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Research Article

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VENTRICULAR FUNCTION AND AUTONOMIC NERVOUS ACTIVITY DURING CYCLOPROPANE ANESTHESIA IN MAN *

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In 1949 Moe, Rennick, Freyburger and Malton expressed surprise at the prevalent clinical use of cyclopropane, because its administration appeared to reduce cardiac contractility conspicuously in both intact dogs and canine heart-lung preparations (1). The effects of cyclopropane in heart-lung preparations have been repeatedly confirmed (2–4), but uncertainty attaches to measurements of cardiac contractility made during cyclopropane anesthesia in intact animals because they indicate every possible result from stimulation to pronounced depression (5–7).

Since the question of cardiac competence during cyclopropane anesthesia achieves practical importance only when it relates to man, we believe it essential that it be answered in man. What follows is the result of an attempt to do so.

METHOD

The subjects were 20 normal adult volunteers (5 resident physicians, 11 hospital orderlies, and 4 hospital patients prior to minor elective operations) 6 of whom were studied on two or more occasions. Each had fasted since the previous evening. All were studied in the morning in the supine position on a standard operating table.

The following measurements were made in all instances: arterial pressure, by means of a Statham P23D strain gauge connected by polyethylene tubing to a 21-gauge thin-walled needle inserted in a brachial artery; right ventricular pressure, with a P23AA gauge connected to 0.9 mm ID polyethylene tubing which was introduced into an antecubital vein through a 13-gauge thin-walled needle; electrocardiogram (lead ii), with needle electrodes; and cardiac output by dye dilution (8), by means of 3- to 5-mg doses of T-1824 dye injected from a calibrated syringe through the ventricular catheter. The duration of injection ranged from 2 to 3 seconds. The optical density of arterial blood was measured by drawing it at a constant rate through a photometer. The relationship between density and dye concentration was established by measuring the density change produced by adding known amounts of dye to blood which had been withdrawn during the output determinations. Linearity of the photometer was satisfactory over the range 0 to 15 mg of T-1824 per L blood. Approximately 25 ml of blood was withdrawn for each output determination; the blood withdrawn was replaced by an equal volume of physiological saline solution. For the ventricular pressure measurements the transducer lay in the plane 5 cm dorsal to the angle of Louis. The rise-time for the transducer-catheter system was 0.05 second.

In the anesthetized subjects respired gases were withdrawn through a 20-gauge needle inserted into the airway and analyzed for P_{CO_2} by the method of Collier, Affeldt and Farr (9). In addition, end-expired gas samples were obtained from the same source by intermittent sampling with a 10 ml glass syringe and analyzed for cyclopropane (10). The P_{CO_2} determinations were corrected for the presence of the anesthetic gas (11). In four conscious and three anesthetized subjects intrapleural pressure changes were estimated by measuring the pressure in a 5 cc balloon containing 2 cc of air and situated in the midportion of the esophagus.

All of the pressure and electrocardiographic data were recorded by a Grass polygraph which incorporated circuits for obtaining mean values by electrical damping. The output of the densitometer was recorded by a Texas Instrument recording galvanometer.

Stroke volume was determined by dividing flow rate by the cardiac rate obtaining during each measurement of cardiac output. Heart rate was counted during a period sufficient to include at least 10 respiratory cycles. The stroke work of the right ventricle was estimated as equal to stroke volume times mean right ventricular pressure during ventricular systole. Mean end-diastolic right ventricular pressures were determined by averaging all such pressures recorded during the 20 seconds preceding and the 20 seconds following dye injection. Cardiac rhythm was normal during all of the measurements reported. Duplicate estimations of cardiac output agreed within 10 per cent; standard deviation of the difference was 5 per cent.

In preliminary studies it was found that right ventricular function before and during cyclopropane anesthesia could not easily be compared because administration of the gas typically increased stroke volume, stroke work, and end-diastolic pressure. For this reason two maneuvers were subsequently employed that altered all three

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variables in the same direction. Stroke volume, work, and end-diastolic pressure were intentionally increased by passive elevation of the subjects' lower extremities; the same variables were reduced by the administration of atropine.

