Autonomic Influences on Cardiac Function in the Newborn Lamb

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ABSTRACT

The influences of reflexly induced changes of sympathetic outflow to the heart on left ventricle contractility, heart rate, and systemic vascular resistance were studied in 26 technically successful experiments with newborn lambs ranging in age from 1 to 11 days. Reduction of brachiocephalic artery perfusion pressure was associated with a large increase of heart rate and of systemic vascular resistance. Under conditions of constant aortic pressure, heart rate and cardiac output, cephalic hypotension in most preparations induced a rapid onset of a fall of left ventricular end-diastolic pressure and an increase in the maximal rate of rise of left ventricular pressure (dp/dt max). Ventricular function curves obtained under conditions of constant aortic pressure and heart rate were shifted to the left. The average increase of stroke volume at left ventricular end-diastolic pressure of 10 cm H$_2$O (SV$_{10}$) was 23.3%, and of dp/dt max was 30.7% in the reactive preparations. The average of the largest responses for each preparation was an increase of SV$_{10}$ of 42%, and for left ventricular dp/dt max, 48.9%. Three preparations previously subjected to carotid sinus nerve sectioning showed similar responses. No evidence for diminution of the response following parasympathetic blockade with atropine was found. In all preparations, ganglionic blockade virtually or completely eliminated the response.

ADDITIONAL KEY WORDS CNS perfusion ventricular contractility myocardial function carotid sinus reflexes ventricular performance nervous control of heart rate reflex changes of systemic vascular resistance

There is much evidence to suggest that regulation of the circulation of the newborn is to some extent under neural control. Stimulation of the efferent limb of both divisions of the autonomic nervous system results in changes of cardiac rate which are comparable to those of adults of the same species (1, 2). In the newborn rabbit it has been possible to demonstrate the presence of functioning pressoreceptor reflexes originating from carotid sinus and aortic arch stretch receptors which are capable of influencing arterial pressure and possibly also heart rate (3, 4). In addition, the presence of tonic baroreceptor activity was shown by an increase of arterial pressure following sectioning of the carotid sinus and depressor nerves (3).

While there is clear evidence for neural influences on arterial pressure and heart rate, little is known concerning the extent to which activity of the autonomic nervous system contributes to cardiac contractility in the newborn or of mechanisms which may regulate this activity. The principal purpose of this communication is to describe experiments designed to demonstrate changes of ventricular function induced by alterations of sympathetic outflow to the myocardium. A preliminary report on these findings has appeared (5).

Methods

Thirty-one term lambs varying in age from 1...
to 11 days were studied. Twenty-six were lightly anesthetized with thiopental sodium (15 mg/kg, intravenously) followed by the administration of chloralose (30 mg/kg) approximately 15 min later. Four were given sodium pentobarbital, (15 to 20 mg/kg) and 1 was given 20 mg/kg sodium pentobarbital followed by 20 mg/kg chloralose.

The animals were prepared for measurement of left ventricular function using a preparation which is similar to that previously described (6), but which also permitted separate perfusion of the brachiocephalic artery (Fig. 1). The trachea was intubated and the chest was opened in the midline. Ventilation was maintained with a Harvard respiratory pump. Heparin (3 mg/kg) was given intravenously. The thoracic aorta was cannulated and the left ventricular output (minus coronary flow) was measured with a Shipley-Wilson rotameter. Arterial pressure could be controlled by means of an adjustable constant pressure reservoir. Cardiac output could be augmented by means of a pump-operated arteriovenous by-pass which permitted blood to be pumped from the flowmeter circuit to the external jugular vein.

A Sarns roller pump (pump II, Fig. 1) was used to perfuse the cannulated brachiocephalic artery. A shunt was placed between the brachiocephalic artery perfusion line and the line to the external jugular vein which permitted part or all of the flow from pump II to be diverted away from the brachiocephalic artery and returned directly to the external jugular vein. Hence, the perfusion pressure within the brachiocephalic vascular bed could be altered as desired without changing total cardiac output.

