Importance of the Carotid Sinus Baroreceptors in the Regulation of Myocardial Performance

GERALD GLICK with the technical assistance of ROBERT M. LEWIS and MARIAN G. SEGAL

From the Departments of Pharmacology and Medicine, Baylor College of Medicine, Houston, Texas 77025

ABSTRACT The question of whether the carotid sinus baroreceptors modulate myocardial performance remains controversial. Several studies that have stressed their importance have been criticized because the possible role of cerebral ischemia and of other important variables was not eliminated. To reinvestigate this problem, we studied 21 dogs placed on total cardiopulmonary bypass. In each of these animals the carotid sinus regions were isolated and perfused with fully oxygenated blood at a constant flow rate; perfusion pressure was changed by varying the resistance to outflow from the isolated segments. Several indices of myocardial performance were assessed: right and left ventricular contractile force with Walton-Brodie strain gauge arches; the maximal rate of change in contractile force, dF/dt; the pressure developed within an isovolumic balloon inserted into the left ventricle; and the maximal rate of change of this pressure, dP/dt. When the pressure distending the carotid sinuses was raised from an average value of 34.1 ±2.8 (SEM) mm Hg to 190.1 ±4.7 mm Hg, right ventricular contractile force fell 14.9 ±2.3% ($P < 0.001$); right ventricular dF/dt decreased 16.7 ±3.0% ($P < 0.01$); left ventricular contractile force declined 14.9 ±3.3% ($P < 0.01$); left ventricular dF/dt fell 19.3 ±4.0% ($P < 0.01$); peak systolic pressure in the isovolumic balloon declined 18.2 ±3.7% ($P < 0.001$); and dP/dt decreased 34.1 ±4.0% ($P < 0.01$). Prior adrenalectomy and vagotomy and maintenance of heart rate at a constant level did not influence these results. The inverse relation between carotid sinus perfusion pressure and the indices of contractility that was observed in this investigation strongly suggests that the carotid sinus baroreceptors are an important regulatory mechanism in the control of myocardial performance.

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INTRODUCTION

Although it is universally accepted that reflexes initiated within the carotid sinus exert considerable control over heart rate and systemic vascular resistance, the role played by these baroreceptor reflexes in the regulation of the contractile state of the heart remains controversial. This controversy has arisen because studies that purport to show the importance of the baroreceptors in the regulation of myocardial performance (1–3) have been criticized by other investigators who claim that variables that might have influenced the results were not adequately controlled (4–6). Among these variables were the extent of cerebral ischemia produced by the experimental intervention, concurrent alterations in carotid body chemoreceptor stimulation and changes in venous return, heart rate, outflow impedance, circulating catecholamines, coronary blood flow, and coronary perfusion pressure. To try to clarify the possible role of the carotid sinus baroreceptors in the reflex regulation of cardiac performance, we undertook a series of experiments in dogs in which the carotid sinus regions were isolated and separately perfused with oxygenated blood, and the variables mentioned above were either eliminated or held constant. Our results strongly support the contention that the carotid sinus baroreceptors do, indeed, modulate myocardial performance.

METHODS

To investigate the effects of varying the level of carotid sinus pressure on cardiac performance, we carried out experiments on 21 dogs that had been placed on total cardiopulmonary bypass, as illustrated in Fig. 1. These animals, weighing between 17.5 and 30.0 kg, were anesthetized with a combination of morphine sulfate (3 mg/kg subcutaneously), urethane (480–960 mg/kg intravenously), and alpha chloralose (48–96 mg/kg intravenously). In group I, consisting of 18 dogs, the systemic venous return was drained by three large bore catheters; one catheter was placed in the superior vena cava via the azygos vein; the second was inserted through the tip of the right atrial appendage into