In a typical study the subject reclined with his arms supported on arm boards while the needles and catheters previously mentioned were inserted under local (1 per cent lidocaine) anesthesia. After this a half-hour period of rest was permitted during which oxygen [1] was breathed from the face mask of a standard anesthesia machine. Preliminary duplicate measurements of systemic arterial pressure, heart rate, right ventricular pressure, and stroke volume were then completed. After this both lower extremities were rapidly elevated by an assistant to make an angle of approximately 45° with the horizontal. A second set of measurements was then made as rapidly as possible (within approximately 1 minute), after which the legs were restored to their previous position. It was found essential to teach the subjects not to strain as their legs were being moved; with practice this was easily accomplished. In 11 conscious subjects these measurements and maneuvers were repeated in order to study reproducibility, the effects of atropine, and the changes caused by bilateral blockade of the stellate ganglia. Atropine sulfate was given intravenously in repeated doses of 0.1 to 0.2 mg until heart rate increased approximately 20 beats per minute, after which the measurements were repeated. In all subjects atropine was subsequently given until cardiac rate failed to increase further in response to increased dosage. The dose necessary to accomplish this ranged from 0.8 to 2.0 mg. The stellate ganglia were blocked bilaterally via the anterior approach by 10 to 15 ml of 1 per cent lidocaine.

In 6 subjects, after completion of control measurements (including those made with the legs elevated), general anesthesia was induced with cyclopropane in oxygen administered from a standard anesthesia machine, by means of a face mask during induction and subsequently via a cuffed Magill's tube of appropriate size placed in the trachea under direct vision. These individuals received no drugs before the induction of anesthesia. Respirations were not assisted, but end-expired P_{CO_2} was maintained at levels not exceeding 50 mm Hg by limiting the inspired cyclopropane concentration to levels that did not unduly depress respiration. The selected concentration of cyclopropane in end-expired air was maintained constant by methods previously described (12) for at least 30 minutes before definitive measurements of cardiac function were made. In two instances observations were also made during the induction of anesthesia. After 1 hour of cyclopropane administration the hemodynamic measurements were repeated in duplicate, after which the lower extremities were again elevated in order to increase venous return while another set of measurements was completed. Atropine was then given as in the studies during consciousness, and the measurements repeated with extremities horizontal and elevated. Finally, the effects of stellate ganglion blockade were measured. In view of the blood loss entailed by these procedures (about 250 ml), studies were not repeated in the same individual more often than at monthly intervals.

Four anesthetized subjects were studied after subcutaneous injections (in thigh or arm) of lidocaine in amounts simliar to those needed to block the stellate ganglia. This served to distinguish between the effects of actual interruption of nervous function and those attributable to systemic action of the blocking drug.

Data were analyzed statistically by Student's t test. Significance was attached to p levels of 0.05 or less.

RESULTS

Observations in conscious subjects. Elevation of the lower extremities caused transient increases in right ventricular end-diastolic pressure, stroke volume, right ventricular stroke work, and mean brachial arterial pressure. Heart rate was slightly reduced. These changes were reversed in time even though the legs remained elevated; subsidence of the initial effects began within 30 seconds and was reasonably complete within 5 minutes. For this reason measurements of the hemodynamic effects of leg raising were completed as rapidly as possible—usually within 1 minute after the legs were raised.

A crucial point was whether the increase in right ventricular pressure occasioned by elevating the extremities resulted predominantly from increased filling pressure or from raised intrapleural pressure (caused either by straining on the part of the subject or by a shift in the position of viscera resulting passively from the maneuver). This question was answered from measurements of esophageal pressure. The changes in intrapleural pressure caused by elevating the lower extremities were negligible. In four studies the average increase in esophageal pressure caused by elevating the legs was 0.1 mm Hg. In contrast, the average increase in end-diastolic right ventricular pressure (filling pressure) accompanying leg-raising was 2 mm Hg.

Administration of atropine to these subjects had several pronounced reactions. Atropine reduced end-diastolic right ventricular pressure, reduced stroke volume and work, but increased cardiac rate and output, and (usually) mean arterial pres-

[1] Oxygen (rather than air) was administered during the control period in an effort to approximate the oxygen concentration (roughly 85 per cent) that the subjects inspired during anesthesia.

