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Research Article

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ABSTRACT The effects of carotid chemoreceptor stimulation with intracarotid injections of either nicotine, 0.2 μg/kg, or cyanide, 2 μg/kg, were compared with the effects of bilateral carotid occlusion on left ventricular (LV) pressure, *dP/dt*, and diameter in conscious dogs instrumented with ultrasonic diameter gauges and miniature pressure gauges. With heart rate maintained constant, carotid chemoreceptor stimulation increased mean arterial pressure by 27±3%, LV end diastolic diameter by 4±0.9% and LV *dP/dt* by 21±2%. With ventilation controlled during succinylcholine infusion, carotid chemoreceptor stimulation increased mean arterial pressure by 43±2% and *dP/dt* by 37±5%, values significantly greater, $P < 0.01$, than were observed in dogs with spontaneous ventilation. Similarly, in dogs with spontaneous ventilation after vagotomy, carotid chemoreceptor stimulation also increased *dP/dt* by a greater amount, i.e., by 48±9%. The increases in LV end diastolic diameter were not affected significantly by either cholinergic blockade with atropine or beta adrenergic blockade with propranolol. Although cholinergic blockade did not affect the inotropic or pressor responses significantly, beta adrenergic blockade attenuated the pressor response and essentially abolished the inotropic response. Bilateral carotid occlusion increased mean arterial pressure and LV end diastolic diameter by similar amounts to those observed with chemoreceptor stimulation, but increased *dP/dt* significantly less, $P < 0.02$, i.e., by 13±2%. As was observed with chemoreceptor stimulation, inotropic responses were not affected significantly by cholinergic blockade, but were essentially abolished by beta adrenergic blockade. Thus, in the conscious dog with heart rate constant, carotid chemoreceptor stimulation induces a clear positive inotropic effect, which is greater in the absence of the attenuating influences of pulmonary inflation reflexes, and for an equal elevation in arterial pressure appears to exert a greater increase in myocardial contractility than does carotid baroreceptor unloading.

INTRODUCTION

Carotid chemoreceptor activation induces intense peripheral vasoconstriction mediated by the sympathetic nervous system and bradycardia, mediated by the parasympathetic nervous system (1–4). Its role in the control of myocardial contractility remains controversial, perhaps in part because of the fact that the reflex activates both arms of the autonomic nervous system, which exert opposing inotropic actions. Several prior studies have indicated that vagal activation plays the dominant role during carotid chemoreceptor activation with concomitant reductions in contractile state (5–7). In direct contrast other studies have indicated a positive inotropic action for the carotid chemoreceptor reflex (8, 9). Finally, Ehrhart et al. (10) found a slight increase in left ventricular (LV)[1] *dP/dt* and slight decrease in LV contractile force, whereas Stern and Rapaport (11) indicated that the aortic chemoreceptor reflex induced positive inotropic effects but the carotid chemoreceptor reflex induced no inotropic effect. It must be pointed out that all of these studies (5–11) have been performed in anesthetized animal preparations, where the unknown mitigating effects of the anesthetic and general surgery play an undetermined role in the interpretation of these data.

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[1] *Abbreviation used in this paper:* LV, left ventricular.

Accordingly, the goal of the present study was to examine the extent to which the carotid chemoreceptor reflex regulates myocardial contractility in conscious dogs, where the effects of anesthesia and recent surgery are absent. This was accomplished by injecting small quantities of nicotine or cyanide into the carotid artery to stimulate the chemoreceptors. It must be kept in mind that in the conscious dog the carotid chemoreceptor reflex elicits an intense increase in respiratory drive, which could modify the effects of the carotid chemoreceptor reflex through stimulation of pulmonary inflation afferents (4, 12, 13). Therefore, a secondary goal was to identify the extent to which the effects on contractility would be modified by the concomitant increase in respiration and stimulation of pulmonary inflation afferents. This was accomplished by examining the effects of carotid chemoreceptor stimulation in the conscious dogs with spontaneous respiration, and then with controlled respiration during succinylcholine infusion. In addition, a series of dogs were studied after bilateral cervical vagotomy, which eliminates the major afferent pathway of the pulmonary inflation reflex (14), while leaving the carotid chemoreceptor reflex intact. An additional goal of this study was to compare the effects of carotid chemoreceptor stimulation on myocardial contractility with carotid baroreceptor unloading, a reflex exerting major positive inotropic effects in the anesthetized dog (15–17) but with only a weak action in the conscious dog (18). Finally, the efferent autonomic arms of these reflexes were examined, by repeating the experiments after cholinergic and beta adrenergic blockades.