Pressures were measured with Sanborn trans-
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ducers within the aortic arch, the brachiocephalic artery, and the left ventricular chamber by means of a 13-gauge blunt needle passed through the apex. The maximal rate of rise of left ventricular pressure (dp/dt max) was computed by an RC differentiating circuit. Blood temperature was continuously measured with a Yellow Springs probe and telethermometer and maintained at 39 ± 1°C by employing a circulating warm water bath heat exchanger in most experiments. Arterial pH, Po2 and Pco2 were measured frequently with an Instrumentation Laboratories blood-gas analyzer and pH system.

The ductus arteriosus was ligated. Heart rate was maintained constant 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 extracorporeal tubing, flowmeter, and reservoir were primed with freshly drawn heparinized (5 mg/100 ml) sheep blood.

From the foregoing measurements, ventricular function curves were plotted relating stroke volume to left ventricular end-diastolic pressure at constant mean aortic pressures and heart rate. In order to facilitate quantitative comparison, the stroke volume at left ventricular end-diastolic pressure of 10 cm H2O was employed as an index of contractility and has been called the SV10 (7). The influence of brachiocephalic hypotension was compared prior to and following ganglionic blockade with Arfonad (0.1 mg/kg per min). In a few experiments 100 mg tetraethylammonium chloride (TEAC) or hexamethonium (25 mg) was used instead of Arfonad. Evidence was obtained for tonic sympathetic support of the heart by measuring ventricular function before and after ganglionic blockade and comparing these changes with infusions of norepinephrine (1 to 2 μg/kg per min).

Results

Data were obtained from 23 technically successful experiments from a total of 28. Similar studies were done in 3 additional lambs which were subjected to bilateral carotid sinus denervation.

REFLEX EFFECTS OF CEPHALIC HYPOTENSION ON HEART RATE AND SYSTEMIC VASCULAR RESISTANCE

Many of the circulatory alterations induced by brachiocephalic artery hypotension may be seen in the original traces from a 1-day old lamb shown in Figure 2. Mean aortic pressure was held at 55 mm Hg. Reduction of brachiocephalic perfusion pressure (BPP) from 90 to 15 mm Hg was followed by an increase of heart rate from 183 to 240 beats/min, and a fall of left ventricular output from 775 to 615 ml/min. The left ventricular end-diastolic pressure (LVEDP) fell below control values. There was, nevertheless, a large increase of dp/dt from approximately 3,000 to approximately 5,500 mm Hg/sec. The described changes began 10 sec after reduction of brachiocephalic artery pressure and were completely reversed by reinstatement of brachiocephalic artery perfusion.

The heart rate and systemic vascular resistance responses may be further described by a representative experiment with a 2-day old lamb weighing 3.1 kg. The average values from five sequential tests are indicated. Reduction of BPP from 69 to 11 mm Hg was the consequence.
associated with an increase of heart rate of 37 (range, 10 to 50) beats/min, from 128 to 165 beats/min. Concurrently, systemic vascular resistance increased by 25 (range, 18 to 34) mm Hg/liter per min, from 70 to 95 mm Hg/liter per min. When brachiocephalic artery perfusion was resumed, BPP returned to 65 mm Hg, the heart rate slowed to 132 beats/min, and systemic vascular resistance fell to 74 mm Hg/liter per min.

The data for the increase of heart rate resulting from cephalic hypotension are summarized in Figure 3. With the vagi intact, the average increase of heart rate in 49 tests with 17 lambs was 38 beats/min (range, 10 to 95). Heart rate changes following elimination of parasympathetic function by vagotomy or atropine administration were obtained on four occasions in 3 animals. The average increase was 25 beats/min (range, 15 to 35). Following ganglionic blockade, the heart rate responses to cephalic hypotension were essentially eliminated. In 15 tests with 13 lambs, the average heart rate change was only 2 beats/min (range, 0 to 5). No difference in the magnitude of the heart rate response was observed between the younger animals and the older animals. With 6 lambs, 1 to 2 days of age, the average heart rate response was 32 beats/min (range, 15 to 64); with 5 lambs 4 to 8 days of age, the average heart rate response was 38 beats/min (range, 10 to 87).