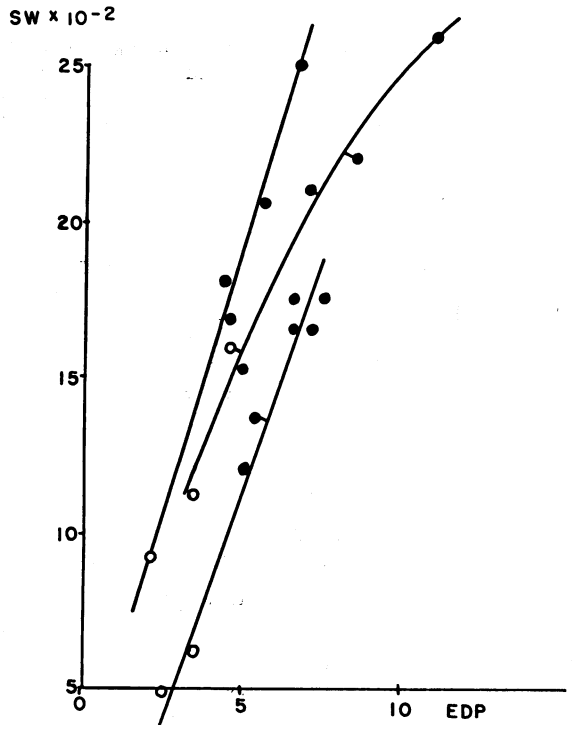

FIG. 1. EFFECTS OF ATROPINE ON RELATION BETWEEN STROKE WORK AND END-DIASTOLIC PRESSURE. Closed circles, before atropine; open circles, after atropine.

sure. It did not, however, alter the relationship between stroke work and filling pressure that was established by elevation of the lower extremities. Figure 1 illustrates this finding in three representative cases. It indicates that reduced filling pressure after atropine administration was associated with a proportionate reduction in stroke work.

Stellate ganglion blockade was devoid of any conspicuous action. Cardiac rate decreased slightly on average, but the changes encountered were inconsistent. Cardiac output was inconsistently affected. Filling pressure increased appreciably in only three of nine cases. Comparisons of the relation between stroke work and filling pressure were possible before and after ganglion blockade in four subjects. No clear effect was apparent. Figure 2(A) illustrates a representative case. During blockade the rate at which right ventricular filling pressure returned toward normal (while the legs remained elevated) was reduced when compared with observations made prior to the block.

Observations in anesthetized subjects. In six subjects hemodynamic measurements were compared during consciousness and during cyclopropane anesthesia (Table I). The two most consistent effects of administration of anesthetic in these subjects were: *1*) to increase right ventricular end-diastolic pressure, and *2*) to increase stroke work.

An attempt to investigate the significance of these changes was made by raising the legs in unanesthetized subjects and by administering small doses of atropine to anesthetized individuals. When stroke work in anesthetized subjects was reduced by atropine to the level observed before cyclopropane administration, ventricular end-diastolic pressure was only slightly greater (about 1 mm Hg) in anesthetized than in conscious individuals. Data from the four most complete studies are shown in Figure 3; the results in the other two subjects were similar.

Table II summarizes the results of administering atropine to 11 subjects who were and 9 who were not anesthetized with cyclopropane. The subjects were the same in five cases, and the doses of atropine were essentially the same in both groups, although the average dose of atropine given the conscious subjects somewhat exceeded that administered during anesthesia (1.4 vs 1.1 mg). The difference in dose was attributable to the fact that maximal cardiac rates were obtained in the anesthetized subjects at lower doses than in conscious subjects. The table shows

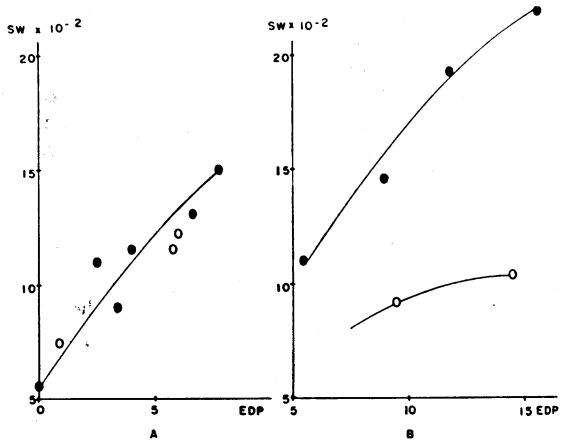

FIG. 2. EFFECTS OF STELLATE GANGLION BLOCKADE ON VENTRICULAR CONTRACTILITY. A, unanesthetized. B, anesthetized with cyclopropane. Closed circles, before blockade; open circles, during blockade.