METHODS

19 mongrel dogs weighing between 25 and 35 kg were anesthetized with pentobarbital sodium 30 mg/kg. Through a thoracotomy in the fifth left intercostal space, miniature pressure gauges (P22; Konigsberg Instruments, Inc., Pasadena, Calif.) were implanted within the left ventricle through a stab wound in the apex, ultrasonic diameter transducers were sutured to the endocardium of the opposing anterior and posterior walls of the left ventricle and stimulator electrodes were sutured to the right ventricle. Catheters were implanted in the left atrium and aorta. In 13 of the 19 dogs, an additional catheter was implanted in one of the common carotid arteries with the tip just proximal to the carotid sinus insuring that the artery remained patent, while hydraulic cuff occluders were implanted around both carotid arteries in 10 of the 19 dogs. At a subsequent operation using a short acting barbiturate, sodium thiamylal (10 mg/kg, i.v.), the vagi were sectioned bilaterally in five dogs through a cervical incision. In three dogs the carotid sinus nerve on the side of the intracarotid catheter was sectioned, using sodium thiamylal anesthesia and a cervical incision.

Miniature pressure gauges were calibrated *in vitro* and *in vivo* against Statham P23 Db (Statham Instruments, Inc., Oxnard, Calif.) strain gauge manometers connected to the left atrial and aortic catheters. At the time of autopsy, the position of the gauges within the ventricular cavity was confirmed. An improved ultrasonic transit time dimension gauge was used to measure LV diameter (19). The instrument generates a voltage linearly proportional to the transit time of acoustic impulses travelling at the sonic velocity of $\cong 1.5 \times 10^6$ mm/μs between the 3 MHz piezoelectric crystals, thus giving a record of instantaneous internal LV diameter. At a constant room temperature the thermal drift of the instrument is minimal, i.e., <0.01 mm in 6 h. The frequency response is flat to 60 Hz. Any drift in the measurement system, in the instrument electronics, the data tape recorder and the oscillograph that displayed data were eliminated during the experiment by periodic calibrations. This involved substitution of pulses of precisely known duration from a crystal-controlled pulse generator having a basic stability of 0.001%. The position of the ultrasonic transducers was confirmed at the time of autopsy. Respiration was monitored continuously by a pneumograph connected to a Statham P23 Db strain gauge manometer.

The experiments were conducted 3 wk to 2 mo postoperatively, when the dogs had recovered from operation and were again vigorous and healthy. While the dogs were resting quietly, control records of LV pressure and diameter, the time rate of change of pressure, dP/dt, and heart rate were obtained. These variables were recorded continuously during all interventions.

Chemoreceptor stimulation was accomplished by injection of nicotine (0.2 μg/kg) or sodium cyanide (2.0 μg/kg) into the intracarotid catheter. These two agents used for stimulating the carotid chemoreceptor reflex induced similar effects on heart rate, LV and arterial pressures and dP/dt. Baroreceptor unloading was accomplished by inflating the hydraulic occluders implanted on the common carotid arteries. Dogs were also studied in the conscious state after: (*a*) cholinergic blockade with atropine, 0.1 mg/kg; (*b*) beta adrenergic receptor blockade with propranolol, 1.0 mg/kg; and (*c*) combined cholinergic and beta adrenergic blockades. The adequacy of beta receptor blockade was tested with isoproterenol (1 μg/kg, i.v.) and that of cholinergic blockade was tested with acetylcholine (40 μg/kg, i.v.).

To examine the effects of chemoreceptor stimulation and carotid occlusion in the absence of changes in ventilation and secondary pulmonary inflation reflex effects, dogs were also studied with respiration controlled during succinylcholine infusion (2 mg/kg per min). As these dogs were not anesthetized, care was taken so as not to perform any intervention or experiment that was not tolerated by the conscious dogs in the absence of succinylcholine, as done previously in conscious rabbits and conscious dogs (4, 13, 20, 21). The dogs were intubated in the present study after the larynx had been sprayed with a topical anesthetic (Cetacaine, Cetylite Industries, Inc., Long Island City, N. Y.). Ventilation was controlled by a respirator, as routinely done in conscious patients. These interventions were all tolerated well and evoked no evident discomfort in the conscious dogs when their breathing was spontaneous.