**REFLEX EFFECTS OF CEPHALIC HYPOTENSION ON LEFT VENTRICULAR CONTRACTILITY**

The contractility of the ventricle was assessed from the relationship of stroke volume to LVEDP and from the maximal rate of rise in pressure within the left ventricular chamber under conditions of constant mean aortic pressure and constant heart rate achieved by electrical pacing. The various response patterns are illustrated by the original traces shown in Figure 4 and in Figures 5A and 5B (Fig. 4 is from a 4-day-old lamb). The aortic pressure was maintained constant at a mean value of 75 mm Hg and the heart was electrically paced at a rate of 215 beats/min. Left ventricular output was maintained nearly constant at approximately 580 ml/min. Reduction of BPP from a mean value of approximately 80 mm Hg to approximately 20 mm Hg was associated with reduction of LVEDP from 11 to 8 cm H2O and an increase of left ventricle dp/dt max from 2,000 to 2,500 mm Hg/sec. With resumption of brachiocephalic perfusion, the LVEDP rose to 14 mm Hg and the dp/dt max fell to 1,875 mm Hg/sec.

The original tracings shown in Figures 5A and 5B are from a 2-day-old lamb. As shown in the left panel of Figure 5A, when the BPP was 60 mm Hg and the heart rate 188 beats/min, the end-diastolic pressure was 10 cm H2O and the dp/dt max 2,675 mm Hg/sec. At the arrow, BPP was reduced to 10 mm Hg and within 8 sec the dp/dt began to increase. After approximately 60 sec, the LVEDP was 9 cm H2O and the dp/dt max had increased to 5,000 mm Hg/sec at a slightly greater heart rate (210 beats/min). In addition, the diastolic interval was somewhat wider. Thus, in contrast with Figure 4, in which a substantial fall of LVEDP but a modest increase of dp/dt max (about 25%) were observed, the animal shown in Figure 5A manifested an 87% increase of dp/dt max but only a 1 cm H2O reduction of LVEDP. In this example, the positive inotropic response was more dramatically portrayed by speed.
Parameters (dp/dt) than by force parameters (SV<sub>10</sub>.

Although the principal manifestation of a positive inotropic response was an increase of speed of ventricular contraction under the conditions shown in Figure 5A, if the same ventricle was made to operate from a much higher LVEDP, the change in this parameter resulting from cephalic hypotension became more pronounced, as shown in Figure 5B. In this example, with heart rate constant at 200 beats/min, reducing BPP from 60 to 10 mm Hg was associated with a reduction of LVEDP from 23 to 8 cm H<sub>2</sub>O. There was a 31% increase of dp/dt max to be contrasted with the 87% increase noted previously. These inotropic responses were rapidly reversed by reinstitution of cephalic perfusion.

In order to define more precisely certain of the performance characteristics of the ventricle over a broad range of cardiac output, ventricular function curves relating stroke volume to end-diastolic pressure at constant aortic pressure and heart rate were obtained. An example from a 4-day-old lamb is shown in Figure 6. The characteristic response to cephalic hypotension was a shift to the left of the ventricular function curve from its control position. When cephalic perfusion was resumed, the curve returned to its original control position.

To facilitate quantitative comparison, the stroke volume obtained at LVEDP of 10 cm H<sub>2</sub>O was determined and the percent change of this value, together with that of the dp/dt max, was computed for each animal. The data are listed in Table 1. The average percent change of SV<sub>10</sub> for all responses from all the lambs was 13.4 (± 1.66 se)% increase. That for dp/dt max was 21.2 (± 1.65 se)% increase. Also listed in Table 1 is the maximal percent response for each animal. For the entire
series of lambs these averaged 31.1 (± 2.1 SE)% increase of SV$_{10}$ and 41.1 (± 2.4 SE)% increase of dp/dt max.