the inferior vena cava; and the third, which had multiple side holes, was inserted through the right atrial appendage and lay in the right atrium and right ventricle to collect the coronary sinus drainage. No ties were placed around the vena cavae and no dissection was performed near them nor near the ascending aorta or pulmonary artery. These precautions were taken to insure that nerves destined for the heart were not inadvertently injured (7). The venous return was drained by gravity into a rotating disc oxygenator that was primed with blood from donor dogs and was aerated with a gas mixture of 97% oxygen and 3% carbon dioxide. This mixture, in the oxygenator employed, produced a P_{CO_2} in the physiologic range and a P_{O_2} of approximately 150 mm Hg. The oxygenated blood then passed through a heat exchanger that maintained the temperature of the blood at 37°C. At this point the stream of blood was divided into two parts. The larger portion was pumped by a roller pump (American Optical Corp., Bedford, Mass.) into the femoral artery and provided the systemic perfusion pressure. By changing the speed of this pump, we could change systemic pressure at will, and could, thereby, prevent the changes in arterial pressure that ordinarily resulted from changes in baroreceptor stimulation. The smaller portion of fully oxygenated blood, which averaged 96 ml/min, passed through a peristaltic pump (Harvard Apparatus, Inc., Millis, Mass., Model 500-1200) and into the common carotid arteries, which were ligated low in the neck. The internal carotid arteries beyond the carotid sinus and all the small arterial branches in this region were tied off. Thus, blood could exit only through the cannulas that were placed distally in the external carotid arteries and thence into the external jugular vein. Flow was kept constant throughout each experiment; pressure within the isolated segments of carotid artery was regulated by changing the resistance to outflow by means of a screw clamp. Perfusion pressure within the segment was measured through a catheter inserted into the cranial thyroid artery; systemic arterial pressure was measured through a catheter in the brachial artery. The animal's temperature was constantly monitored by means of a thermistor probe placed in the femoral vein (Tele-Thermometer, Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio).

To assess changes in the contractile state of the heart several indices of myocardial contractility were used as previously described in detail (8). First, changes in isometric contractile force were measured by means of Walton-Brodie strain gauge arches sutured to the right ventricle in all 18 studies and also to the left ventricle in 12 of the studies. Second, since changes in the velocity of contraction from any given fiber length are characteristic of alterations in myocardial contractility (9), the maximal rate of change in contractile force, dF/dt, was determined continuously by electronic differentiation (Biotronex Laboratory, Inc., Silver Spring, Md., model BL-620). Third, in 11 of these animals a small balloon containing 4–5 ml of saline was attached to a wide bore metal cannula and was placed via the left atrial appendage through the mitral valve into the left ventricle. A vent was also inserted through the appendage to drain any thebesian or bronchial arterial drainage and to indicate whether aortic regurgitation occurred. Changes in the absolute pressure developed within the balloon and in the maximal rate of pressure rise, dP/dt, were taken as additional indices of changes in myocardial contractile state.

Heart rate was held constant in 11 experiments by electrical pacing of the right ventricle with a constant current stimulator (Nuclear-Chicago Corp., Des Plaines, Ill.). Bilateral cervical vagotomy was performed in nine dogs. Bilateral adrenalectomy was carried out in five studies 2 days before placing the animals on total cardiopulmonary bypass; these dogs were maintained on cortisone. The effects of changing pressure in the carotid sinus regions were examined before and after infusion of trimethaphan (Arfonad) in two experiments, and before and after denervation of the carotid sinuses in another two experiments. All four of these dogs displayed prominent reflexes immediately before these maneuvers were carried out.