During the experiments involving chemoreceptor stimulation, arterial blood sampled from the aortic catheter was collected in a heparinized glass syringe. Arterial blood gases were measured with a Radiometer acid base analyzer (PHM 71 MK2) and blood microsystem (BMS 3 MK2) (Radiometer Co., Copenhagen, Denmark).

The data were recorded on a multichannel tape recorder and played back on a direct writing oscillograph. A cardiotachometer triggered by the pressure pulse provided instantaneous continuous records of heart rate. Continuous records of dP/dt were derived from the LV pressure signal using Philbrick operational amplifiers (Teledyne Philbrick, Dedham, Mass.) connected as a differentiator and having a frequency response of 700 Hz. A triangular wave signal with known slope (rate of change) was substituted for the pressure signal

to calibrate the differentiator directly. Peak responses were compared to control values with the paired t test whereas responses in groups having different numbers were compared with the unpaired t test (22).

RESULTS

When the effects of carotid chemoreceptor stimulation were examined in eight conscious animals with spontaneous rhythm, there was a significant rise in mean arterial pressure of 18±2 mm Hg from 101±4 mm Hg and an early bradycardia, heart rate fell by 18±3 beats/min from 89±3 beats/min whereas LV dP/dt did not change significantly. To avoid the complicating influences of changes in heart rate, only experiments performed with constant heart rate will be discussed.

Effects of carotid chemoreceptor stimulation (Table I)

Spontaneous ventilation (Fig. 1). With heart rate maintained constant at 163±4.2 (SEM) beats/min, chemoreceptor stimulation increased mean arterial pressure by 27.2±2.7 from a control of 102±2.9 mm Hg, LV systolic pressure by 31.9±3.9 from 124±1.3 mm Hg, LV end diastolic diameter by 1.34±0.29 from a control of 31.17±0.75 mm and LV dP/dt by 640±70 mm Hg/s from 2,980±140 mm Hg/s. All these responses were significant, $P < 0.01$. Arterial blood gases did not change significantly from control levels of 85±3 mm Hg for P_{O_2}, 30±1 mm Hg for P_{CO_2} and 7.40±0.02 for pH.

Controlled ventilation (Figs. 1, 2). With heart rate

TABLE I
Effects of Chemoreceptor Stimulation

	Control ±SEM	Peak response ±SEM	Δ Control ±SEM
Mean arterial pressure, *mm Hg*			
Spontaneous ventilation			
No block (n = 13)	102±2.9	129±4.6	27.2±2.7‡
Cholinergic block (n = 10)	106±3.8	135±4.9	28.6±2.3‡
Beta and cholinergic block (n = 7)	105±5.5	128±4.9	22.9±3.3‡
Vagotomy (n = 5)	124±6.8	165±7.6	40.6±8.9*‖
Controlled ventilation			
No block (n = 10)	121±6.7	172±9.3	51.0±3.3‡‖
LV systolic pressure, *mm Hg*			
Spontaneous ventilation			
No block (n = 13)	124±1.3	156±4.5	31.9±3.9‡
Cholinergic block (n = 11)	129±4.3	158±4.2	29.4±2.4‡
Beta and cholinergic block (n = 7)	125±5.7	153±11	28.0±5.9‡
Vagotomy (n = 5)	144±7.6	193±4.4	49.0±8.2‡§
Controlled ventilation			
No block (n = 10)	140±6.0	202±10	61.8±4.7‡‖
LV dP/dt, *mm Hg/s*			
Spontaneous ventilation			
No block (n = 13)	2,980±140	3,620±180	640±70‡
Cholinergic block (n = 11)	3,490±200	4,120±240	630±80‡
Beta and cholinergic block (n = 7)	2,500±220	2,570±230	70±50‖
Vagotomy (n = 5)	3,650±300	5,450±630	1,800±410‡‖
Controlled ventilation			
No block (n = 10)	3,000±230	4,040±260	1,040±120‡‖
LV end diastolic diameter, *mm*			
Spontaneous ventilation			
No block (n = 9)	31.17±0.75	32.51±0.89	1.34±0.29‡
Cholinergic block (n = 8)	29.64±0.72	31.16±0.75	1.52±0.27‡
Beta and cholinergic block (n = 7)	33.14±1.11	34.82±0.98	1.68±0.42‡
Vagotomy (n = 5)	29.57±0.99	31.77±0.97	2.20±0.63*
Controlled ventilation			
No block (n = 7)	30.73±1.25	32.77±1.37	2.04±0.44‡

* Significant change from control, $P < 0.05$.
‡ Significant change from control, $P < 0.01$.
§ Change significantly different from unblocked state with spontaneous ventilation, $P < 0.05$.
‖ Change significantly different from unblocked state with spontaneous ventilation, $P < 0.01$.

