Cardiac and Respiratory Effects of Aortic Arch Baroreceptor Stimulation

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ABSTRACT

The reflex cardiac and respiratory effects of stepwise pressure variations in the isolated aortic arch were determined in anesthetized dogs. Elevation of pressure in the aortic arch depressed respiratory movements, decreased heart rate in the unpaced heart, and diminished peak pressure in the paced, isovolumetric left ventricle preparation. The threshold for these reflex effects was an aortic arch pressure of approximately 100 mm Hg. The maximum rate of change of these variables as a function of aortic arch pressure occurred at a pressure of about 175 mm Hg. Aortic arch pressures of 300 mm Hg or more were necessary to achieve maximal reflex effects. Heart rate changes were mediated by parasympathetic pathways predominantly, although reciprocal sympathetic influences were also involved. Both divisions of the autonomic nervous system mediated the effects upon ventricular performance.

ADDITIONAL KEY WORDS

regulation of respiration cardiac reflexes pressoreceptor reflexes
parasympathetic blockade cardiac regulation sympathetic blockade
ventricular performance myocardial contractility bretylium tosylate
anesthetized dogs

It has been generally recognized for the past half-century that arterial baroreceptors located principally in the carotid sinuses and aortic arch, are intimately involved in the reflex regulation of the cardiovascular system. Investigation of the baroreceptor reflexes has been virtually restricted to the receptors in the carotid sinuses, primarily because of the relative ease of their surgical isolation. In the comparatively few studies of the aortic arch baroreceptors, the pressure changes usually were not confined to that region, but probably involved the left side of the heart, the pulmonary vasculature, and other regions as well (1-5). In 1908, Oyster and Hooker (6) isolated the aortic arch surgically and studied the cardiac response to pressure variations in that region. However, their technique required interruption of the entire blood circulation.

Therefore, the responses to aortic arch pressure variations had to be distinguished from the responses to various other rapidly changing conditions, including cephalic ischemia. Mechanical devices (7) and balloons (8) have been employed to limit changes in the region of the aortic arch, but data obtained with such techniques are not readily quantifiable.

Recently, techniques have been devised for isolation of the aortic arch while maintaining the blood circulation (9-12). In the present study, these techniques have been modified to permit investigation of the effects of pressure variations confined to the isolated aortic arch upon heart rate, left ventricular performance, and respiratory muscle activity.

Methods

Experiments were conducted upon 14 mongrel dogs that were anesthetized with morphine sulfate (2 mg/kg im) followed 30 min later by an infusion of urethane and chloralose (80 and 6 mg/ml iv, respectively). The anesthetic mixture was administered slowly until the animal was lightly anesthetized; i.e., it was insensitive to painful stimuli, but still possessed a wink reflex. The average volume of urethane-chloralose mixture administered was 8 to 9 ml/kg. The trachea was cannulated through a midline cervical incision and intermittent positive pressure res-
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FIGURE 1
Schema of the experimental preparation. Abbreviations: RA and LA, right and left atria; RV and LV, right and left ventricles; AA and DA, ascending and descending aorta; PA, pulmonary artery; SVC, superior vena cava; BCA, brachiocephalic artery; RSA and LSA, right and left subclavian arteries; RCA and LCA, right and left common carotid arteries; F, funnel; OXY, oxygenator; RES, overflow reservoir; Cl, screw-clamp; SG, strain gauge; H, heating tape; and TP, thermistor temperature probe.

Expiration was begun. The chest was opened transversely at the level of the fourth intercostal space.

In order to isolate the aortic arch (Fig. 1), a loose ligature was applied about the ascending aorta after careful dissection from the main pulmonary artery. A second loose ligature was placed about the descending aorta 3 to 4 cm beyond the origin of the left subclavian artery and a third was applied about the aorta 2 to 3 cm distal to the second ligature. All branches of the aorta between the origin of the left subclavian artery and the third loose ligature were tied. A fourth loose ligature was placed about the brachiocephalic artery near its origin. Dissection of all vessels for the purpose of applying ligatures was carried out carefully to keep to a minimum the number of nerve fibers that might be damaged. Heparin (3.4 mg/kg) was administered intravenously to prevent blood coagulation, and
T-cannulas were inserted into the right and left common carotid arteries.

Cannulas were inserted into the superior vena cava and into the right atrium and ventricle; the venous return to the right heart was drained by gravity to the venous end of a rotating-disc oxygenator. The more distal of the two ligatures about the descending aorta was tied, and the cephalic half of the animal was perfused at a constant pressure near 100 mm Hg by connecting the carotid artery T-cannulas to an elevated overflow reservoir. A thermistor probe was used to measure the temperature of the perfusing blood. Heating tapes were applied about the tubing of the perfusion system, and the power was regulated to keep blood temperature at 37°C.

