Control of Heart Rate by the Autonomic Nervous System

STUDIES IN MAN ON THE INTERRELATION BETWEEN BARORECEPTOR MECHANISMS AND EXERCISE

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ABSTRACT

The control of heart rate by the autonomic nervous system was investigated in conscious human subjects by observing the effects of β-adrenergic blockade with propranolol, of parasympathetic blockade with atropine, and of combined sympathetic and parasympathetic blockade. The increase in heart rate with mild exercise in supine men was mediated predominantly by a decrease in parasympathetic activity; at higher levels of work, however, sympathetic stimulation also contributed to cardiac acceleration. When the response to 80° head-up tilt was compared with the response to exercise in the same subject supine, it appeared that the attainment of an equivalent heart rate was associated with a significantly greater degree of sympathetic activity during tilting than during exercise. Although heart rate was always higher at any given pressure during exercise than it had been at rest, the changes in heart rate that followed alterations in arterial pressure were found to be of similar magnitudes at rest and during exercise; it was therefore concluded that the sensitivity of the baroreceptor system was not altered during exercise. Investigation of the efferent pathways concerned in mediating the baroreceptor-induced changes in heart rate suggested that the relative roles of the sympathetic and parasympathetic systems were nearly equal in the resting state. During exercise, on the other hand, changes in sympathetic activity appeared to be the predominant mechanism by which speeding and slowing of the heart was achieved. It thus appears that baroreceptor-induced alterations in heart rate may be mediated by increased or decreased activity of either efferent system; the ultimate balance, however, is critically dependent on the preexisting level of background autonomic activity.

ADDITIONAL KEY WORDS **propranolol** **atropine** **sympathetic nervous system** **tilting** **beta-adrenergic receptors** **heart rate control** **baroreceptor reflex**

■ The central nervous system controls heart rate by varying the impulse traffic in sympathetic and parasympathetic nerve fibers terminating in the sinoatrial node. Although there has been considerable interest in the mechanisms by which the heart rate is altered in response to exercise, postural changes, and stimulation of the baroreceptors, the relative roles of the two divisions of the autonomic nervous system in mediating these changes in rate in conscious man have not been clarified. Furthermore, little information is available concerning the manner in which the heart rate response to baroreceptor stimulation is modified during exercise.

In the present study, the relative roles of the efferent pathways which mediate the heart rate response to exercise in supine man were investigated by observing the separate and combined effects of β-adrenergic blockade and parasympathetic blockade on cardiac acceleration. The cardiac acceleration resulting from head-up tilting was studied in a

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similar way, thus allowing a comparison of the mechanisms of speeding under conditions of exercise and changes of posture. The sensitivity of the control of heart rate by the baroreceptor system was then compared at rest and during exercise, and the efferent pathways utilized were studied by observing the effects of the autonomic blocking agents.

Methods

Five normal volunteers and one patient (AS) who had undergone a successful mitral commissurotomy five months earlier were studied; their ages ranged from 19 to 28 years. All of the subjects were males and in good physical condition, but none was a trained athlete. All studies were carried out in the postabsorptive state.

1. EXERCISE IN SUPINE POSITION AND CHANGE OF POSTURE

Before any measurements were made, each subject was thoroughly familiarized with the use of the bicycle ergometer in the supine position and with the tilt table. In the definitive investigation, the subject was first placed on the tilt table in the supine position and his heart rate was determined from the ECG for 30 sec. He was then tilted, first to 45° and then to 80° from the horizontal, and the heart rate was recorded in each position when the cardiotachometer and ECG tracings showed that the rate was stable. Heart rate was then recorded with the subject at rest on the bicycle ergometer in the supine position and during the fourth minute of exercise at each of a series of work levels which were carried out consecutively without intervening rest periods. Oxygen uptake ($\dot{V}o_2$) was recorded throughout the period of exercise using a continuous flow system.[1] The protocol outlined above was repeated on three subsequent days; the cardiac sympathetic nerves were blocked on one, the parasympathetic nerves on another, and both on the third. Stimulation of the heart through the sympathetic nerves and by circulatory catecholamines secreted by the adrenals was inhibited by the β-adrenergic blocking agent propranolol* given in a dose of 0.25 mg/kg iv; it has previously been shown that 0.15 mg/kg reduces the effectiveness of infused isoproterenol at least 90%.[2] Throughout this paper this is referred to as sympathetic blockade, although only the β-receptors were blocked. No untoward effects of propranolol were observed in any of the subjects at this higher dosage. Parasympathetic blockade was induced with 2 mg of atropine given intravenously. Combined sympathetic and parasympathetic blockade (double blockade) was produced by the simultaneous administration of both drugs.

2. THE BARORECEPTOR SYSTEM

The studies at rest were carried out with the subject seated in a chair and those during exercise while he walked on a motor-driven treadmill. The subjects were completely familiarized with walking on the treadmill before the study commenced, and a speed and grade were found which consistently resulted in a heart rate between 90 and 125 beats/min. The oxygen requirements at this level of exercise ranged from 960 to 1,950 ml/min. Arterial pressure was recorded through a short teflon catheter that had been introduced percutaneously into the brachial artery and connected to a Statham P23AA pressure transducer; heart rate was determined for 30-sec periods from the simultaneously recorded ECG. Increases of arterial pressure were produced by the intravenous infusion of phenylephrine, a pressor agent that in the doses used is without measurable direct cardiac effect[3]; the rate of administration was controlled by a constant speed pump.