It is clear from Table 1 that a few of the animals were completely or nearly completely areflexic, as indicated by little or no change of SV$_{10}$ or dp/dt max. Accordingly, an increase of SV$_{10}$ of 10% or more and/or an increase of dp/dt max of 20% or more was arbitrarily chosen as constituting sufficient evidence for an increase of ventricular contractility. Eighteen of the 23 animals fulfilled these criteria. Of this group, 9 were 1 to 3 days of age and 9 were 4 to 11 days of age. The data for the average and maximal responses in these reactive lambs are summarized in Figure 7. The average value for all of the responses for SV$_{10}$ was 23.3 (± 2.02 SE)% The average of the maximal response was 42 (± 3.29 SE)% The average increase of dp/dt max for all of the responses was 30.7 (± 2.7 SE)% The maximal responses averaged 48.8 (± 3.43 SE)%.

Although as many as 18 responses to cephalic hypotension (average 6.6) were studied in a given lamb, the magnitude of the individual responses varied substantially in most preparations. Figure 8 exemplifies this variability. Throughout the experiment the BPP was reduced to approximately the same level and held there until maximal responses were obtained (generally about 90 sec). It is clear that there was moderate variation in SV$_{10}$ and more substantial variation in dp/dt. As would be anticipated, over a variable length of time the responses often diminished and in some instances disappeared.

HEART RATE AND CONTRACTILITY RESPONSES FOLLOWING CAROTID SINUS NERVE (HERING'S NERVE) SECTIONING

In 3 lambs the carotid sinus regions were
exposed and Hering's nerves were identified and sectioned bilaterally. Evidence for sinus denervation included elimination of a rise of arterial pressure following occlusion of the common carotid arteries and a rise of both heart rate and arterial pressure immediately after sectioning of each nerve individually. The responses to cephalic hypotension in the sinus-denervated preparations did not differ from those with intact sinus nerves. A large increase of heart rate and systemic vascular resistance was observed. Under conditions of constant heart rate and mean arterial pressure, cephalic hypotension induced an increase of $SV_{10}$ and $dp/dt$ max which was reversible with resumption of brachiocephalic artery perfusion. All of the responses were eliminated by ganglionic blockade.

**INFLUENCE OF AUTONOMIC BLOCKING AGENTS ON CARDIAC CONTRACTILITY**

Inhibition of parasympathetic influences on the heart by bilateral cervical vagotomy or atropine administration caused a reduction or, in one instance, complete elimination of the heart rate response to cephalic hypotension. No evidence was obtained, however, to suggest that the myocardial contractility responses to this intervention were altered. In a representative experiment with a 4-day-old lamb, for example, cephalic hypotension prior to atropine administration resulted in a 19% increase of $SV_{10}$ and a 22% increase of $dp/dt$ max (average of five tests). Following the administration of 1 mg of atropine, the heart rate increased by about 30 beats/min. Nevertheless, the response in terms of $SV_{10}$ (average of five tests) was unchanged. The $dp/dt$ response was actually considerably greater (43%) than that prior to atropine.

Although parasympathetic blockade apparently had little influence on the myocardial response to cephalic hypotension, gan-
Left ventricular function curves show shift of curve to left (closed circles) when cephalic perfusion was reduced. With resumption of cephalic perfusion the curve returned to its original control values (open triangles). Arrow indicates LVEDP at 10 cm H₂O. Aortic pressure and heart rate were constant for all curves.

Ganglionic blockade with Arfonad, TEAC or hexamethonium greatly reduced or completely abolished the response. This is shown in a representative experiment with a 4-day-old lamb shown in Figure 9. Prior to ganglionic blockade, cephalic hypotension increased SV₁₀ from 6.8 to 10.8 ml. After infusion of Arfonad, 0.1 mg/kg per min for approximately 5 min, the test was repeated. Reducing the brachiocephalic artery perfusion pressure to approximately the same level caused a much smaller increase of SV₁₀, from 5.8 to 6.3 ml. The infusion of Arfonad was then stopped and 6 min later BPP was again reduced; partial recovery from the ganglionic blockade had occurred, as indicated by an increase in SV₁₀ from 6.3 to 8.5 ml.