The descending aorta was then occluded, 2 to 3 cm distal to the origin of the left subclavian artery, by means of a Potts clamp. An incision was made in the segment of the aorta between the Potts clamp and the previously tied ligature. A soft rubber catheter (o.d., 5/16 inch; i.d., 3/16 inch), connected to the overflow reservoir, was introduced through this incision and passed toward the Potts clamp, which was then released. The more proximal of the two ligatures about the descending aorta was tied just snugly enough to prevent loss of blood from the aortic incision, but not too tightly to prevent further passage of the catheter. The catheter was then threaded through the aortic arch until its tip could be palpated in the ascending aorta. An incision was made in the tip of the catheter, and a 1-cm long piece of rigid plastic tubing was inserted into the ascending aorta. The ligature around the ascending aorta was securely tied about this rigid tip. Through this catheter, the coronary arteries were perfused from the overflow reservoir at a constant pressure of about 100 mm Hg. Once coronary perfusion was established, the ligature about the brachiocephalic artery and the more proximal ligature about the descending aorta were tied. Isolation of the aortic arch was completed by ligating the left subclavian artery about 2 cm from its origin.

The proximal segment of the left subclavian artery was cannulated to permit access to the lumen of the aortic arch, so that it could be subjected to a range of pressure variations. Changes in pressure were exerted within the entire aortic arch, except for the portion of the ascending aorta on the cardiac side of the ligature which was used to anchor the tip of the coronary perfusion catheter. The possibility cannot be ignored, therefore, that this segment of the ascending aorta might contain baroreceptors with thresholds and sensitivities different from those reported in this paper.

Aortic arch pressure was measured by using a Statham P23AA strain gauge in the tubing adjacent to the left subclavian artery cannula. The desired level of pressure was achieved by using three screw clamps. The first clamp was on the tubing leading to the overflow reservoir; its function was to introduce sufficient resistance to flow such that upstream pressure could be elevated to levels (in excess of 300 mm Hg) considerably above the hydrostatic level of the overflow reservoir (about 100 mm Hg). The second clamp was on the tube leading from the outflow line from the pump to the cannula in the left subclavian artery; its function was to introduce sufficient resistance to flow such that when aortic arch pressure was adjusted to pressures below 100 mm Hg, there would still be adequate pressure available in the parallel line to permit filling the overflow reservoir. Clamps 1 and 2 were preset early in each experiment, prior to obtaining any data. The actual experimental variations in aortic arch pressure were achieved by adjusting a third clamp, which was on a shunt line running between the tube connected to the left subclavian artery cannula and the venous end of the oxygenator. Tightening clamp 3 resulted in an elevation of pressure in the aortic arch by distending it with oxygenated blood from the arterial end of the oxygenator; loosening the clamp caused a drop in pressure.

Left ventricular performance was assessed by means of a paced, innervated, isovolumetric left ventricle preparation, which has been described in detail previously (13, 14). A balloon was introduced into the left ventricular cavity through a small incision in the left auricular appendage. The balloon was anchored at the ventricular apex (14), and filled with a measured volume of saline. Pressure in the balloon was measured by means of a second Statham P23AA strain gauge. A Teflon tube with multiple side holes was also inserted into the left ventricle through a second atrial incision to transport the Thebesian drainage from the venous end of the oxygenator. Pacing was achieved by stimulating the right atrium and ventricle synchronously with a Grass stimulator, model S-4.

Aortic arch pressure and pressure within the left ventricular balloon were recorded on a Beckman S-II Dynograph and on magnetic tape (Honeywell, LAR 7400). The mean heart rate was recorded by an integrating tachometer, and the time interval between consecutive beats by an interval duration meter (15). The pH of the blood leaving the arterial end of the oxygenator was recorded by means of a Radiometer pH meter, type TTT 1c. Blood pH was maintained at a level of 7.4 by adjusting the rate of a slow drip of a saturated solution of NaHCO₃. Respiratory movements were registered by connecting an elastic string from a point on the rib cage to

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The changes in heart rate, left ventricular pressure, and respiratory movements with variations in pressure in the isolated aortic arch in a representative experiment. In the panel on the left, the heart was not paced; in the panel on the right, the heart was paced at 120 beats/min.}