TABLE I

Hemodynamic actions of cyclopropane in six subjects *

Study no.	Arterial pressure Mean		Heart rate	Stroke work	E.D.P.	Cyclo.	Remarks
	mm Hg		*beats/min*	*ml×mm Hg*	*mm Hg*	*vol %*	
59–17	120/76	94	46	1,710	5.0	0	Sleeping
	118/73	92	49	2,110	13.5	14	P_{CO_2} = 44
59–20	147/83	114	88	1,580	5.0	0	Resting
	135/67	94	77	2,050	9.5	18	P_{CO_2} = 37
59–25	128/72	89	64	1,360	6.7	0	Resting
	165/100	118	70	2,350	14.0	17	P_{CO_2} = 50
59–27	128/73	94	64	1,670	6.5	0	Sleeping
	118/60	80	57	2,540	12.6	18	P_{CO_2} = 39
60–42	91/63	76	54	925	5.1	0	Sleeping
	100/70	82	52	1,350	11.1	19	P_{CO_2} = 50
60–44	128/78	95	74	1,150	5.8	0	Resting
	130/75	95	68	2,760	12.2	18	P_{CO_2} = 48
Average	124/74	94	65	1,400	5.7		Before anesth.
	128/74	94	62	2,193	12.2		During anesth.
Difference		0	−3	+793	+6.5		
Significance				$p < 0.01$	$p < 0.01$		

* E.D.P. = end-diastolic pressure; cyclo. = end-expired cyclopropane concentration; P_{CO_2} = end-expired CO_2 tension in mm Hg.

that the increase in cardiac rate produced by atropine in the anesthetized subjects was twice that observed in unanesthetized persons, that cardiac output was elevated only slightly (10 per cent) in conscious subjects but markedly (40 per cent) in anesthetized individuals, and that stroke work and filling pressure were also more conspicuously changed by atropine in anesthetized than in conscious subjects. Mean arterial blood pressure was slightly increased by atropine in both conscious and anesthetized subjects, but the difference in response was neither striking nor statistically significant.

In Table III the effects of stellate ganglion blockade in nine conscious and seven anesthetized subjects are compared. Blockade was associated with insignificant hemodynamic changes in the conscious subjects. Blockade in the subjects anesthetized with cyclopropane was followed by conspicuous reduction in cardiac output, cardiac rate, and (often) mean arterial blood pressure. The rate of ventricular pressure increase during systole (dp/dt) also decreased. Filling pressure, in contrast, increased after blockade.

That these actions were not caused by systemic absorption of the blocking drug (lidocaine) was shown by injecting the same drug in the same

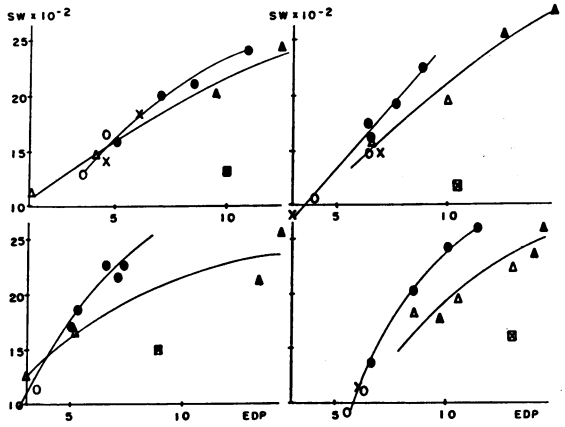

FIG. 3. VENTRICULAR FUNCTION BEFORE AND DURING CYCLOPROPANE ANESTHESIA. Closed circles, effects of elevating extremities during consciousness; open circles, effects of atropine in absence of anesthesia; ×, effects of stellate ganglion blockade during consciousness; closed triangles effects of elevating extremities during anesthesia; open triangles, effects of atropine during anesthesia; boxed ×, effects of stellate ganglion blockade during anesthesia.