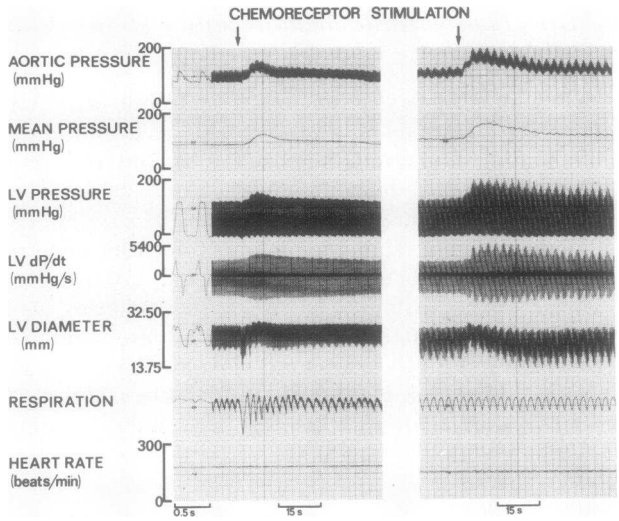

FIGURE 1 The effects of carotid chemoreceptor stimulation are compared in the same dog on phasic and mean arterial pressure, LV pressure, dP/dt, LV diameter, respiration monitored by a pneumograph, and heart rate, with spontaneous respiration (left panel), and with respiration controlled (right panel). Heart rate was held constant. Carotid chemoreceptor stimulation increased respiration markedly with an increase in aortic and LV pressures and dP/dt. In the right hand panel, with ventilation controlled, the same carotid chemoreceptor stimulus induced larger increases in pressures and dP/dt.

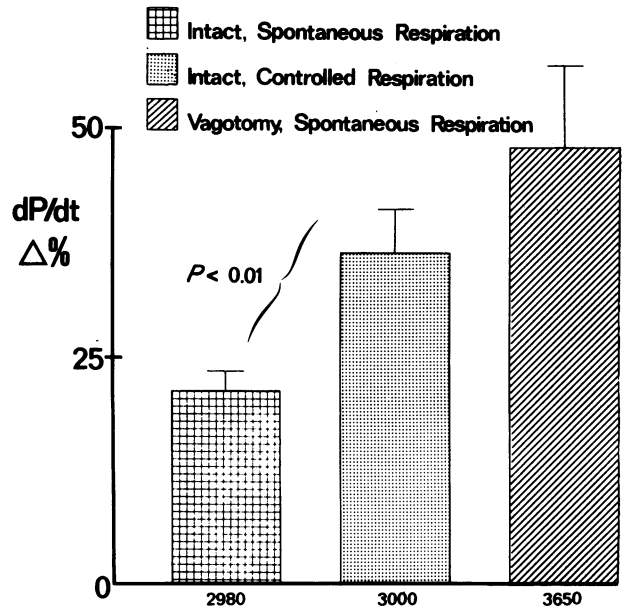

FIGURE 2 The effects of carotid chemoreceptor stimulation on dP/dt are compared in intact dogs with spontaneous respiration (checked bars), intact dogs with controlled respiration (dotted bars) and after bilateral vagotomy with spontaneous respiration (lined bars). Control values are noted as the base of the bars. Carotid chemoreceptor stimulation induced a greater increase in dP/dt when either respiration was controlled in intact dogs or after vagotomy with spontaneous respiration.

maintained constant at 162±4.9 beats/min, chemoreceptor stimulation increased mean arterial pressure by 51±3.3 from a control of 121±6.7 mm Hg, LV systolic pressure by 61.8±4.7 from 140±6.0 mm Hg, LV end diastolic diameter by 2.04±0.44 from 30.73±1.25 mm and dP/dt by 1,040±120 mm Hg/s from 3,000±230 mm Hg/s. All of these responses were significant, $P < 0.01$, and, with the exception of end diastolic diameter, were significantly greater, $P < 0.01$, than those observed with spontaneous ventilation.

