Baroreceptor and chemoreceptor influences on sympathetic discharge to the heart

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DOWNING, S. EVANS, AND JOHN H. SIEGEL. Baroreceptor and chemoreceptor influences on sympathetic discharge to the heart. Am. J. Physiol. 205(3): 471-479. 1963.—Baroreceptor and chemoreceptor influences in the regulation of sympathetic discharge to the heart were investigated, utilizing electroneurographic recordings from the left inferior cardiac nerve in the cat. Spontaneous discharge patterns exhibited phasic inhibition with the heartbeat and with inflation of the lungs. This was shown to be the consequence of baroreceptor and afferent vagal activity, respectively. Increasing blood pressure with epinephrine or angiotensin II caused marked inhibition of discharge which was abolished by baroreceptor deafferentation. No increase of cardiac sympathetic discharge occurred after the introduction of hypoxic blood into the isolated carotid sinus. Systemic hypoxia caused a marked increase in sympathetic discharge which persisted after denervation of the peripheral chemoreceptors. A similar but less pronounced response to systemic hypercapnia was found. Systemic hypoxia frequently produced bradycardia which could be converted to tachycardia by atropine. This was associated with a large and continuous increase of cardiac sympathetic discharge to the heart. It is concluded that in systemic hypoxia both sympathetic and parasympathetic discharge to the heart is enhanced.

The early studies of Bronk et al. (1) demonstrated that cardiac sympathetic discharge is frequently rhythmic with the heartbeat, and concluded that this impulse grouping was the result of afferent activity from the baroreceptors causing central inhibition with each systole. They also observed that cardiac sympathetic discharge was increased by asphyxia and decreased by hyperventilation. Alexander (2) examined the response of the spinal sympathetic cardiovascular centers to hypoxia and hypercapnia using techniques similar to those of Bronk et al. (1). In contrast with these investigators Alexander reported that many of his preparations manifested a rhythmic, pulsatile discharge synchronous with the heartbeat after careful elimination of all afferents. He concluded that the pulsatility under these circumstances was due to the increased flow of blood to the spinal cord consequent upon the rise in blood pressure with each heartbeat. Thus, each ventricular systole inhibited sympathetic discharge by briefly increasing the oxygen supply to the spinal cardiovascular centers. Whereas hypoxia increased the impulse traffic in the inferior cardiac nerve, hypercapnia did not alter the discharge pattern in these preparations.

Recent hemodynamic investigations have shown that whereas total body hypoxia produces an increase of ventricular contractility (3, 4), hypoxic stimulation of the separately perfused carotid bodies failed to increase ventricular contractility (4). These studies also confirmed the earlier observations (5, 6) that bradycardia, not tachycardia, is the primary response to carotid-body hypoxia, and indicated that the peripheral chemoreceptors may not participate in producing the increased cardiac sympathetic response in systemic hypoxia.

The investigations to be described were designed to examine with electrophysiological techniques those mechanisms responsible for the observed alterations of sympathetic discharge to the heart consequent to changes of systemic arterial pressure and to variations of arterial oxygen and carbon dioxide content. An evaluation of the influence of baroreceptor and chemoreceptor reflexes was made and compared with responses presumably originating in the central nervous system. A preliminary report on these experiments has been given (7).

METHODS

Cats were anesthetized with pentobarbital sodium, 30 mg/kg. Endotracheal intubation was performed and constant mechanical respiration maintained with a Harvard respirator. Observations were made on five animals in which all baroreceptor and chemoreceptor systems were intact. These will be subsequently referred to as “intact preparations.” In four animals the vagi were cut bilaterally but the carotid sinus nerves were left intact. In four additional animals Hering’s nerves were cut bilaterally and observations were made before and after subsequent bilateral cervical vagotomy (Fig. 1).

