Responses of the Heart to Stimulation of Aortic Body Chemoreceptors in Dogs

F. Karim, R. Hainsworth, O.A. Sofola, and L.M. Wood

SUMMARY We stimulated the aortic chemoreceptors in dogs that were anesthetized with chloralose and artificially ventilated by perfusing the isolated aortic arch with venous blood. Inotropic responses were determined by measuring the maximum rate of change of left ventricular pressure (dP/dt max) with aortic pressure and heart rate held constant. Stimulation of the aortic chemoreceptors resulted in an average increase in heart rate of 14 ± 2.0 beats/min (mean ± SE) from 166 ± 7.7 beats/min and an increase in dP/dt max of 501 ± 85 mm Hg/sec from 3508 ± 154 mm Hg/sec. These changes were statistically significant (P < 0.001). The afferent pathway of the reflex was shown to be in the vagus nerves and the efferent pathway in the cardiac sympathetic nerves. In some of the dogs, the carotid chemoreceptors were also stimulated. This resulted in decreases in heart rate and dP/dt max of 48 ± 24 beats/min and 795 ± 142 mm Hg/sec. Thus we have shown that stimulation of aortic chemoreceptors evokes chronotropic and inotropic responses opposite to those evoked from stimulation of carotid chemoreceptors. Circ Res 46: 77-83, 1980

STIMULATION of the carotid body chemoreceptors, with ventilation held constant, results in reflex bradycardia (Daly and Scott, 1958) and negative inotropic responses (Hainsworth et al., 1979). However, there has been no adequate study of the effect of physiological stimulation of the aortic body chemoreceptors on the inotropic and chronotropic state of the heart. Several groups of investigators have attempted to stimulate these receptors by injection of drugs such as nicotine into the open aortic arch, but the results are inconclusive largely because of inadequate localization of the stimulus.
the inferior vena cava through a saphenous vein. Additional doses of chloralose (about 10 mg/kg every 15 minutes) were given to maintain a state of light surgical anesthesia. The neck was opened in the midline, the trachea was cannulated, and the dog was ventilated with positive pressure by means of a Starling “Ideal” pump using 40% oxygen in nitrogen humidified at room temperature. The rate of the pump was 18 strokes/min, and the stroke volume was approximately 17 ml/kg. When the pleura was opened, a resistance to expiration was inserted, equivalent to 3 cm H₂O.

The regions of both common carotid bifurcations were vascularly isolated and perfused at constant pressure, as previously described (Hainsworth and Karim, 1973, 1976). In four experiments in which we stimulated the carotid chemoreceptors, the blood was drained, through the catheters in the lingual arteries, into an external jugular vein. In the remaining experiments, blood was allowed to flow through the internal carotid arteries. The technique for isolating the aortic arch region was similar to that described previously (Hainsworth et al., 1970; Hainsworth and Karim, 1972; Hainsworth et al., 1975; Karim et al., 1978). Briefly, the left 2nd to 5th ribs were removed to expose the aortic arch. The pericardium was opened, and strings were placed around the ascending aorta and the origins of the left subclavian and brachiocephalic arteries in preparation for aortic cannulation. The descending aorta was mobilized by cutting the upper four pairs of intercostal arteries between ties.

Two silver-ring electrodes were sewn onto the right atrial appendage for pacing. In all but two dogs, a miniature pressure transducer (model P13, Konningsberg Instrument Inc.) was introduced into the left ventricle through the left atrial appendage and secured in place by a tie around the base of the appendage. In the remaining two dogs, a short stainless steel cannula with side holes (length = 5 cm, bore = 1.2 mm) was inserted into the left ventricle through the apical dimple, tied in place by means of a purse-string suture, and firmly clamped in position. The dogs were given heparin (Pularin, Evans Medical Ltd., 500 IU/kg followed by 50 IU/kg every 30 minutes), and the circuit (Fig. 1) was filled with dextran solution (Dextraven 150, Pisons Pharmaceuticals Ltd.) or a mixture of dextran and blood obtained from another dog. Temporary bypasses were connected between the proximal ends of the left subclavian and a femoral artery to allow some circulation to the caudal part of the body during cannulation procedure.