Spontaneous ventilation–cholinergic block. Atropine increased heart rate by 92±14 from 79±5.0 beats/min, mean arterial pressure by 7.0±1.4 from 96±4.4 mm Hg, LV systolic pressure by 7.3±1.7 from 115±3.0 mm Hg and reduced LV end diastolic diameter by 5.10 ±0.76 from 32.00±1.46 mm. These changes were significant, $P < 0.01$. However, LV dP/dt did not change significantly from 3,450±80 mm Hg/s. In animals paced before and after atropine, LV dP/dt still did not change significantly with the drug, while LV end diastolic diameter, mean arterial pressure, and LV systolic pressure did not change significantly.

With heart rate maintained constant at 200±6.8 beats/min, chemoreceptor stimulation increased mean arterial pressure by 28.6±2.3 from 106±3.8 mm Hg, LV systolic pressure by 29.4±2.4 from 129±4.3 mm Hg, LV end diastolic diameter by 1.52±0.27 from 29.64 ±0.72 mm and dP/dt by 630±80 from 3,490±200 mm Hg/s. All of these changes were significant, $P < 0.01$, but none were significantly different from those observed in animals before cholinergic blockade.

Spontaneous ventilation–beta adrenergic block and cholinergic block. With heart rate maintained constant at 146±5.2 beats/min, carotid chemoreceptor stimulation increased mean arterial pressure by 22.9 ±3.3 from a control of 105±5.5 mm Hg, LV systolic pressure by 28.0±5.9 from 125±5.7 mm Hg, LV end diastolic diameter by 1.68±0.42 from 33.14±1.11 mm, while LV dP/dt did not change significantly from a control level of 2,500±220 mm Hg/s. When the results from this group of animals ($n = 7$) were compared with those from the cholinergic blockade group ($n = 11$), the response of dP/dt to chemoreceptor stimulation was significantly different, $P < 0.01$, the response of mean arterial pressure was less, but not statistically significant, and the response of LV end diastolic diameter was similar. However, in the same six animals specifically studied, both before and after beta adrenergic blockade in the presence of cholinergic blockade, the response of mean arterial pressure was significantly reduced, $P < 0.05$, by beta adrenergic blockade; chemoreceptor stimulation increased mean arterial

pressure by 31±2% before beta blockade, and by 2±3% after beta blockade. In three animals, beta adrenergic blockade was administered in the absence of cholinergic blockade and similar results were observed, i.e., the increases in dP/dt were abolished.

Spontaneous ventilation–vagotomy (Fig. 2). With heart rate constant at 157±11 beats/min, chemoreceptor stimulation increased mean arterial pressure by 40.6 ±8.9 from a control of 124±6.8 mm Hg, LV systolic pressure by 49.0±8.2 from 144±7.6 mm Hg, LV end diastolic diameter by 2.20±0.63 from 29.57±0.99 mm and LV dP/dt by 1,800±410 from 3,650±300 mm Hg/s. While all the above changes were significant, the increases in dP/dt and mean arterial pressure were significantly greater, $P < 0.01$, than observed in the animals before vagotomy, as was the increase in LV systolic pressure, $P < 0.05$.

Spontaneous ventilation–carotid sinus nerve section. After ipsilateral carotid sinus nerve section intracarotid nicotine or cyanide failed to alter either respiration or any circulatory parameters.

Effects of bilateral carotid occlusion (Table II)

Spontaneous ventilation (Fig. 3). With heart rate maintained constant at 156±8.0 beats/min, carotid occlusion increased mean arterial pressure by 27.6±2.4 from a control of 102±3.5 mm Hg, LV systolic pressure by 24.8±3.0 from 117±3.6 mm Hg, LV end diastolic diameter by 1.05±0.18 from 33.00±0.98 mm, LV dP/dt by 350±50 from 2,820±150 mm Hg/s. All these changes were significant, $P < 0.01$.

Controlled ventilation. With heart rate maintained constant at 160±5.7 beats/min, carotid occlusion increased mean arterial pressure by 27.1±3.7 from a control of 102±5.4 mm Hg, LV systolic pressure by 28.0 ±2.7 from 121±5.2 mm Hg, LV end diastolic diameter by 1.11±0.23 from 32.24±1.59 mm and LV dP/dt by