TABLE II

Hemodynamic actions of atropine *

Status	Subjects		Mean art. pressure	Heart rate	Cardiac output	Stroke work	E.D.P.	Cyclo.
	no.		*mm Hg*	*beats/min*	*L/min*	*ml×mm Hg*	*mm Hg*	
Conscious	11	Average	99 → 104	65 → 99	6.5 → 7.3	1,510 → 1,085	5.6 → 2.1	0
		Change	+5	+34	+0.8	−425	−3.5	
Anesthetized	9	Average	93 → 100	66 → 136	6.2 → 9.0	2,180 → 1,250	11.7 → 3.1	16.2
		Change	+7	+70	+2.8	−930	−8.6	
		Difference	+2	+36	+2.0	−505	−5.1	
		Significance	0	$p < 0.01$	$p < 0.05$	$p < 0.01$	$p < 0.01$	

* See footnote to Table I.

amounts subcutaneously in four subjects anesthetized with cyclopropane. Twenty to 30 minutes after injection there was no significant change in cardiac rate, cardiac output, mean arterial pressure, or right ventricular pressure in any of these subjects (Table IV).

In four anesthetized subjects the effects of stellate ganglion blockade on ventricular function were studied in detail by constructing curves relating stroke work and filling pressure. In contrast to the results in conscious subjects, blockade of the stellate ganglia in anesthetized individuals reduced stroke work, increased end-diastolic ventricular pressure, and flattened the slope of the line relating the two variables. Typical examples of the results of stellate ganglion blockade in conscious and anesthetized subjects are shown in Figures 2, A and B, and Figure 3.

DISCUSSION

It is agreed that cyclopropane depresses cardiac contractility in isolated mammalian hearts (or heart-lung preparations), that the degree of depression is related to cyclopropane concentration, and that depression begins at concentrations that are less than those needed to produce surgical anesthesia in intact animals (1–4). As has already been mentioned, there has been poorer agreement concerning effects of cyclopropane in intact animals and men.

The present study was planned to correct a number of deficiencies that could have accounted for these discordant results. It was believed essential to study normal men who were not given sedatives, muscle relaxants, or anesthetics other than cyclopropane, who were not subjected to surgical operation during study, who did not require ventilatory assistance, and who could be exposed to a constant concentration of cyclopropane long enough to insure substantial equilibration. These criteria were met in the subjects studied.

The most important question posed by the present results is the usefulness of relationship between stroke work and end-diastolic pressure in analyzing ventricular function in intact man. The results obtained cannot be viewed as direct measurements of myocardial contractility. The

TABLE III

Hemodynamic actions of stellate ganglion blockage

Status	Subjects		Mean art. pressure	Heart rate	Cardiac output	E.D.P.*	Cyclo.
	no.		*mm Hg*	*beats/min*	*L/min*	*mm Hg*	
Conscious	9	Average	104 → 101	97 → 93	5.9 → 6.0	4.7 → 4.8	0
		Change	−3	−4	+0.1	+0.1	0
Anesthetized	7	Average	100 → 94	127 → 95	7.8 → 6.4	5.4 → 11.7	17.6
		Change	−6	−32	−1.4	+6.3	0
		Difference	−3	−28	−1.5	+6.2	
		Significance	0	$p < 0.01$	$p < 0.05$	$p < 0.01$	

* Right ventricular pressures are compared at equal levels of stroke work. See Table I for abbreviations.

operation of barostatic reflexes must affect the results (13), since it is not possible to impress hemodynamic changes on the intact body without calling forth compensatory adjustments. Little can be said about these effects in the present study, but it is relevant that cyclopropane in concentrations producing "light" anesthesia in man is believed not to modify the sensitivity of carotid sinus reflexes (14). To whatever extent these data do measure myocardial contractility they suggest no remarkable diminution in competence; the present results in no way resemble those observed in heart-lung preparations.