**Results**

**AUTONOMIC NERVOUS SYSTEM INTACT**

The effects of stepwise variations in aortic arch pressure upon heart rate, left ventricular performance, and respiratory (rib cage) movement are illustrated in Figure 2. During the registration of the left half of the figure, the heart was unpaced. Prominent fluctuations in heart rate and left ventricular systolic pressure (LVSP) were manifest at the frequency of the respiratory movements (15). As the pressure was raised in steps of approximately 100 mm Hg, there was a progressive reduction in the frequency of the heart beat and of the respiratory movements. With aortic arch pressure equal to 0 (left edge of left panel), LVSP was 78 mm Hg, respiratory frequency was 8.5/min, and mean heart rate was 105 beats/min (as determined by the integrating tachometer, the tracing of which is not included in the figure). At the highest aortic arch pressure (280 mm Hg), respiratory frequency was 4.0/min and mean heart rate was 72 beats/min. The amplitude of the rhythmic fluctuations in heart rate was considerably augmented. As aortic arch pressure was then lowered in steps to approximately zero, heart rate, LVSP, and respiratory frequency returned to or near the control values. For any given aortic arch pressure, the responses were similar whether pressure was being varied in an ascending or in a descending sequence. Reproducible responses were obtained when the series of ascending and descending pressure variations were repeated.

After these observations had been recorded, the heart was paced at a constant rate of 120 beats/min to permit evaluation of the magnitude of the reflex alterations of ventricular performance. In the right panel of Figure 2 are displayed the changes in LVSP as aortic arch pressure was varied in steps from 0 to 290 mm Hg. The control level of LVSP was 63 mm Hg (left edge of right panel). With each rise of aortic arch pressure, LVSP decreased; at the maximum aortic arch pressure of 290 mm Hg, LVSP was 56 mm Hg. As aortic arch pressure was subsequently lowered in steps, LVSP again increased.

The composite data from the entire series of experiments are presented in Figure 3. Definite changes in heart rate, LVSP, or respiratory frequency were never seen when aortic arch pressure was elevated from zero to levels below 75 or 80 mm Hg. Only small reductions in these variables were evoked by aortic arch pressure rises up to 125 mm Hg, but
FIGURE 3

Composite data from 13 animals in which aortic arch pressure was varied in steps while both divisions of the autonomic nervous system were intact. The changes in heart rate, left ventricular systolic pressure, and respiratory rate are expressed as percentage of the value at aortic arch pressure equal to zero. Open circles represent mean values of each function within each range of aortic arch pressure listed along the abscissa. Vertical lines represent the standard error of the mean. Only one value is included in each pressure range from any single experiment; where more than one observation was made within a given range, the value used for that experiment represents the mean of those values within that range.

The magnitude of these reductions progressively increased as aortic arch pressure was elevated as high as 325 mm Hg. The percentage reductions in heart rate and respiratory rate were approximately twice as great as the percentage diminution of LVSP. The steepest portion of these curves occurred at an aortic arch pressure of approximately 175 mm Hg. The maximum reflex effect was not ascertained in these experiments; it apparently requires an aortic arch pressure in excess of 300 mm Hg.

SYMPATHETIC BLOCKADE

To distinguish between the roles of the two divisions of the autonomic nervous system in the cardiac response to aortic baroreceptor stimulation, parasympathetic effects were blocked in some experiments and sympathetic influences were blocked in others. Segments of records are shown in Figure 4 from a continuation of the same experiment depicted in Figure 2. In panel A, aortic arch pressure was elevated to 240 mm Hg for 1 min. This resulted in a reduction in the mean heart rate to 70 beats/min from a control rate of 96 beats/min. The magnitude of the respiratory sinus arrhythmia was considerably greater at the elevated aortic arch pressure, just as in Figure 2. In panel B, with the heart paced at 120 beats/min, a similar pressure rise in the aortic arch evoked a decline in LVSP to 78 mm Hg from a control level of 84 mm Hg.

At the arrow in panel B, bretylium tosylate (30 mg) was introduced into the venous end of the oxygenator. This dose has been found to block completely the effects of strong sympathetic nervous stimulation in this system after 20 min (16). Complete blockade was verified at the end of each of the present experiments in which bretylium was administered by stimulating the stellate ganglia with 5 msec pulses at 15 v and 15 cycle/sec; no changes in heart rate or LVSP were detectable. Approximately 1 min after adding bretylium, this drug had traversed the dead space of the system and had reached the heart. The characteristic rise in LVSP (16) then occurred; this is shown to the right of the arrow in panel B.