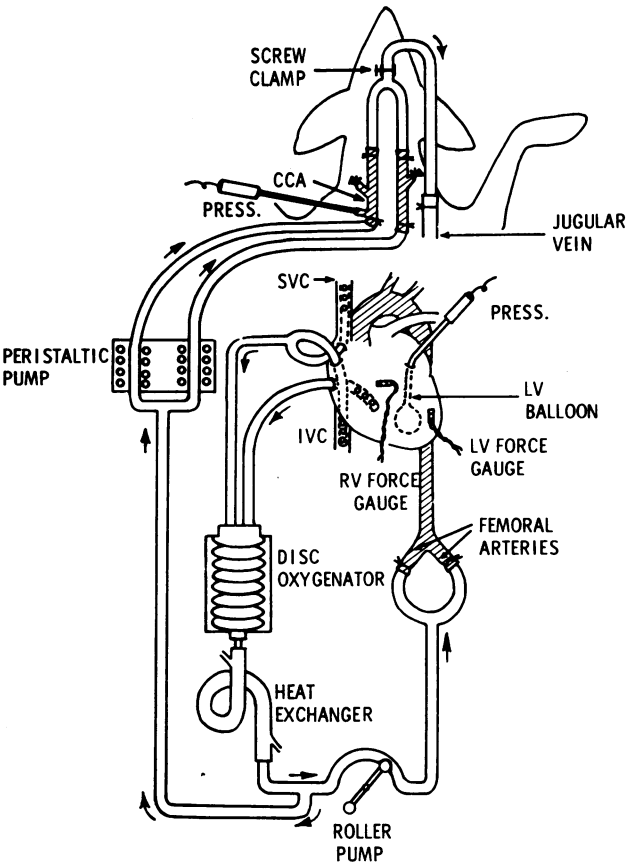

FIGURE 1 Diagrammatic representation of the experimental model used. SVC, superior vena cava; IVC, inferior vena cava; CCA, common carotid artery; PRESS, pressure. Arrows indicate the direction of blood flow. See text for details.

In group II, consisting of the remaining three animals, the experimental preparation was modified slightly to allow measurement of total coronary flow. In these experiments, the adventitia was carefully dissected from the superior and inferior vena cavae in a manner designed to minimize damage to nerve fibers, and the cannulas lying within these vessels were securely tied in place. The flow from the cannula within the right heart was then drained into a separate graduated cylinder and represented the total coronary flow. This flow was determined gravimetrically with a Statham P23Db strain gauge which measured the pressure at the bottom of the cylinder through a sidearm. This system was calibrated by adding known amounts of the dog's own blood to the cylinder at the end of the experiment.

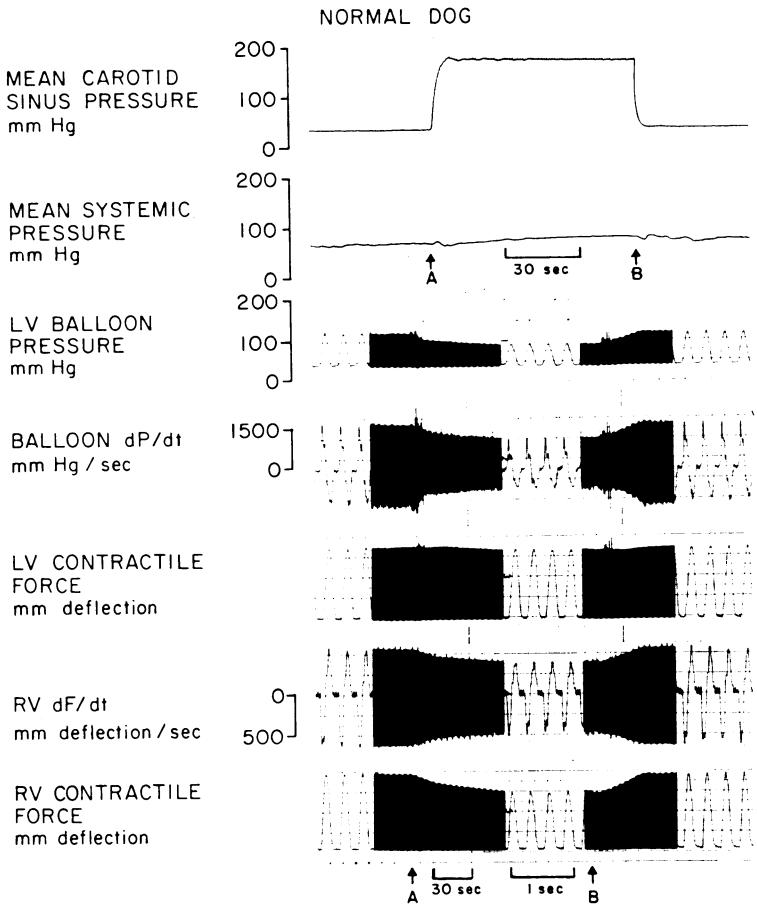

FIGURE 2 Original tracings from an experiment in which the perfusion pressure within the carotid sinuses was suddenly raised at point *A* and was then suddenly lowered at point *B*. The two top channels were recorded on a Grass machine and the lower channels were recorded on a Brush machine, which accounts for the fact that the two sets of arrows are not aligned. The reflex changes produced in myocardial performance continued for as long as the carotid sinus pressure was elevated, and then returned promptly to control levels when the pressure was reduced.