Ganglionic blockade was usually associated with a reduction of heart rate and a small reduction of contractility. In the experiments shown in Figure 10, for example, Arfonad administration resulted in a modest shift to the right of the ventricular function curve indicating a reduction of contractility. For comparative purposes in the same animal, a noradrenaline infusion was given following blockade. The shift to the left was less with 1 μg/kg per min, but greater with 2 μg/kg per min than the shift to the right of the curve following Arfonad administration. Thus, in this experiment, tonic sympathetic outflow to the myocardium was equivalent to an infusion of between 1 and 2 μg/kg per min of noradrenaline.

Discussion

In 1939, Bauer (8) concluded from measurements of heart rate in rabbits that the aortic arch and carotid sinus reflexes were not active until the thirtieth and fortieth day from birth respectively. The implication of these findings is that the cardiovascular system of the newborn rabbit is not under control of the baroreceptors until several weeks after birth. More recent work, however, has clearly demonstrated that the baroreceptor reflexes are present in the rabbit at birth and that the low arterial pressure existing at birth is sufficient to activate them (3). Thus, electroneurographic recordings from the depressor and carotid sinus nerves indicated many afferent nerve fibers discharging synchronously with the heart beat as early as 1 hour from birth (3, 4). Electrical stimulation of the depressor nerves caused a fall of arterial pressure. Raising the pressure in an isolated carotid sinus also induced a reflex fall of arterial pressure. Carotid occlusion caused an increase of about 20% in mean arterial pressure, which was nearly abolished by carotid sinus nerve sectioning. Evidence for a tonic baroreceptor influence upon the circulation was obtained by demonstrating a rise of arterial pressure when either the depressor nerves or carotid sinus nerves were sectioned (3). These and other findings (2) suggest that the autonomic nervous system is active at birth and that the circulation of the newborn is regulated to some extent by neural mechanisms.

The present studies were designed to as-
### Table 1

Reflex Changes of Contractility Engendered by Cephalic Hypotension (Tabulated Data from All Lambs)

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>Lamb no.</th>
<th>Anesthesia</th>
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<th>Average change</th>
<th>Maximal change</th>
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<td>$dp/dt$ %</td>
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*n* = Number of tests with each animal from which average changes were computed.

C = chloralose; P = pentobarbital.

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**Figure 7**

Reflex responses of left ventricular $SV_{IO}$ and $dp/dt$ max to cephalic hypotension. In each panel, average indicates mean value of all responses and maximal indicates mean value of largest responses observed in a given animal. Standard error of mean is also shown.

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certain whether reflex alterations of sympathetic outflow to the myocardium of sufficient magnitude to alter the performance characteristics of the ventricle can be demonstrated in the newborn. Accordingly a preparation was designed which would permit independent perfusion of the cephalic portion of the animal at the desired pressure, while maintaining the remainder of the circulation under suitably controlled conditions to permit meaningful measurement of cardiac function. In this preparation it should be recognized that reducing brachiocephalic artery pressure not only reduces the pressure in the carotid sinuses but must also decrease blood flow to the central nervous system. Ischemia of the central nervous system has been shown in the adult to increase sympathetic outflow to the heart (9, 10).

The characteristic response to cephalic hy-
Potension was a variable, but generally large, increase of heart rate and an increase of systemic vascular resistance. Ventricular contractility measured under suitably controlled conditions increased in most preparations. The largest responses in the reactive animals were often impressive. Thus, in one preparation, the SV$_{10}$ more than doubled as did the dp/dt

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**Figure 8**

Left ventricular SV$_{10}$ and dp/dt max responses to cephalic hypotension in a successive series of tests with 4-day-old lamb. Connected points indicate control values; arrows indicate responses to cephalic hypotension. There is substantial variability in the magnitude of responses throughout the course of the experiment.