Panel C was recorded 20 min after the administration of bretylium. When aortic arch pressure was raised to 250 mm Hg, heart rate decreased to 75 beats/min from a control level of 100 beats/min and the magnitude of the respiratory sinus arrhythmia increased considerably. The heart was then paced at 120 beats/min, and repetition of the elevation of aortic arch pressure (panel D) evoked a decrease in LVSP to 110 mm Hg from a control level of 121 mm Hg. Subsequently,
both vagus nerves were sectioned, resulting immediately in a rise in LVSP and heart rate in the unpaced heart. The increase in LVSP is ascribable both to the increase in heart rate per se (17) and to the release of the ventricular myocardium from the negative inotropic effect of tonic vagal activity (16). Panel E was recorded shortly after vagotomy. Elevation of aortic arch pressure to 250 mm Hg caused no perceptible change in the frequency of the unpaced heart and evoked a small reduction in LVSP. Similar, small artifacts were observed in the LVSP tracings during aortic arch distension in approximately one-third of all experiments after bilateral vagotomy (whether or not blocking agents had previously been given). In the remaining experiments, no changes in LVSP were detectable after bilateral vagotomy.

Four experiments were conducted in which sympathetic blockade was achieved by the administration of bretylium tosylate. When aortic arch pressure was elevated from zero to a level between 200 and 250 mm Hg, LVSP was diminished by 5, 5, 6, and 9% (heart paced), and heart rate (heart not paced) was reduced by 22, 36, and 41% (in the fourth experiment, aortic arch pressure was not elevated while the heart was unpaced).

PARASYMPATHETIC BLOCKADE

Segments from the records of an experiment in which the response to aortic baroreceptor stimulation was ascertained after parasympathetic blockade are displayed in Figure 5. Panels A and B were recorded while both divisions of the autonomic nervous system were intact. With the heart paced at 150 beats/min (panel A), a stepwise elevation of aortic arch pressure to 280 mm Hg resulted in a decrease in LVSP to 100 mm Hg from a control level of 124 mm Hg. There was also a marked reduction in respiratory frequency. A similar stimulus to the aortic baroreceptors with the heart unpaced caused cardiac deceleration to 100 beats/min from control frequency of 130 beats/min (not shown in Fig. 5).

After these observations had been made, the pacing frequency was increased to 180 beats/min and atropine sulfate (8 mg) was introduced into the venous end of the oxygenator (at the arrow along the left edge of panel C). After a time delay of about 1 min, which was required for the atropine to traverse the dead space of the perfusion system, there was a rise in LVSP from 110 mm Hg to a value of 134 mm Hg (just prior to the first rise of aortic arch pressure in panel C). This rise in LVSP after atropine is ascrib-
Changes in heart rate, left ventricular pressure, and respiratory movements with variations of aortic arch pressure before and after parasympathetic blockade with atropine sulfate (given at left arrow in panel C). The heart was paced to the left of the right arrow in panel C, and unpaced to the right of this arrow. Between panels C and D, both vagi were sectioned in the neck. In panel B, the paper speed was increased to 50 mm/sec to display the configuration of the left ventricular pressure curves.

able to a release of the ventricular myocardium from tonic vagal depression (16). Elevation of aortic arch pressure to 320 mm Hg evoked a reduction of LVSP to 98 mm Hg.

At the right-hand arrow in panel C, the pacing was halted. LVSP increased immediately, because ventricular activation proceeded normally rather than over aberrant pathways from the ectopic focus in the right ventricle (18). The spontaneous frequency after atropine was found to be 165 beats/min (as compared with 130 beats/min before atropine). Elevation of aortic arch pressure to 300 mm Hg caused the heart rate to diminish to 145 beats/min. Such stimulation of the aortic arch baroreceptors resulted in cessation of respiratory movements.

Both cervical vagus nerves were sectioned after panel C had been recorded and panel D was registered shortly after completion of vagal transection. Vagotomy had no effect upon heart rate, but did result in cessation of spontaneous respiratory movements. Elevation of aortic arch pressure to 300 mm Hg (panel D) had no appreciable effect upon heart rate (the heart was unpaced in panel D) or upon LVSP. Low frequency respiratory movements reappeared after aortic arch pressure was lowered to 10 mm Hg. Subsequent strong electrical stimulation of the cardiac ends of the vagus nerves did not cause a reduction of heart rate or LVSP, confirming the effectiveness of the blockade by atropine.

In the five experiments in which parasympathetic blockade was achieved with atropine, raising aortic arch pressure from 0 to a mean level of 288 ± 22 (SE) mm Hg evoked a reduction of LVSP of 11.8 ± 3.1 (SE) mm Hg.