In 14 animals the right carotid sinus and body were


denervated and the vagi were transected bilaterally. The left carotid was then vascularly isolated and cannulated for perfusion from a donor animal or by means of a mechanical perfusion system. This was achieved by ligating all branches of the carotid artery distal to the carotid sinus and body, and cannulating the common carotid artery with an "inflow" cannula and the external carotid artery with an "outflow" cannula. Care was taken to maintain the vascular integrity of the carotid body. In preparations utilizing a heparinized donor animal, the carotid artery of the donor was connected to the inflow cannula of the recipient by a flexible metal (lead) tube. This prevented excessive damping of the pulse wave. The outflow cannula was connected by appropriate tubing to the external jugular vein of the donor to complete the circuit. Endosinus pressure was measured by inserting a short polyethylene cannula into the perfused segment of the carotid artery via the facial artery.

In other preparations a mechanical system was utilized to perfuse the isolated carotid region (Fig. 2). This was composed of two reservoirs of heparinized cat blood, one containing hypoxic blood and the other well-oxygenated blood. The pressure within the reservoirs was increased to the desired level by air pressure. By appropriate manipulation of stop cocks, blood from either reservoir could be introduced to the carotid sinus. A pulsatile pressure wave was generated by mechanical compression of a soft segment of tubing leading from the reservoir system to the inflow cannula (8).

The left stellate ganglion was exposed by removing the left forelimb and resecting the posterior segments of the first and second ribs overlying the left stellate ganglion. Care was taken to avoid puncturing the pleura. The inferior cardiac nerve was identified, freed from surrounding connective tissue, and transected as far distally as possible. The nerve was placed on a grounded stainless steel dissecting platform and the field flooded with mineral oil. The nerve dissection was carried out under mineral oil with the aid of a 10X binocular dissecting microscope. Multifiber preparations were obtained and their electrical activity was picked up with stainless steel electrodes. The signals were filtered and amplified by a Tektronix 122 low-level preamplifier, and were displayed by one beam of a Tektronix 502 dual-beam oscilloscope. They were also monitored aurally by way of a simple audio system.

Continuous measurements of femoral arterial, left carotid, and endotracheal pressures were made utilizing Statham transducers and a Sanborn recorder. The out-
FIG. 3. In each record upper trace = endotracheal pressure, middle trace = femoral arterial pressure, lower trace = electoneurogram from inferior cardiac nerve. Carotid sinus nerves and vagi intact in A, sectioned in B. Record A: inhibition of discharge with each heartbeat and with lung inflation. Record B: respiratory and cardiac inhibition absent after deafferentation. Record speed in this and subsequent records, 70 mm/sec. Time marks, 0.1 sec.

FIG. 4. Continuous record of cardiac sympathetic discharge during rapid increase of pressure in isolated left carotid sinus. Rising line in electroneurogram record = carotid sinus pressure. Pressure records below: TP = endotracheal pressure; CSP = left carotid sinus pressure; FAP = femoral arterial pressure. A = put of two of these channels was passed into a beam-switching device (designed by Dr. Peter Frommer) and displayed on the second beam of the oscilloscope face. In early experiments a DuMont camera with 35-mm film was employed.

Ventilation with various gas mixtures was achieved by filling a Douglas bag with the desired mixture and connecting it to the inlet of the respirator. The outlet line from an arm of the endotracheal tube was made unidirectional by placing the end 5 mm below the surface of a cylinder of water. In many experiments decamethonium (Syncurine), 0.5 mg, was used to prevent excessive spontaneous respiratory efforts. This drug had no detectable direct effect on the impulse traffic in the inferior cardiac nerve. Where applicable, tests were made for completeness of baroreceptor deafferentation by the very rapid intravenous infusion of 5–10 ml isotonic saline. When even a single baroreceptor nerve was intact, this infusion caused a temporary inhibition of discharge. If no alteration of sympathetic discharge occurred the deafferentation was assumed to be complete. At the end of the experiments hexamethonium Cl (Bistrium), 2–10 mg/kg was given. This caused rapid and complete cessation of discharge, indicating the fibers to be postganglionic.