After these animals' reflexes had been tested, propranolol 1 mg/kg intravenously was given acutely to one of these dogs and practolol 1 mg/kg was given to the other two. Propranolol blocks both the myocardial beta receptors and also the beta receptors within the coronary circulation. Practolol, on the other hand, specifically blocks the myocardial beta receptors (10, 11). Myocardial performance in these dogs was assessed by means of Walton-Brodie strain gauge arches sutured to the right ventricle in all three studies and to the left ventricle in two studies.

Student's *t* test for paired data was used to test the significance of differences between means.

RESULTS

The typical effects on cardiac performance produced by changing the distending pressure within the perfused carotid segments are shown in Fig. 2, and the data obtained from all the experiments in group I are plotted graphically in Figs. 3 and 4. Because, as shown in Fig. 5, adrenalectomy and vagotomy did not significantly affect the results obtained, the data from all the animals were grouped together for purposes of illustration and statistical analysis. When the perfusion pressure within the carotid sinus was suddenly increased from an average value of 34.1 ±2.8 mm Hg to 190.1 ±4.7 mm Hg, the various indices of myocardial performance displayed reciprocal descreases. Thus, right ventricular contractile force fell an average of 14.9 ±2.3% (SEM) ($P < 0.001$) and the maximal rate of development of contractile force, dF/dt, fell an average of 16.7 ±3.0% ($P < 0.01$) (Fig. 3).

The indices of left ventricular performance displayed similar directional changes. Left ventricular contractile force declined an average of 14.9 ±3.3% ($P < 0.01$) and left ventricular dF/dt decreased an average of 19.3 ± 4.0% ($P < 0.01$) (Fig. 4). The peak systolic pressure developed within the isovolumic balloon fell an average of 18.2 ±3.7% ($P < 0.001$) (not plotted) and the maximal rate of rise of pressure within the balloon decreased an average of 34.1 ±4.0% ($P < 0.01$) (Fig. 4). By changing the speed of the roller pump appropriately, we could maintain aortic mean pressure at a relatively constant level despite changes in baroreceptor stimulation (Figs. 2 and 5). Mean pressure in the aorta when carotid sinus pressure was low averaged 72.9 ±3.6 mm Hg and when carotid sinus pressure was high it averaged 74.8 ±4.3 mm Hg.

When the baroreceptor reflex was interrupted either by disrupting the afferent arm by ligation of the carotid sinus nerve or by blocking the efferent arm with a ganglionic blocking agent, changes in carotid sinus perfusion pressure no longer altered myocardial performance.

The results from the experiments performed on the three dogs of group II, in which coronary flow was measured, are listed in Table I, and a representative tracing is shown in Fig. 6. A total of 20 runs were performed, wherein the perfusion pressure in the carotid sinus was suddenly elevated by increasing the resistance to outflow, and in each instance coronary flow either remained the same or increased slightly, since the aortic pressure was maintained at control levels or slightly higher by means of the roller pump (Table I). In every run, despite either no change or an increase in coronary flow and pressure, an increase in perfusion pressure within the baroreceptor region produced a decrease in all the indices of ventricular performance (Table I, Fig. 6). Treatment with either practolol or propranolol abolished the reflex de-