**Figure 9**

Influence of cephalic hypotension on SV$_{10}$ prior to and during infusion of Arfonad, 0.1 mg/kg per min. Response was virtually absent during Arfonad infusion. Approximately 6 min after stopping Arfonad infusion partial return of the response was observed.
max in another animal. The average increase of the best responses in each animal was also large—42% for SV₁₀ and 49% for dp/dt max. Hence, there can be no doubt that reducing the pressure in the brachiocephalic artery in lambs 1 day of age and older elicits a powerful inotropic response from the myocardium.

It must also be concluded that this response is primarily neural in origin because ganglionic blockade of the autonomic nervous system completely or nearly completely eliminates the response (Fig. 9). In view of the fact that little difference was noted in the magnitude of the response following atropine administration but the response was eliminated by agents which also inhibit sympathetic outflow to the heart, it is likely that the positive inotropic responses were largely the result of increased sympathetic activity and little, if at all, related to withdrawal of parasympathetic activity (11).

The afferent limb of this reflex may include more than one sensory system. The possibility that alterations of baroreceptor activity from the carotid sinus region contributes to the response must be considered. It will be recalled that Sarnoff and co-workers (12) concluded that lowering carotid sinus pressure reduces baroreceptor inhibition of sympathetic outflow to the myocardium. This presumably results in increased cardiac sympathetic activity with an attendant increase of ventricular contractility. On the other hand, Salisbury et al. (13) were unable to confirm these findings and concluded that the ventricular responses were the result of changes of other hemodynamic variables. More recently DeGeest and co-workers were able to demonstrate a small alteration of ventricular contractility consequent to changes of carotid sinus pressure (14). Thus, the evidence that the carotid sinus baroreceptor system is
capable of influencing cardiac function seems to be valid in the adult dog, but the response is quantitatively quite small. It is, therefore, not surprising that in the present experiments no detectable difference was observed in the magnitude or nature of the response to cephalic hypotension following sectioning of the carotid sinus nerves, if indeed this system is active in the newborn lamb.

The possibility that these responses originated at least in part from the carotid chemoreceptors must also be considered. Respiratory efforts, sometimes pronounced, were usually observed during cephalic hypotension. It is likely that these originated from stimulation of the carotid bodies as a consequence of reduced perfusion of these structures during the hypotensive period (15, 16). Although some investigators have reported that carotid chemoreceptor stimulation increases cardiac contractility reflexly (14), others have reported no change or a small reduction of ventricular contractility (18, 19). These observations together with the findings in the present study that the contractility responses were apparently not importantly diminished by bilateral sectioning of Hering's nerves do not support the position that carotid chemoreceptor stimulation was a necessary component of the reflex.

A more likely explanation for the increase of cardiac contractility, and probably in part for the increases of heart rate and systemic vascular resistance, is that reduced blood flow resulted in ischemic stimulation of the central nervous system with activation of sympathetic cardiac and vasomotor centers, such as has been observed in the adult (9, 10, 20). This presumably results from local changes of \( P_{O_2}, P_{CO_2} \) and \( \text{pH} \) within the brain.

In 5 of the 14 lambs less than 4 days of age, no clear evidence for a reflex change of contractility could be elicited and the responses were small in several of the others (Table 1). In contrast, none of the 9 animals, 4 days or older, were completely areflexic. This might suggest the development of more effective reflex control of the heart during the first few days of life. The possibility was considered that sympathetic support of the myocardium was maximal at birth and that with the rapid growth of additional myocardial tissue, which has been shown to occur for several days following birth (21), the requirement for sympathetic support might be reduced. This would thereby provide an increasing range over which the magnitude of sympathetic discharge could be varied. This hypothesis appears to be invalid, however, because at least 5 of the younger animals were more responsive than the average of the older animals. Indeed, one of the most reactive preparations was only 1 day of age. It is more likely that the areflexia in these younger animals was the result of greater sensitivity to mechanical trauma, to anesthesia or to other factors related to the experimental procedure. It seems reasonable to conclude that at least some mechanisms for reflex control of cardiac function are present in the early neonatal period in the lamb. The greater difficulty in demonstrating this in the younger animals may have been technical in nature rather than a developmental change.

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