TABLE II
Effects of Carotid Occlusion

	Control ±SEM	Peak response ±SEM	Δ Control ±SEM
Mean arterial pressure, *mm Hg*			
Spontaneous ventilation			
No block (n = 10)	102±3.5	130±4.9	27.6±2.4‡
Cholinergic block (n = 7)	109±5.0	137±7.0	28.4±3.1‡
Beta and cholinergic block (n = 6)	95±4.8	115±5.6	19.7±2.8‡
Controlled ventilation			
No block (n = 10)	102±5.4	129±7.5	27.1±3.7‡
LV systolic pressure, *mm Hg*			
Spontaneous ventilation			
No block (n = 10)	117±3.6	142±5.4	24.8±3.0‡
Cholinergic block (n = 7)	128±4.0	156±6.7	28.3±3.6‡
Beta and cholinergic block (n = 6)	107±4.0	133±9.7	25.6±7.0*
Controlled ventilation			
No block (n = 10)	121±5.2	149±7.0	28.0±2.7‡
LV dP/dt, *mm Hg/s*			
Spontaneous ventilation			
No block (n = 10)	2,820±150	3,170±140	350±50‡
Cholinergic block (n = 7)	3,400±230	3,820±300	420±80‡
Beta and cholinergic block (n = 6)	2,220±200	2,240±198	20±20§
Controlled ventilation			
No block (n = 10)	2,690±130	3,110±130	420±50‡
LV end diastolic diameter, *mm*			
Spontaneous ventilation			
No block (n = 8)	33.00±0.98	34.05±1.02	1.05±0.18‡
Cholinergic block (n = 7)	30.43±1.22	31.56±1.25	1.13±0.20‡
Beta and cholinergic block (n = 6)	32.64±0.86	33.75±0.87	1.11±0.36*
Controlled ventilation			
No block (n = 7)	32.24±1.59	33.35±1.71	1.11±0.23‡

* Significant change from control, $P < 0.05$.
‡ Significant change from control, $P < 0.01$.
§ Change significantly different from unblocked state with spontaneous ventilation, $P < 0.01$.

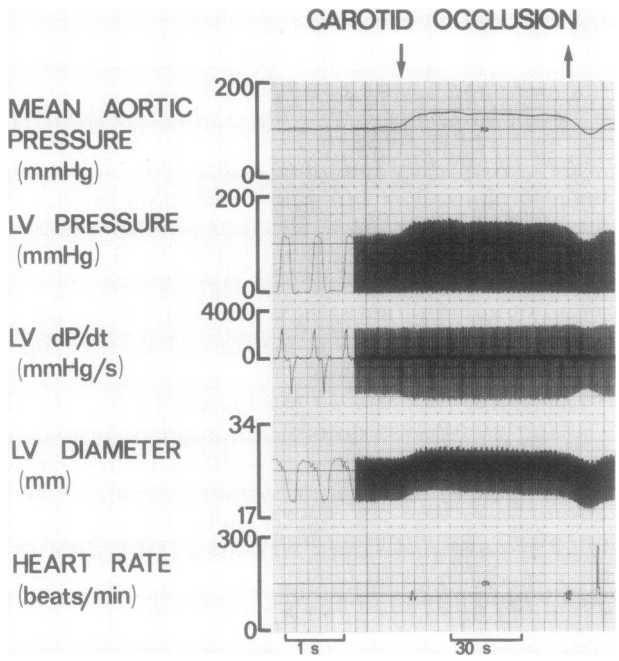

FIGURE 3 The effects of bilateral carotid occlusion are shown on mean arterial pressure, LV pressure, dP/dt and diameter in a conscious dog with heart rate held constant by pacing. Carotid occlusion increased pressure, but increased dP/dt only slightly.

420±50 from 2,690±130 mm Hg/s. All of these changes were significant, $P < 0.01$, but were not significantly different from those observed in the animals with spontaneous respiration.

Cholinergic blockade–spontaneous ventilation. With heart rate maintained constant at 198±11 beats/min, carotid occlusion increased mean arterial pressure by 28.4±3.1 from 109±5.0 mm Hg, LV systolic pressure by 28.3±3.6 from 128±4.0 mm Hg, LV end diastolic diameter by 1.13±0.20 from 30.43±1.22 mm and LV dP/dt by 420±80 from 3,400±230 mm Hg/s. All of these changes were significant, $P < 0.01$, but were not significantly different from those observed in the absence of cholinergic blockade.

Beta adrenergic blockade and cholinergic blockades–spontaneous ventilation. With heart rate maintained constant at 136±26 beats/min, carotid occlusion increased mean arterial pressure by 19.7±2.8 from a control of 95±4.8 mm Hg, LV systolic pressure by 25.6 ±7.0 from 107±4.0 mm Hg, LV end diastolic diameter by 1.11±0.36 from 32.64±0.86 mm, while LV dP/dt did not change significantly from a control of 2,220 ±200 mm Hg/s. The only significant difference, $P < 0.01$, between these responses and those without blockade was that for LV dP/dt, which failed to rise significantly.

