the predominant sympathetic innervation of this structure in the lamb, as in other species, is derived from right sympathetic nerve fibers.

The results of these studies are compatible with existing knowledge of adrenergic transmission, which relates sympathetic nerve stimulation to release of norepinephrine at nerve terminals (7). This may then act on receptor sites (cardiac muscle fibers and the sinoatrial node) to induce an increase in the ventricular contractility and cardiac rate. Further evidence that the heart in the newborn lamb can release norepinephrine is shown by the responses to tyramine administration. This substance is thought to mediate its effect through norepinephrine release from
an intraneuronal pool (8). It is of interest that no differences were found between the tyramine responses in the newborn (1 to 5 days) and those in two lambs 2 months of age. The possibility that tyramine could have released norepinephrine from adrenal medullary sites was considered, but the immediate response (1 to 2 seconds) following left atrial injection in lambs in which the blood flow to abdominal sites was eliminated would argue against this as the mechanism for the cardiac response. The responses to intravenous injection occurred within 3 to 5 seconds, a latency period too short for adrenal medullary release. Furthermore, most workers have failed to find an increase of adrenal vein plasma catecholamine levels following tyramine administration (9, 10).

It is also clear from these studies that the myocardial responsiveness to sympathetic nerve stimulation is unaltered over a wide range of arterial pH (6.9 to 7.5) and is similar to the results previously reported on norepinephrine infusion over the same pH range (11). These results are in agreement with the studies recently reported by Linden et al. for the adult dog (12).

The apparent discrepancy between the results of these studies showing positive inotropic and chronotropic responses to sympathetic nerve stimulation, and the biochemical and histochemical observations of Friedman et al. (2) warranted attention. These investigators have demonstrated low levels of myocardial norepinephrine and tyrosine hydroxylase (the rate-limiting enzyme for catecholamine synthesis), as well as decreased fluorescence of norepinephrine granules in the myocardium of the newborn rabbit and lamb. From these observations, they have suggested that cardiac sympathetic innervation in these species is incomplete at birth. This raises the possibility that these hearts would be supersensitive to catecholamines released from chromaffin tissues into the circulation. But, without kinetic studies it is difficult to draw conclusions about function from changes in amine levels.

In contrast with the above findings, Vogel et al. (13) have reported that cardiac adrenergic innervation is essentially completely established in newborn calves, showing no further development in the early postnatal period. It is of interest that this species has been reported to have delayed postnatal innervation of the adrenal medulla, while in the fetal lamb adrenal medullary innervation is present (14). Although it is possible that adrenal medullary secretion may have a relatively greater influence on cardiac function in the lamb, this has not been established.

The relevance of total norepinephrine content of an organ to its function must be questioned. Studies on adult animals indicate that a small fraction (1% to 2%) of the total norepinephrine store may be sufficient for the release of adequate amounts of neurotransmitter agent, if the norepinephrine is available for release (15). Data from the present studies involving neural stimulation and tyramine administration support the conclusion that the lamb has adequate norepinephrine stores for integrity of function at birth. It should be noted, however, that Glowinski et al. (16) have reported decreased uptake of tritiated norepinephrine in the newborn rat. If this holds for the lamb or other species, there may be a limitation of responsiveness to prolonged sympathetic stimulation.

Decentralization (chronic preganglionic denervation) causes supersensitivity to various substances, including norepinephrine (17), although this is less pronounced than after postganglionic denervation. One could speculate that this situation is comparable to presumed decreased control available from higher cortical centers in the developing animal, which could thus produce a supersensitivity at the receptor site in the fetus and newborn. It is noteworthy, however, that in this and earlier studies (18, 19), major differences in myocardial sensitivity to infusion of norepinephrine or isoproterenol have not been observed in lambs from a few hours to 5 days of age. Dose-response curves have not been systematically obtained, and it is of course possible that smaller age-related differences were not detected.
Failure to demonstrate chronotropic and inotropic responses to glucagon in lambs up to 2 months of age is not readily explained. Large responses to this hormone were demonstrated in virtually identical adult cat preparations. It is unclear whether this represents a species difference or a delayed developmental change. Perhaps more important in terms of the present study is recent evidence suggesting that the cardiac actions of glucagon are not dependent upon beta-receptor stimulation (20, 21), as had been reported in earlier studies (22, 23). This suggests that failure to demonstrate cardiac responses to glucagon in the newborn should not be interpreted as evidence for incomplete development of the beta-receptor system. Rather, it is more likely that the lamb possesses an adenyl cyclase system that responds only to catecholamines and may be blocked with propranolol. This view is consistent with recently reported observations by Friedman and coworkers (unpublished observations) on isolated lamb cardiac muscle preparations.

Previous studies reported from this laboratory on the effects of central nervous system ischemia have demonstrated increased sympathetic stimulation of the myocardium, although neural and neurohumoral mechanisms could not be clearly separated (1). The present studies suggest that the efferent limb of the neural reflex arc is well developed at birth. They confirm the presence of a neurally mediated beta-receptor system and, taken in conjunction with the investigations of Dawes et al. (24) in which neurally mediated alpha-receptor function was demonstrated, indicate that similar mechanisms for circulatory control are available to the heart of the newborn. Quantitative differences between the fetus, newborn, and adult of various species that relate to the proportional amounts of circulatory control which may be mediated by neural or adrenal medullary mechanisms must await further investigation.

Acknowledgments

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References

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