The perfusion circuit (Fig. 1) was connected to the dog as follows. A curved stainless steel cannula was inserted into the aortic arch, and the arch was isolated by tightening the snare around the ascending aorta and clamping the bypass. The aortic blood passed through the aortic cannula and was distributed to the descending aorta and the aortic reservoir, from which blood was distributed to the isolated carotid sinuses, the isolated aortic arch, and the head of the dog through cannulas inserted into the distal end of the left subclavian artery and the proximal end of the left common carotid artery. The pressure of blood in the aortic cannula was maintained by the aortic reservoir in which the pressure of the air above the blood was controlled. The aortic arch was perfused at constant pressure with blood taken either from the aortic reservoir or from a cannula in the inferior vena cava. The temperature of the perfusate was maintained at 37–38°C by use of a heat exchanger. A cotton mesh filter (pore size about 220 μm) was also placed in the perfusion line between the roller pump and the aortic arch. The blood from the aortic arch drained from a cannula (bore = 2 mm) tied in the brachi-
ocephalic artery and was returned to an external jugular vein. Samples of blood were withdrawn from the outflow cannula to measure the \( \text{PO}_2 \), \( \text{PCO}_2 \), and pH of blood perfusing the arch using a blood gas electrode system (Corning, model 165). In some experiments, the blood passed through an oxygen electrode system (Electronic Instruments Ltd.) before draining into an external jugular vein.

Pressures were recorded using Statham (P23 Gb) transducers connected to cannulas (bore = 4 mm) in the central end of the left subclavian artery (aortic arch pressure), aortic cannula (systemic arterial blood pressure), common carotid arteries, and the left ventricle. After amplification by carrier amplifiers (S.E. Laboratories Ltd.), the pressures were recorded on photographic paper by a direct-writing ultraviolet light recorder (S.E. Laboratories Ltd.). The output from the amplifier for the left ventricular pressure transducer was distributed in four ways: (1) directly to a galvanometer to record left ventricular end-diastolic pressure at a high sensitivity (7.5 mm Hg = 10-mm paper); (2) through a variable series resistance to a galvanometer to measure left ventricular pressure at lower sensitivity (20 mm Hg = 10-mm paper); (3) to an analogue differentiator to provide a signal of \( dP/dt \) which was amplified and recorded; and (4) to a digital cardiostatometer (Gilford Instruments Inc.) to record ventricular rate. The differentiator was calibrated to give a frequency response of the cannula and transducer system to be flat (±5%) to better than 80 Hz in the case of the apical cannula and better than 200 Hz for the catheter tip transducer.

During determinations of inotropic responses, the heart was paced by a Grass stimulator (model S4). A thermistor probe (Yellow Springs Instruments Inc.) recorded esophageal temperature which was maintained at 37–39°C by means of electric heaters under the operating table. Arterial \( \text{PO}_2 \), \( \text{PCO}_2 \), and pH were determined frequently during the experiments using a blood gas analyzer (Corning, model 165). Arterial \( \text{PCO}_2 \) and pH were maintained within the ranges of 32–40 mm Hg and 7.30–7.40 units, respectively, by adjusting the stroke of the respiration pump and by intravenous infusions of molar sodium bicarbonate. Since the dogs breathed air enriched with oxygen, arterial \( \text{PO}_2 \) was greater than 113 mm Hg.

The effectiveness of the vascular isolation of the aortic arch was assessed in all experiments by stopping the inflow and noting the pressure, which fell to between 0 and 10 mm Hg. The regions perfused through the aortic arch were visualized at the ends of the experiments by injections, in four dogs, of Evans blue dye, and, in two dogs, of Indian ink into the perfusion tubing at pressures similar to those which perfused the isolated arch during the tests. In all six dogs, no dye or ink was seen either in the aorta, proximal or distal to the isolated segment of the aortic arch, or in the coronary or pulmonary circulations, but dye or ink was found in the region between the aortic arch and pulmonary trunk.

**Experimental Procedure**

About half an hour after the circuit had been connected, the following procedures were carried out.

The isolated aortic arch was perfused with arterial blood at a constant pressure of 151 ± 9.0 mm Hg (mean ± SE, \( n = 11 \)). The pressure of the blood in the aortic cannula was set to 111 ± 4.5 mm Hg and that in the carotid bifurcations to 124 ± 7.5 mm Hg. The heart was paced at a rate higher than that expected during chemoreceptor stimulation. When all measured variables were steady, records were taken. The pacing of the heart then was stopped to record free heart rate. The aortic chemoreceptors were stimulated by perfusing the isolated aortic arch with blood from the inferior vena cava. Records were taken continuously for about 2–4 minutes while pressures in the aortic arch, aortic cannula, and carotid arteries were held constant. The heart again was paced at the same rate as during the arterial perfusion, and a further record was obtained. Pacing then was stopped, the aortic perfusate was changed back to arterial blood, and further records were obtained without and with pacing.

The values of free heart rate and of \( dP/dt \) max during pacing, which were obtained during venous perfusion of the chemoreceptors, were compared with the average values obtained during the two periods of arterial perfusion.

In four of the dogs, we also determined the responses to perfusion of the carotid bodies with venous blood with the carotid and aortic pressures held constant.

The values reported are means ± SE of the mean. Significance was determined by paired t-test.