Comparison of chemoreceptor stimulation and carotid occlusion–spontaneous ventilation (Fig. 4)

Both interventions increased mean arterial pressure, LV systolic pressure, and end diastolic diameter by equivalent amounts. However, carotid chemoreceptor stimulation increased dP/dt by 21±2%, a significantly greater amount, $P < 0.02$, than was observed with carotid occlusion, 13±2%. After cholinergic blockade carotid chemoreceptor stimulation increased dP/dt by 18±2%, significantly more, $P < 0.05$, than with carotid occlusion (12±1%). After cholinergic and beta adrenergic blockades neither intervention increased dP/dt significantly.

DISCUSSION

Baroreceptor unloading increases sympathetic tone to peripheral vessels and the heart while reducing vagal tone (15, 17, 18). In contrast, although carotid chemoreceptor stimulation increases sympathetic tone to the peripheral vasculature (1, 2, 4), vagal tone to the heart increases, causing a decrease in heart rate (1–4). With this in mind, it is conceivable that stimulation of the carotid chemoreceptors could either decrease myocardial contractility as a result of vagal activation or increase contractility as a result of adrenergic activation. Both an increase in contractility (8, 9) and a decrease in contractility (5–7) as well as no effect (11) have been observed in prior studies examining the effects of carotid chemoreceptor stimulation on myocardial contractility.

In the present investigation a clear increase in LV

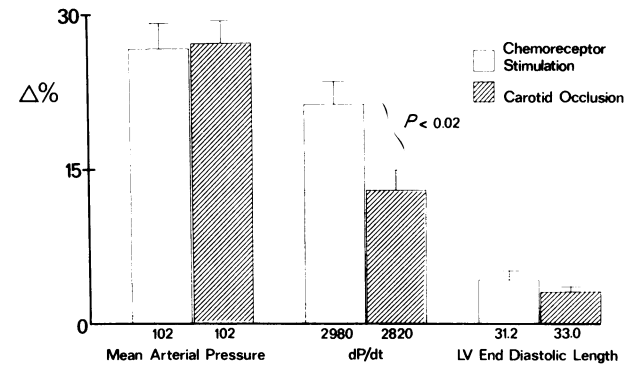

FIGURE 4 The average ±SEM changes for mean arterial pressure, dP/dt and LV end diastolic length are compared for carotid chemoreceptor stimulation (open bars) and carotid occlusion (shaded bars). Control values are noted at the base of the bars. Both of these interventions increased mean arterial pressure and end diastolic length by similar amounts. However, chemoreceptor stimulation induced a significantly greater increase in dP/dt.

dP/dt was observed when the carotid chemoreceptor reflex was stimulated in conscious dogs with intracarotid injections of either nicotine or cyanide (Fig. 1). The increase in dP/dt could not have been attributed to a change in heart rate, afterload, or preload because heart rate was held constant and afterload and preload rose both in the presence and absence of beta adrenergic blockade. In the latter situation, dP/dt did not rise. Thus, the rise in dP/dt was most likely a result of a positive inotropic effect mediated by beta adrenergic receptors.

There are several important differences to point out between this investigation in conscious animals and prior studies conducted in anesthetized preparations. First of all, in the present investigation the cerebral circulation was left intact and the carotid chemoreceptor reflex was stimulated without inducing cerebral hypoxia. It has been shown by Jacobs et al. (3) and Hackett et al. (23), that intracarotid nicotine or cyanide stimulates primarily the carotid chemoreceptor reflex. It is also felt that central nervous system stimulation did not occur, because after ipsilateral carotid sinus nerve section, no change in systemic or LV function was observed with intracarotid nicotine or cyanide. Although Stern and Rapaport (11) used a similar stimulus in anesthetized preparations, and found no effect of carotid chemoreceptor stimulation on LV contractility, in that study, heart rate was not controlled. We also observed insignificant alterations in myocardial contractility with carotid chemoreceptor stimulation when heart rate was not controlled. However, significant increases in the inotropic state were observed in the present study when heart rate was maintained constant by electrical pacing. This finding, i.e. a positive inotropic effect induced by carotid chemoreceptor stimulation with nicotine or cyanide, is consistent with the study of Kahler et al. (8), where the entire carotid circuit was perfused with hypoxic blood.