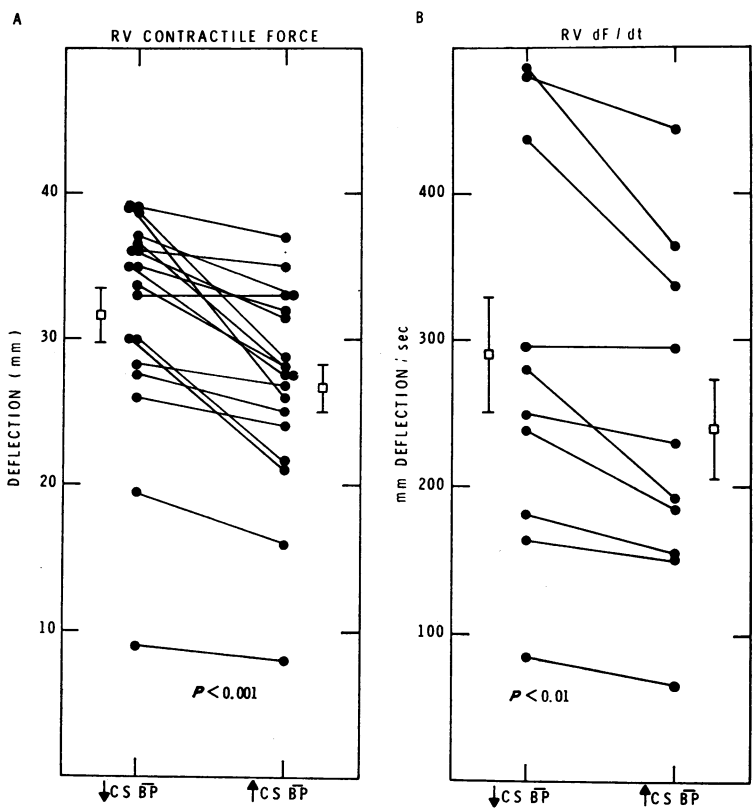

FIGURE 3 Effects of changes in carotid sinus perfusion pressure on right ventricular contractile force (left) and on the maximal rate of change in contractile force (right). The left column of symbols in each panel depicts the values for each of these variables when the distending pressure within the carotid sinuses was low, and the right column of symbols illustrates these values when it was high. The open square and vertical bar at the sides of each panel show the mean and standard error of the mean for each group of data. P values are shown at the bottom of each panel.