This discrepancy implies either an extraordinary innate resistance of the human heart to depressant actions of cyclopropane—which seems unlikely—or antagonism of these actions by bodily reactions. Evidence that sympathetic nervous activity increases when cyclopropane is administered has previously been obtained in man by measuring concentrations of epinephrine and norepinephrine in arterial blood (15). It was found that norepinephrine concentrations increased as anesthetic concentrations did, while epinephrine concentrations were essentially unaltered. These results favored increased activity in sympathetic nerves without a concomitant increase in adrenal medullary secretion, but they could not indicate which sympathetic nerves were involved. In the present study the results of stellate ganglion blockade show that functional integrity of this structure is essential for maintenance of normal myocardial function during cyclopropane anesthesia in man. Evidence that blockade of sympathetic efferent fibers traversing the stellate ganglia and supplying the heart—as distinct from any other kinds of fiber—was responsible for the effects observed, is of four sorts. First, blockade of the stellate ganglia interrupts efferent activity in most of the sympathetic nerves supplying the heart, without directly affecting parasympathetic efferents (16). Second, visceral afferents from stretch receptors in the heart, great veins, and pulmonary vessels traverse the vagi, while those which respond to changes in systemic arterial pressure are found in the vagi and glossopharyngeal nerves (17); neither of these nerves was blocked in the present study. Third, certain visceral afferents (pain) from the heart apparently do traverse the sympathetic chains (18), but there is doubt that these are active in normal individuals who are free of anginal pain. Finally, activity of sympathetic nerves supplying the heart apparently was increased during cyclopropane anesthesia in the present study, as evidenced by the effect of atropine, and blockade of these nerves consequently should have produced functional changes opposite to those caused by their stimulation (19); this was indeed the case.

TABLE IV

Hemodynamic actions of lidocaine in four anesthetized subjects

	Mean art. pressure	Heart rate	Cardiac output	E.D.P.*	Cyclo.
	mm Hg	*beats/min*	*L/min*	*mm Hg*	
Average Change	112 → 113 +1	106 → 110 +4	7.0 → 7.4 +0.4	4.3 → 4.0 −0.3	16.0
Signif.	0	0	0	0	

*See footnote. Table I.

It should be pointed out that the remarkable tachycardia observed in the anesthetized subjects after atropine administration could not have been caused by increased sympathetic nervous activity in extracardiac locations, which might conceivably have affected cardiac rate by increasing plasma concentrations of epinephrine or norepinephrine. Concentrations of epinephrine in arterial plasma have previously been measured in men anesthetized with cyclopropane and were found to be normal (15). Norepinephrine concentrations were increased, but the infusion of this substance into both normal and anesthetized men caused, not tachycardia, but bradycardia.

The relatively pronounced hemodynamic effects of atropine in subjects anesthetized with cyclopropane raises the question of whether cardiac vagal activity exceeded normal in these individuals. The important vagal actions on the heart are thought to be limited to those exerted on cardiac impulse generation and conduction and those exerted on atrial contractility. In contrast to sympathetic nervous actions, animal studies show that vagal stimulation does not alter ventricular contractile force (19). The effects of atropine administration in the present study suggest that this is also true in man, for there were no changes in ventricular end-diastolic pressure that could not be ascribed to corresponding alterations in stroke work. Consequently, ventricular contractility was apparently unaltered by parasympathetic

nervous activity. On the other hand, cardiac output and rate were markedly increased by atropine,[2] which indicates that cardiac vagal activity is important in limiting both in subjects anesthetized with cyclopropane.

SUMMARY AND CONCLUSIONS

1. In the subjects studied the administration of cyclopropane (14 to 19 volumes per cent end-expired) typically increased right ventricular stroke volume, stroke work, and end-diastolic pressure.

2. When stroke work was increased in conscious subjects (by elevation of the lower extremities) or decreased in anesthetized subjects (by administering atropine) all three variables tended to coincide. This is interpreted as meaning that cyclopropane did not seriously reduce myocardial contractility in the subjects studied.

3. This finding appeared to result from an increase in the activity of sympathetic nerves supplying the heart which antagonized direct depressant actions of cyclopropane on the myocardium.

4. The cardiac effects of increased sympathetic nervous activity, excepting those on contractility, appeared to be balanced by cardiac vagal activity.

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[2] There are certain tissues in man that appear to be supplied with cholinergic vasodilator fibers. Atropine in the doses used might have interrupted function in these fibers. However, the available evidence does not favor their having a role in circulatory barostatic reflex responses (20), and the effect of blocking them, if any, should have been to decrease cardiac output without appreciably changing cardiac rate.