It is known that stimulation of the carotid chemoreceptor reflex elicits reflex coronary vasodilatation (13). It has also been reported that an increase in coronary flow, per se, may increase myocardial contractility (24). Thus, it is possible that the increase in coronary flow could have been responsible for the increase in contractility. However, this mechanism seems unlikely in view of the experiments after beta adrenergic blockade where the reflex coronary vasodilatation still occurs (13), but the inotropic response was abolished. If the increase in flow produced the inotropic response, then the response should not have been abolished by beta blockade.

It appears that pulmonary inflation reflexes, which are invoked secondarily, when the carotid chemoreceptor reflex is stimulated, act to restrain the increases in pressure and contractility that occur with carotid chemoreceptor stimulation. After carotid chemoreceptor stimulation in this investigation it was observed that both the pressor and inotropic effects were significantly greater when the effects of the pulmonary inflation reflexes were eliminated (Fig. 1), i.e. when ventilation was controlled under succinylcholine or when the primary afferent pathway of the pulmonary inflation reflex was interrupted by bilateral vagotomy (14) (Fig. 2). The augmented inotropic effect under both of these conditions supports the hypothesis that pulmonary inflation afferents were acting to attenuate positive inotropic effects of carotid chemoreceptor stimulation. This concept is consistent with studies conducted on the peripheral circulations, demonstrating attenuation and even reversal of chemoreceptor-induced sympathetic vasoconstriction through secondary stimulation of pulmonary inflation afferents (4) as well as a study by Glick et al. (25), indicating reflex inotropic depression by stimulation of pulmonary stretch receptors.

To rule out the possibility that succinylcholine infusion, per se, might augment reflex adrenergic drive, responses to bilateral carotid occlusion were examined in the presence and absence of succinylcholine. With bilateral carotid occlusion, there were no significant differences in either the pressor or inotropic responses during succinylcholine infusion, indicating that the drug, per se, was not increasing either adrenergic tone or reflex adrenergic drive. Rather, it was more likely that with ventilation constant during succinylcholine infusion, the increase in respiration was prevented and the inotropic response to chemoreceptor stimulation was not attenuated by pulmonary inflation reflexes.

This magnitude of the inotropic response to chemoreceptor stimulation is modest in comparison with that induced by either exercise (26) or norepinephrine (27). However, it is interesting to note that the inotropic response to chemoreceptor stimulation was greater than that observed with carotid occlusion. Bilateral carotid occlusion elicited only a small inotropic effect in these conscious dogs, as has been observed in our laboratory (18). In this investigation the inotropic responses to carotid occlusion and carotid chemoreceptor stimulation were compared for equipressor stimuli. Keeping in mind the reservation that this represents an oversimplified method for comparing these two reflexes, i.e. a full stimulus-response curve would ideally be studied; it is of interest to note that the chemoreceptor reflex caused a significantly greater inotropic response for an equal elevation in arterial pressure (Fig. 4).

The efferent mechanisms of the inotropic responses to both chemo- and baroreceptor stimulation were also examined. Vagal control of contractility has been shown to play an important role in the response to

carotid chemoreceptor reflex stimulation in anesthetized animal preparations (5, 6). However, if cholinergic control had been important, then after atropine we would have expected to observe an even greater inotropic response to chemoreceptor stimulation. However, this was not observed. Moreover, had cholinergic control been important in the baroreceptor response, a smaller increase in dP/dt would have been observed after atropine, but this was not observed either. Therefore, in these experiments cholinergic control was not an important component of either carotid chemoreceptor stimulation or baroreceptor unloading. However, both responses were essentially abolished by beta adrenergic blockade, indicating they were a result of beta adrenergic stimulation.

Finally, it was important to rule out the possibility that the base-line inotropic state was altered substantially by the administration of atropine. The present studies demonstrated that cholinergic control exerts an important effect on base-line cardiac rate but does not exert an important effect on base-line myocardial contractility. The latter held true even when the opposing influences of the tachycardia and decreases in preload, that were caused by the increase in heart rate, were minimized by pacing the animals at a rapid rate before and after atropine.

In summary, the carotid chemoreceptor reflex in conscious dogs, when stimulated, elicits a significant increase in myocardial contractility mediated through beta adrenergic mechanisms. This increase in contractility is attenuated by secondary stimulation of pulmonary inflation reflexes. Accordingly, when the hyperventilation that occurs with carotid chemoreceptor stimulation is prevented, the inotropic response is significantly greater. Finally, for an equipressor response, the carotid chemoreceptor reflex elicited a greater increase in contractility than did the carotid baroreceptor reflex.

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