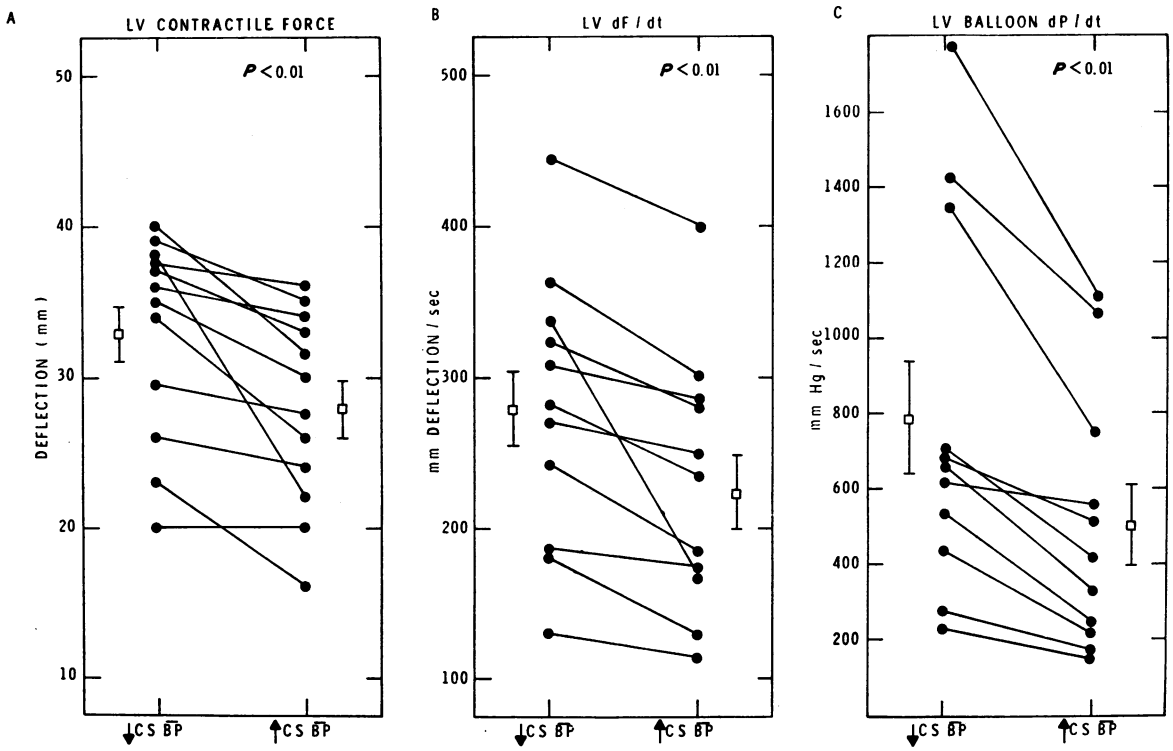

FIGURE 4 Effects of changes in carotid sinus perfusion pressure on left ventricular contractile force (left), maximal rate of change in contractile force (middle), and maximal rate of change in development of pressure in the isovolumic balloon (right). *P* values at the top of each panel. Explanation as in Fig. 3.

crease in myocardial performance that had previously been produced by raising carotid sinus pressure.

DISCUSSION

In their studies of the reflex control of cardiac performance, Salisbury, Cross, and Rieben (4) and, more recently, Downing and Gardner (5, 6) came to the conclusion that reflexes mediated by the carotid sinus baroreceptors did not influence myocardial contractility. Furthermore, they attributed the inotropic effects reported by Sarnoff, Gilmore, Brockman, Mitchell, and Linden (1) primarily to the consequences of varying levels of cerebral ischemia produced by occlusion of the carotid artery, rather than to reflexes. Downing and Gardner (6) also pointed out that both in the study of Sarnoff et al. (1) and in the study of De Geest, Levy, and Zieske (2) the relationship between stroke work or stroke power, on the one hand, and atrial or ventricular diastolic pressure, on the other hand, might not have been valid as an index of myocardial performance, since changes in resistance to ventricular ejection were allowed to occur (12). In the study reported by Manning and Lindgren (3), which also indicated that the baroreceptors did regulate cardiac function, either changes in aortic pressure, and therefore, in coronary perfusion pressure, or changes in aortic impedance and venous return occurred that might have compromised the validity of their data. Finally, these three studies used electrical stimulation of the carotid sinus nerve as one means of evoking reflex alterations (1–3). Such stimulation adds another variable since not only baroreceptor fibers, but also chemoreceptor fibers from the carotid body are activated. Chemoreceptor stimulation appears to exert either a negative inotropic effect (13) or to have no significant effect on myocardial contractility (14).

It is against this background that the validity of the methodology reported here must be judged. With the experimental model used in this study we could increase or decrease baroreceptor stimulation at will merely by changing the resistance to outflow from the isolated carotid segments. Since flow through the segment was kept constant throughout each experiment and since the blood used was fully oxygenated and at physiologic temperatures, it is unlikely that changing levels of chemoreceptor stimulation were produced. When vasomotor reflexes were induced as a result of increasing or decreasing the perfusion pressure in the carotid sinus, the consequent changes in arterial pressure could be compensated for by altering the amount of blood discharged by the roller pump. Thus, changes in the contractile state of the heart produced by homeometric