**Results**

**\( \text{PO}_2 \), \( \text{PCO}_2 \), and pH of Perfusate**

The values of \( \text{PO}_2 \), \( \text{PCO}_2 \), and pH of the arterial perfusate were 105 ± 3.0 mm Hg, 39 ± 0.22 mm Hg, and 7.37 ± 0.001 units, respectively. The corresponding values for the venous perfusate were 31 ± 1.0 mm Hg, 54 ± 1.0 mm Hg, and 7.28 ± 0.004 units.

**Responses to Perfusion of the Aortic Arch with Venous Blood**

During arterial perfusion, in 19 tests in 11 dogs, the values of the variables measured were as follows: aortic arch perfusion pressure, 151 ± 9.0 mm Hg; carotid sinus pressure, 124 ± 7.5 mm Hg; systemic arterial pressure, 111 ± 4.5 mm Hg; heart rate (when not paced), 166 ± 7.7 beats/min (results from 10 dogs only); left ventricular end-diastolic pressure (in four dogs measured), 5.8 ± 1.13 mm Hg; left
ventricular systolic pressure, 154 ± 5.2 mm Hg; and left ventricular dP/dt max, 3508 ± 154 mm Hg/sec.

With the heart not paced, perfusion of the aortic arch with venous blood resulted in an increase in heart rate of 13.6 ± 2.0 beats/min (8.2 ± 1.2%). This response was statistically significant (P < 0.001). The average values of heart rate from each dog, during perfusion of the aortic arch with arterial and venous blood, are listed in Table 1. Figure 2A shows an example of the responses obtained.

With the heart paced at 200 ± 4 beats/min, perfusion of the aortic arch with venous blood resulted in an increase in dP/dt max of 501 ± 85 mm Hg/sec. The average values of dP/dt max obtained from each dog during pacing are given in Table 1, and an example of experimental records is shown in Figure 2B.

Responses to Perfusion of the Aortic Arch with Venous Blood at Pressures below Threshold for Baroreceptors

In five dogs, we increased aortic pressure in steps of about 20 mm Hg to determine the lowest pressure that resulted in reflex changes in heart rate and dP/dt max. Values between 120 and 140 mm Hg were obtained as the threshold for baroreceptors. These values are similar to those reported previously (Hainsworth et al., 1970; Hainsworth and Karim, 1972). The effects then were determined of perfusing the aortic arch with venous blood with the perfusion pressure held below this level. Heart rate, measured in two of the dogs, increased by 12 and 27 beats/min from 180 and 179 beats/min; dP/dt max, in all five dogs when the heart was paced, increased by 383 ± 79 mm Hg (+10.5 ± 1.8%). These responses were not significantly different from those obtained at higher aortic arch perfusion pressures.

Effect of Section or Cold Blockade of the Vagus Nerves

In one dog both cervical vagosympathetic trunks were cut, and in another they were cooled to a surface temperature of 8°C by a thermoelectric module (De La Rue Frigistor Ltd.). Before the nerves were cut, perfusion of the aortic arch with venous blood resulted in an increase in dP/dt max (heart paced) of 375 mm Hg/sec from 3435 mm Hg/sec. No response was obtained after the nerves were cut. In the other dog before the nerves were cooled,

### Table 1 Heart Rate and Left Ventricular Inotropic Responses to Venous Perfusion of the Isolated Aortic Arch

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<th>Dog no.</th>
<th>A</th>
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<th>% Change</th>
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</table>

Values listed are the averages obtained from each dog during perfusion of the aortic arch with arterial (A) and venous (V) blood with constant pressures in the aortic arch, carotid sinuses, and aortic cannula (systemic). Heart rate (HR) was held constant by electrical pacing of the heart when inotropic responses were determined.
dP/dt max increased by 323 mm Hg/sec from 2910 mm Hg/sec. When the nerves were cooled, venous perfusion of the aortic arch increased dP/dt max by only 52 mm Hg/sec from 2490 mm Hg/sec.

Effect of Crushing or Blocking Efferent Sympathetic Nerves

In one dog both ansae subclaviae were crushed, and in another the efferent sympathetic nerves to the heart were blocked by intravenous propranolol (0.5 mg/kg). The responses of heart rate and dP/dt max to venous perfusion of the aortic arch before crushing the ansae were +6 beats/min and +600 mm Hg/sec and before giving propranolol +20 beats/min and +293 mm Hg/sec. After crushing the ansae or giving propranolol, no responses of either heart rate of dP/dt max were obtained.