Discussion

The minimum intravenous pressure required for activation of the aortic arch baroreceptor reflex equals or exceeds that reported in other dogs for the carotid sinus baroreceptor reflex. In most of the experiments described herein, perceptible effects upon heart rate, LVSP, or respiratory movements were not observed until aortic arch pressure was raised to 80 or 100 mm Hg (Figs. 2 and 3). When the carotid sinus baroreceptors were activated by nonpulsatile pressures, similar thresholds have been found by several investigators (19-23), while others (24-30) have reported lower threshold values.

The threshold for the aortic arch baroreceptor reflex had been found to be 60 to 65 mm Hg in the rabbit (20, 31). The appreciably lower level than that found in the dog in the
present study may represent in part a species difference. Unquestionably, however, a major reason for the difference is the fact that the thresholds in the rabbit were determined for normally pulsatile pressures. Pulsatile pressures at a given mean level exert more potent baroreceptor reflex effects than do steady pressures at the same mean level (21, 22, 32). The pressures employed in the present study were essentially steady. Pulse pressures in the tubing just upstream from the left subclavian artery cannula averaged about 20 mm Hg (Fig. 2). Pulse pressures within the aortic arch, however, were undoubtedly considerably less because of the effective damping action of the hydraulic resistance of the arterial cannula combined with the large capacitance of the aortic arch itself. On the basis of afferent action potential recordings, Homma and Suzuki (12) have found the threshold for the aortic arch baroreceptors to be well under 50 mm Hg for steady pressures. However, as Ead et al. (21) have previously indicated, the threshold for excitation of baroreceptor sensory nerve endings is below that necessary for evoking reflex responses.

The pressures required to evoke maximal responses are significantly different for the aortic arch and the carotid sinus baroreceptors. Even at pressures of 300 mm Hg, the cardiac and respiratory responses to aortic baroreceptor stimulation still did not appear to be maximal (Fig. 3). In every instance, aortic arch pressures in the range from 275 to 324 mm Hg evoked a greater response than did pressures from 225 to 274 mm Hg. Maximal effects are achieved by carotid sinus baroreceptor stimulation at considerably lower pressure levels, usually from 180 to 250 mm Hg (21, 24-30, 33, 34). In one study (28), however, maximal effects have been reported with carotid sinus pressures in excess of 270 mm Hg in some animals.

Just as with the carotid sinus baroreceptor reflexes (16, 23), the efferent cardiac pathways of the aortic arch baroreceptor reflexes include fibers from both divisions of the autonomic nervous system. The effects upon heart rate are mediated primarily by the vagi (Fig. 4), although reciprocal sympathetic changes are also involved (Fig. 5), in accordance with previous concepts (35). The exaggeration of the respiratory sinus arrhythmia with elevated aortic arch pressure (Figs. 2 and 4) is characteristic of enhanced parasympathetic tone (15, 36).

The present series of experiments demonstrates that reciprocal action of both divisions of the autonomic nervous system affects ventricular performance during aortic arch baroreceptor stimulation (Figs. 4 and 5). The relative importance of each division cannot be assessed, however, because the pharmacological blockade which was employed to block selectively one division probably also alters the activity of the other division. Such difficulties of quantification have previously been discussed with respect to the carotid sinus baroreceptor reflexes (16).

The slowing of the respiratory rate with stimulation of receptors localized in the aortic arch (Figs. 2-5) confirms the observations of J.-F. and C. Heymans (37, 38) relative to the influence of receptors in the cardio-aortic region. In the present study, aortic arch pressures were varied upward from zero. At the lowest pressures, it might be presumed that aortic body chemoreceptors were excited as a result of low perfusion rates (28, 39, 40). Decrease in chemoreceptor activity as well as increase in baroreceptor activity probably occurred as pressure was increased in the aortic arch from initial low pressures. It is likely, however, that the effects observed are ascribable almost exclusively to baroreceptors rather than to chemoreceptors. Alterations in heart rate, LVSP, or respiratory muscle activity were not detectable as aortic arch pressure was varied between 0 and 75 mm Hg (Fig. 3). Such pressure changes would certainly be expected to increase perfusion rates through the aortic bodies, and hence to decrease chemoreceptor activity. It is conceivable that the aortic bodies or their nervous connections might have been damaged by the dissection between the ascending aorta and pulmonary artery; this was required to place the ligature which anchored the coronary perfu-
Stimulation of the aortic body chemoreceptors usually increases heart rate (41), but produces relatively slight effects upon respiration (11, 41, 42). Their influence upon ventricular performance remains to be determined.

References
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