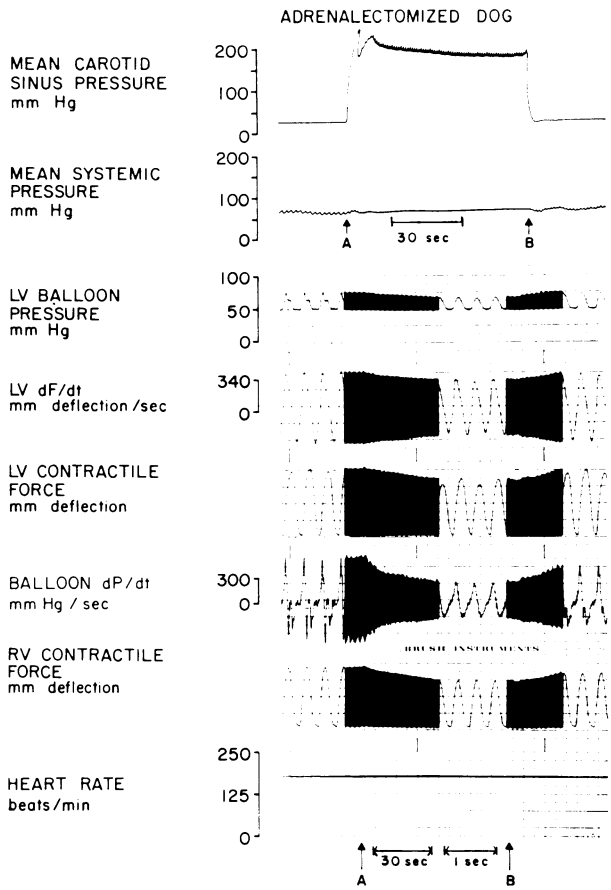

FIGURE 5 Original tracings from an experiment performed on a dog that had been subjected to bilateral adrenalectomy and vagotomy. Note the accentuation of pulsus alternans that occurred during elevation of carotid sinus pressure as a consequence of reflex inhibition of sympathetic support to the heart (best seen in the tracing of left ventricular contractile force).

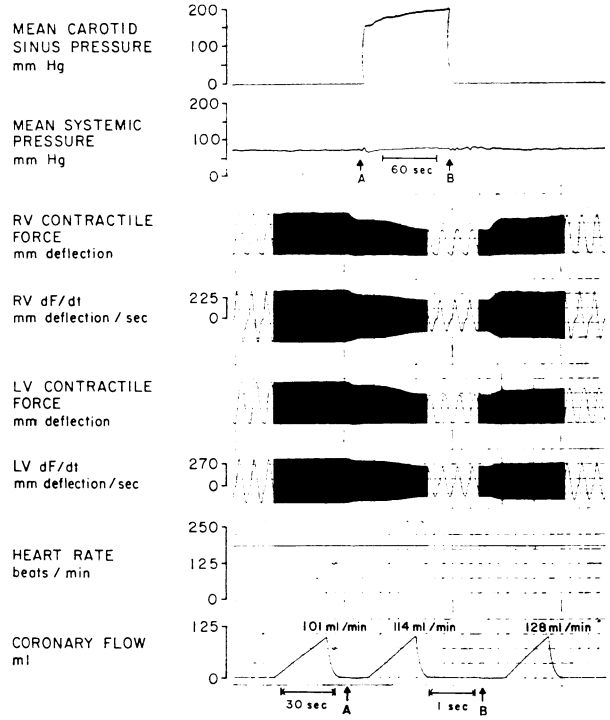

FIGURE 6 Effects of changing carotid sinus perfusion pressure in a dog (No. 2) from group II in which coronary flow was determined by a gravimetric technique. Note that although coronary flow and coronary perfusion pressure both rose slightly during the period of increased pressure within the carotid sinuses, reflex decreases were produced in all the indices of myocardial performance. The heart was paced electrically and the vagi were intact. Later in this experiment, the reflex was abolished by the administration of practolol 1 mg/kg.

TABLE I

Effects of Increasing Perfusion Pressure in the Isolated Cartoid Sinus Areas in Dogs in Which Coronary Flow Was Measured

Dog No.	No. of runs	RVCF	RV dF/dt	LVCF	LV dF/dt	Coronary flow	
						Low CSBP	High CSPB
		%Δ				*ml/min*	
1	7	−22.7 ±0.5	−22.1 ±0.9	−22.0 ±1.3	−26.0 ±1.6	312 ±12.0	338 ±12.6
2	6	−34.5 ±1.8	−34.3 ±2.6	−26.3 ±1.5	−27.3 ±2.1	158 ±20.1	185 ±24.3
3	7	−26.4 ±1.8	−30.4 ±2.6	NM	NM	246 ±36.7	271 ±33.9

Values listed represent means ± standard errors of the mean for each dog. RVCF, right ventricular contractile force; RV dF/dt, rate of change in right ventricular contractile force; LVCF, left ventricular contractile force; LV dF/dt, rate of change in left ventricular contractile force. Low CSBP shows the coronary flow when carotid sinus blood pressure was low, and High CSBP shows the coronary flow when carotid sinus blood pressure was high; %Δ, per cent change; NM, not measured. Dogs 1 and 3 were vagotomized throughout; dog 2 was vagotomized after the second run, but the responses noted were qualitatively and quantitatively similar before and after vagotomy.