Comparison of the Cardiac Responses to Venous Perfusion of the Aortic Arch and Carotid Bifurcations in the Same Dog

In four dogs, perfusion of the isolated carotid bifurcations with venous blood resulted in a decrease in heart rate of 48 ± 24 beats/min from 147 ± 20 beats/min (−31.3 ± 13.7%) and a decrease in dP/dt max of 795 ± 144 mm Hg/sec from 3824 ± 295 mm Hg/sec (−20.6 ± 3.3%). In the same preparations, perfusion of the aortic arch with venous blood resulted in an increase in heart rate of 11 ± 3.1 beats/min from 157 ± 16 beats/min (+7.0 ± 2.0%) and an increase in dP/dt max of 476 ± 151 mm Hg/sec from 3630 ± 382 mm Hg/sec (+13.0 ± 3.0%). An example of the opposite inotropic responses to stimulation of the aortic and carotid chemoreceptors in the same dog is shown in Figure 3, and the averages of the values obtained from all four dogs during venous perfusion of the carotid bifurcations are listed in Table 2.

Discussion

Our experiments have shown that perfusion of the aortic arch with venous blood, in dogs anesthetized with chloralose, consistently results in increases in the rate and the inotropic state of the heart. The responses were abolished by cutting or cooling the vagus nerves in the neck or by crushing the cardiac sympathetic nerves or blocking their effect with propranolol. This shows that the afferent pathway for the reflex was in the vagus nerves and the efferent pathway in the cardiac sympathetic nerves. The key question to be answered is whether we can assume that the effects produced by perfusing the aortic arch with venous blood are due to stimulation of aortic chemoreceptors.

The region of the aorta that was isolated vascularly from the rest of the circulation contains most of the arteries to the chemoreceptors (Comroe, 1939; Coleridge et al., 1970). We confirmed the effectiveness of the isolation procedure in all dogs by stopping the perfusion and noting that the pressure in the isolated aortic arch fell to near venous levels. Furthermore, in four of the dogs, we determined the region perfused through the aortic segment by injection of Evans blue dye or Indian ink into the isolated arch at normal perfusion pressures and observed staining only in the region between the aorta and the pulmonary artery. No staining was seen in the coronary arteries, in the aorta proximal or distal to the isolated segment, or in the pulmonary circulation. The venous blood, therefore, would not have changed the activity of the afferent nerves in the pulmonary or coronary regions.

The only other mechanism to exclude is whether the responses may have been due to reduced activity of aortic baroreceptors during perfusion of the aortic arch with venous blood. This is unlikely because the responses to perfusion with venous blood were not different when the perfusion pressure was held below the threshold for the aortic baroreceptor reflexes (Hainsworth et al., 1970; Hainsworth and Karim, 1972). Also A.U. Kadiri, C.M. Malpus, and C. Kidd (personal communication) showed that baroreceptors, at least those at
the right subclavian angle, were not affected by perfusion with venous blood for periods of up to 4 minutes. The responses to perfusion of the aortic arch with venous blood were not mediated by the receptors with afferents running in the sympathetic nerves (Lioy et al., 1974; Malliani and Pagani, 1976) because we showed that the reflex was dependent on the integrity of the vagus nerves.

Some of the aortic bodies receive their blood supply from the left coronary artery (Comroe, 1939; Coleridge et al., 1970), and these would not have been stimulated in the present experiments. Therefore, the responses obtained are not likely to have been the maximum that the aortic chemoreceptors are capable of producing. Furthermore, there was a wide variation in both the inotropic and chronotropic responses obtained from the different dogs (see Table 1). This variation may have been due to variations in the levels of anesthesia; in the numbers of aortic bodies perfused, which may vary from dog to dog (Coleridge et al., 1970); and in the amounts of damage caused to the chemoreceptors and their nerves during the dissection. It is also possible that the dissection may have caused variable degrees of damage to some of the efferent cardiac nerves.

There have been previous investigations that attempted to examine the cardiac responses from aortic chemoreceptors. These have involved the injection into the ascending aorta of substances known to stimulate chemoreceptors. Dawes and Comroe (1954) injected phenylbiguanide into the aorta and noted a decrease in heart rate. Comroe and Mortimer (1964) and Stern and Rapaport (1967) inserted delay coils in the carotid arteries to separate temporally the stimuli to aortic and carotid chemoreceptors. Injections of nicotine resulted in initial increases in heart rate in most experiments (Comroe and Mortimer, 1964) and in the inotropic state (Stern and Rapaport, 1967). The criticism of the studies involving injections of drugs into the nonisolated aorta is that the site of action cannot be localized. Nicotine has a widespread action on many nerve endings and ganglia (e.g., Coleridge and

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Values listed are averages obtained from each dog during perfusion of carotid bifurcations with arterial (A) and venous (V) blood at constant aortic arch pressure (169 ± 17 mm Hg), carotid sinus pressure (129 ± 13 mm Hg), aortic cannula pressure (51) ± 9 mm Hg). Heart rate also was held constant at 198 ± 1.5 beats/min when inotropic responses were determined.

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_Circ Res._ 1980;46:77-83
doi: 10.1161/01.RES.46.1.77

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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