Although it is recognized that all the fibers of the inferior cardiac nerve may not innervate the myocardium, it is likely that this is the predominant distribution (1, 9).
FIG. 5. A: FAP = femoral arterial pressure. First bar, start continuous infusion of angiotensin II, 1 μg/kg min. Second bar, stop angiotensin infusion. Electroneurograms below correspond to letters in pressure trace above. FAP and endotracheal pressure recorded on each electroneurographic record. W = control; X = on angiotensin 90 sec; Y = on angiotensin 14 min; Z = off angiotensin 4 min. Carotid sinus nerves previously sectioned. Vagi intact. Electroneurogram record speed = 70 mm/sec. Pressure record speed = 0.5 mm/sec. B: events after bilateral cervical vagotomy (carotid-sinus nerves previously sectioned). W = control; X = on angiotensin II 300 sec; Y = on angiotensin 6 min; Z = off angiotensin 4 min.
The discharge activity of this nerve will be referred to as the cardiac sympathetic discharge.

RESULTS

Spontaneous cardiac sympathetic discharge patterns. In the five intact animal preparations the discharge patterns demonstrated rhythmicity both with the heartbeat and with respiration (Fig. 3A). After each heartbeat the discharge intensity decreased and was usually followed by a brief period of complete inhibition. After bilateral carotid sinus denervation and vagotomy the discharge pattern was altered such that the grouping of impulses was random and occurred with no temporal relation to the heartbeat (Fig. 3B). Before denervation, superimposed on the cardiac rhythm there was a secondary respirator rhythm which showed maximal inhibition during the inspiratory phase (Fig. 3A). The inhibition occurring during lung inflation was usually not complete.
and the cardiac rhythmicity continued throughout the respiratory cycle; the extent of inhibition was dependent on the degree of lung inflation. The respiratory inhibitory rhythm was also abolished by bilateral vagotomy and carotid sinus denervation (Fig. 3B), or by bilateral vagotomy alone. In experiments in which the vagi were cut but the carotid innervation left intact only severe overinflation accompanied by wide swings in arterial pressure could still produce a respiratory rhythm.

Baroreceptor influence on cardiac sympathetic discharge. After section of the vagi and right carotid sinus nerve, in preparations in which the vascularly isolated left carotid sinus was perfused from a donor cat, it was possible to establish a vascular rhythm of discharge in the sympathetics of the recipient. This rhythmic inhibition was in phase with the cardiac pulse of the donor but not with the heartbeat of the recipient. The rhythmic inhibition was best accomplished by using a high pressure in the isolated sinus, presumably because only one intact barosensory system was being utilized. Lowering the pressure in the perfused sinus caused an increase of discharge activity. Raising the endosinus pressure rapidly caused complete inhibition in all preparations (Fig. 4).

In preparations with carotid sinus denervation but with the vagi intact, raising the systemic blood pressure rapidly by the intravenous infusion of 5 ml normal saline, 10 μg epinephrine, or 1 μg angiotensin II caused temporary complete inhibition of all discharge activity. This was abolished by vagotomy. With the vagi intact, if the blood pressure was maintained at a higher level, as after blood infusion or continuous angiotensin II infusion, the discharge was reduced as long as the arterial pressure remained elevated (Fig. 5A). No alteration of discharge was observed with continuous angiotensin II infusion after vagotomy (Fig. 5B).

Influence of chemoreceptors in regulation of cardiac sympathetic discharge. In three reactive preparations hypoxic blood was introduced into the isolated left carotid sinus after denervation of the contralateral sinus and bilateral cervical vagotomy. The carotid-body reflex was active in these preparations as manifested by an increased respiratory effort with the introduction of the hypoxic blood into the sinus. Little alteration of cardiac sympathetic discharge was discernible when hypoxic blood was introduced into the sinus in these preparations. As shown in Fig. 6, raising the pressure in the sinus from 35 to 130 mm Hg reduced the cardiac sympathetic discharge, but the discharge intensity showed little difference with either hypoxic or saturated blood in the sinus at either pressure level.

In contrast with the failure to demonstrate significant chemoreceptor influence on the heart, it was consistently observed that the systemic arterial pressure changes in response to alterations of carotid sinus pressure were greatly enhanced by the presence of hypoxic blood in the sinus. As illustrated in Fig. 6, the presence of hypoxic blood in the isolated sinus caused a greater rise of arterial pressure when the sinus pressure was lowered (A), and a greater fall of arterial pressure when the sinus pressure was returned (B) than did equivalent changes with saturated blood in the sinus (C and D).