autoregulation (15) could not account for the results we observed. The cerebral circulation in this preparation was derived entirely from the vertebral arteries and around the circle of Willis to the territory of the carotid arteries. It is generally accepted, however, that in the dog adequate cerebral perfusion is supplied by the vertebral arteries in the absence of the carotid arteries (16). In any case, the perfusion pressure would be nearly the same during an intervention because systemic arterial pressure was held at control levels or slightly higher, thereby preventing any possible decrease in oxygen delivery to the brain. Because of the relative constancy of aortic pressure, the diminution in cardiac performance observed when the pressure within the carotid sinuses was raised could not be the result of a decrease in coronary perfusion pressure (Figs. 2 and 5). In the experimental model used, it was necessary to maintain the aortic pressure within relatively narrow limits because we observed that if we intentionally lowered mean arterial pressure as little as 3–5 mm Hg by slowing the roller pump, significant decreases in myocardial performance were produced.

Because the right ventricle was collapsed as a result of the drains placed in the vena cavae and right side of the heart, changes in systemic venous return could not influence the isometric contractile force gauge that was sutured to the right ventricle. The reflex alterations produced in the indices of left ventricular performance also could not be ascribed to changes in left ventricular shape or end-diastolic pressure since this chamber was continuously drained and was collapsed around the isovolumic balloon. That the changes produced were indeed reflex in nature is substantiated by the finding that when the reflex arc was interrupted, alterations in carotid sinus pressure no longer produced changes in myocardial performance. The changes that occurred in cardiac function were not secondary to variations in the amount of catecholamines secreted by the adrenal glands because similar results were obtained in the dogs that had been adrenalectomized. In addition, when large doses of norepinephrine were injected into the inferior vena cava, 25–45 sec elapsed before a cardiac response was observed because the drug had to pass through the oxygenator before it could reach the coronary circulation. In contrast, the reflex responses occurred almost immediately when carotid sinus pressure was elevated and returned promptly to control levels when the pressure was lowered (Figs. 2 and 5). The changes in myocardial function also could not be accounted for by changes in heart rate since similar findings were obtained in the 11 animals in which heart rate was controlled and in the seven animals in which it was allowed to fluctuate. Bilateral vagotomy was performed in nine dogs to eliminate the possible complicating effects of stimulation of the baroreceptors and chemoreceptors located in the arch of the aorta (17), the sensory receptors located in the atria and ventricles (18), and the stretch receptors located in the lungs (19).

Despite the fact that the aortic pressure was held relatively constant during baroreceptor stimulation, it is possible that changes could have been produced within the coronary circulation to cause an increase in coronary vascular resistance. Such changes could have been mediated reflexly or could have been secondary to metabolic changes produced by the changes in contractility. To eliminate the possibility that the decreases in myocardial performance might have been secondary to a diminution in coronary blood flow resulting from alterations in coronary vascular tone, coronary flow was measured directly in three experiments. In each study, myocardial contractility decreased when baroreceptor stimulation was increased, even though coronary flow was either maintained at control levels or slightly higher. Thus, the decreases in contractility could not have been secondary to decreases in coronary flow. The possibility that the changes in myocardial performance were secondary to vasoconstrictive stimuli to the coronary arteries is further militated against by the fact that beta receptor blockade eliminated the reflex, presumably by eliminating the changes in sympathetic tone to the myocardium. Under these conditions, vasoconstrictive stimuli to the coronary arterial bed would still have been operative.

We believe that our findings presented here demonstrate that the contractile state of the myocardium is modulated by baroreceptor reflexes originating in the carotid sinus. We cannot account for the fact that Salisbury et al. and Downing and Gardner could not show such a reflex (4–6), but for the reasons enumerated above we believe our observations are valid. These findings may have clinical implications since electrical stimulation of the carotid sinus nerves has been advocated for the treatment of intractable angina pectoris and for hypertension (20, 21). In addition, although the homotransplanted heart is capable of functioning adequately (22), it is, nevertheless, deprived of an important reflex control system. We look upon this reflex control of cardiac performance as a fine tuning mechanism that acts in concert with other homeostatic mechanisms such as the level of bloodborne catecholamines, the Frank-Starling mechanism, and changes in aortic impedance, in venous return, and in heart rate to bring about a matching of cardiac output with bodily requirements.

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