Effect of systemic hypoxia on cardiac sympathetic discharge. The administration of 5% O₂ to the intact preparation repeatedly caused a moderate to marked increase in dis-
FIG. 9. Heart rate response to atropine during systemic hypoxia. A: room air in respirator, heart rate = 198; B: 5% O₂ in respirator for 110 sec, heart rate = 161, signal mark indicates charge activity in each of the five animals in which this was done. This was nearly always accompanied by a large rise in blood pressure and a widening of the pulse pressure. In spite of the rise in arterial pressure the cardiac sympathetic discharge was increased (Fig. 7). After 1–2 min of 5% O₂ the arterial pressure sometimes fell to initial levels or below, but the discharge continued at its increased level. With 10% O₂, only a modest increase of discharge was evident and the blood pressure remained moderately elevated. Soon after the animal was changed from low O₂ mixtures to breathing room air a considerable reduction of discharge occurred. This was usually less than the initial intensity on room air with complete inhibition in some animals, but returned to control levels within 2 min or less.

In preparations in which bilateral carotid denervation had been done but the vagi were intact, systemic hypoxia with 5% O₂ produced an increased discharge and the pulsatile inhibition was either diminished or abolished (Fig. 8A, B). After bilateral vagotomy there was an undiminished increase of the sympathetic discharge with hypoxia (Fig. 8C, D). With less severe hypoxia (10% O₂) a modest increase in discharge was occasionally seen after vagotomy. A reduction of sympathetic discharge was never observed with either 5 or 10% O₂ mixtures.

In three intact preparations the administration of 5% O₂ for several minutes repeatedly produced a substantial reduction in heart rate, whereas the cardiac sympathetic discharge remained greatly increased. In two of these preparations 0.4 mg atropine was given intravenously during such an episode of bradycardia. This was associated with a prompt increase of heart rate. For example, in one experiment (Fig. 9) the heart rate was 198/min on room air (A). After 3 min of being respired with 5% O₂, the rate had slowed to 161 (B), even though the discharge was increased. Atropine, 0.4 mg, was administered intravenously and after 30 sec the rate increased to 218/min (C). Subsequent episodes of hypoxia produced intravenous injection of 0.4 mg atropine; C: 5% O₂ continued in respirator, 30 sec after atropine injection, heart rate = 218.

Influence of systemic hypercapnia on cardiac sympathetic discharge. The administration of 10% CO₂ (in 20% O₂, 70% N₂) produced a moderate or marked increase in discharge intensity in both the intact and deafferented preparations (Fig. 10) when respiration was controlled with decamethonium and artificial ventilation. If the animal were permitted to respond with hyperpnea, inhibition during inspiration was enhanced in those with intact vagi. Five per cent CO₂ (in 20% O₂, 75% N₂) failed to significantly alter the discharge intensity in either preparation.

In order to investigate the possibility of response potentiation, a gas mixture containing 5% O₂ and 5% CO₂ (in nitrogen) was compared with 5% O₂ (in nitrogen), also with 5% CO₂ (in 20% O₂, 75% N₂). The usual intense response was observed to 5% O₂. No response to 5% CO₂ was seen. The combination of gases produced a response not readily differentiated from 5% O₂ alone.

DISCUSSION

These investigations indicate that the baroreceptor reflexes have a major role in the regulation of sympathetic discharge to the heart. The peripheral chemoreceptor reflexes, on the other hand, have little influence. This study and the prior observations of Alexander (2) show that the gas composition of the blood perfusing the central nervous system may greatly influence the level of cardiac sympathetic discharge. It is also apparent from these and other studies (4) that there is a functional dichotomy between those areas which influence the sympathetic discharge to the heart and that to the periphery. Whereas carotid-body hypoxia increases sympathetic activity to the periphery (10, 11), there is either no effect or a decrease of sympathetic discharge to the heart.
In the present study, convincing evidence of cardiac sympathetic withdrawal during carotid-body stimulation was not obtained. This may be explained by the intrinsic difficulty of discriminating small quantitative changes in the multifiber electroneurogram. In view of the small changes in heart rate (about 10%) attributable to sympathetic withdrawal (4) correspondingly small alterations of discharge intensity would be expected. Any reduction in the level of discharge in response to carotid-body stimulation was very small when compared with carotid-sinus stimulation. Of greater importance was the failure to demonstrate an increase of cardiac sympathetic discharge consequent to carotid-body stimulation, whereas systemic hypoxia produced a large increase, presumably originating within the central nervous system.

In preparations with intact baroreceptor reflexes the cardiac sympathetic discharge was momentarily inhibited by each pulse wave, resulting in a rhythmic discharge with the heartbeat. After sectioning the carotid...
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sympathetic discharge to the heart. Although other poxia may enhance the activity of the sympatheticeral chemoreceptor stimulation during systemic hypoxia. Also, the is not consonant with increased sympathetic discharge, observations that carotid body hypoxia causes cardiac to the heart. These data indicate that, although periph-

tical chemoreceptors. After sectioning the carotid-sinus nerves and the vagi, the response was greatly diminished during systemic hypoxia. Thus, chemoreceptor impulses may increase the excitability of the medullary centers such that the response to other stimuli, possibly including baro-

receptor stimuli, is accentuated.

The administration of low oxygen mixtures caused a large increase of cardiac sympathetic discharge. That the peripheral chemoreceptors are not responsible for the increased discharge was demonstrated by the failure of hypoxia stimulation of a separately perfused carotid body to increase the discharge, and by the fact that sectioning the chemoreceptor afferent nerves failed to decrease the response during systemic hypoxia. Also, the observations that carotid body hypoxia causes cardiac slowing and a reduction of myocardial contractility (4) is not consonant with increased sympathetic discharge to the heart. These data indicate that, although peripheral chemoreceptor stimulation during systemic hypoxia may enhance the activity of the sympathetic vasomotor centers, it is not responsible for an increased sympathetic discharge to the heart. Although other peripheral chemoreceptors may be found which act differ-

cently on the cardiac sympathetic centers than those known at present, it seems most probable that direct stimulation of the central nervous system itself is responsible for increased cardiac sympathetic discharge resulting from systemic hypoxia.

The possibility remains that a circulating humoral factor such as potassium may appear in systemic hypoxia and stimulate the cardiac sympathetic centers directly. However, the very rapid onset of inhibition of discharge when the animal is returned to breathing room air (within 5 sec) diminishes the likelihood of this explanation.

When systemic hypoxia was maintained for several minutes, bradycardia commonly developed in the intact preparations. This was associated with no reduction in cardiac sympathetic discharge. The administration of atropine caused an abrupt increase of heart rate which continued until the hypoxia was relieved. These findings demonstrate that simultaneous activation of cardiac sympathetic and parasympathetic centers occurs during systemic hypoxia. The parasympathetic bradycardia may be largely the result of peripheral chemoreceptor stimulation (2, 5, 6, 15). The increased cardiac sympathetic activity is probably in response to direct stimulation of centers within the central nervous system. Thus, in systemic hypoxia the usual reciprocal nature of the two divisions of the autonomic nervous system is abolished and both increase their activity simultaneously.

Systemic hypercapnia also elicits substantial increases of sympathetic discharge in either the intact or deafferented preparation. This requires the inhalation of 10% CO₂, and is not seen with 5% CO₂. Alexander (9) was unable to elicit this response in his spinal prepara-

tions. It is possible that the relatively depressed condition of the spinal preparations prevented this observation.

From the evidence presented it would seem reasonable to conclude that in systemic hypoxia the peripheral chemoreceptors reflexly stimulate the sympathetic vasomotor centers and the parasympathetic cardiacinhibitory centers but have little reflex effect on the cardiac sympathetic centers. The increased cardiac sympathetic discharge during systemic hypoxia or systemic hypercapnia appears to be the consequence of direct rather than reflex stimulation of centers within the central nervous system.

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REFERENCES