In each experiment, the subject was first studied at rest. When mean arterial pressure and heart rate had stabilized, the arterial pressure was raised in steps by infusing phenylephrine in doses varying from 0.05 to 0.40 mg/min, and heart rate was recorded when the pressure had stabilized at the new level for at least 1 min. After discontinuing the phenylephrine, the subject walked on the treadmill at the predetermined speed and grade; arterial pressure and heart rate were recorded after 5 min and again after 7 min to ensure that a steady state had been reached. The effects on heart rate of elevating arterial pressure with graded doses of phenylephrine were then determined during exercise as at rest, but larger doses of the drug, up to 0.80 mg/min, were required to produce elevations of arterial pressure during exercise comparable to those achieved at rest. After discontinuing the phenylephrine and allowing its effects to wear off, nitroglycerin (0.4 mg or 0.8 mg) was given sublingually while the subject was still exercising, and arterial pressure and heart rate were recorded at the peak of the drug effect. The effects of reducing arterial pressure were studied again after the heart rate had stabilized at rest. The entire study was repeated on three subsequent days in the same way as in the posture studies. The action of cardiac sympathetic nerves was inhibited on one occasion, the parasympathetics on another, and both on the third, utilizing the doses of blocking agents described above. The experiments were usually completed within 45 min of administra-

*1-Isopropylamino-3-(1-naphthyloxy)-2-propanol hydrochloride.

tion of the blocking drug; when the study continued longer, a supplemental dose (0.1 mg/kg of propranolol; 1 mg atropine) was given. The subjects were in sinus rhythm under all of the experimental conditions studied.

Results and Interpretations

1. RELATIVE ROLES OF PARASYMPATHETIC AND SYMPATHETIC EFFERENTS IN THE HEART RATE

A. Response to Exercise in Supine Position

Four normal subjects were investigated and all showed qualitatively similar responses (table 1); the results in one are illustrated in figure 1, left. In the control studies, carried out with both the sympathetic and parasympathetic efferents intact, the heart rate at rest averaged 52/min in the four subjects and rose in an approximately linear manner with increasing $\dot{V}o_2$. Following blockade of both sympathetic and parasympathetic efferents (double blockade), the resting heart rate rose above the control level in all subjects (average increase of 42/min), but there was little or no further increase with mild exercise ($\dot{V}o_2$ up to 500 ml/min); small increases in rate, averaging 10/min, occurred at higher levels of work ($\dot{V}o_2$ 900 to 1300 ml/min). When the cardiac sympathetic system alone was blocked, the parasympathetic remaining intact, the resting heart rate fell by an average of 4/min. The rate increased normally with mild exercise in every subject, but there was less speeding at the higher levels of work in three of the four (GM, RR, and RJ: table 1, fig. 1). When the parasympathetic system was inhibited, leaving the sympathetic intact, resting heart rate increased by an average of 46/min above control; cardiac acceleration in response to mild exertion was reduced and in two subjects was abolished, but the rate rose normally at the higher levels of exercise.

It thus appears that in the supine resting state, parasympathetic restraint is the dominant influence on heart rate (fig. 1, Pr), and the accelerating effects of sympathetic stimulation (fig. 1, Sr) are minor. The speeding of the heart in response to mild exercise appears to result largely from withdrawal of

TABLE 1

Effects of Autonomic Blockade on Heart Rate Response to Supine Exercise

Subject		Control		Sympathetic blockade		Parasympathetic blockade		Double blockade	
		$\dot{V}o_2$ ml/min	HR /min	$\dot{V}o_2$ ml/min	HR /min	$\dot{V}o_2$ ml/min	HR /min	$\dot{V}o_2$ ml/min	HR /min
GM	Rest	233	59	242	59	275	93	330	85
	Exercise	455	77	317	70	355	101	369	86
		700	98	509	78	514	107	515	89
		913	108	651	81	691	113	661	94
				994	96	922	134	953	104
RR	Rest	271	49	299	43	284	94	292	86
	Exercise	385	58	405	59	408	96	389	86
		499	65	510	65	479	96	486	86
		770	81	774	75	745	110	797	89
		1033	91	1038	83	1011	122	1030	96
PY	Rest	259	49	343	47	309	115	290	113
	Exercise	418	59	510	60	507	112	457	108
		701	72	686	70	705	107	651	108
		919	79	898	80	877	111	845	111
		1069	92	1038	84	980	127	1012	113
RJ	Rest	234	49	229	44	225	84	244	90
	Exercise	436	65	418	54	425	88	410	87
		677	77	627	66	656	94	634	88
		755	82	940	79	940	110	878	93
		1289	115	1358	90	1248	122	1255	100

Control = autonomic nervous system functioning normally; double blockade = combined sympathetic and parasympathetic blockade; $\dot{V}o_2$ = oxygen consumption; HR = heart rate.

parasympathetic inhibition, since cardiac acceleration is essentially unimpaired by sympathetic blockade but tends to be inhibited by parasympathetic blockade and double blockade. At higher levels of exercise, however, cardiac acceleration must result in part from sympathetic stimulation, since sympathetic blockade reduces the augmentation of heart rate in comparison to the control study. The finding that the increments in rate during heavy exercise are smaller after double blockade than after parasympathetic blockade alone further identifies the contribution of the sympathetic system. These results were obtained in young healthy male adults, and it is possible that a different balance of autonomic effect might obtain in a different group of subjects.

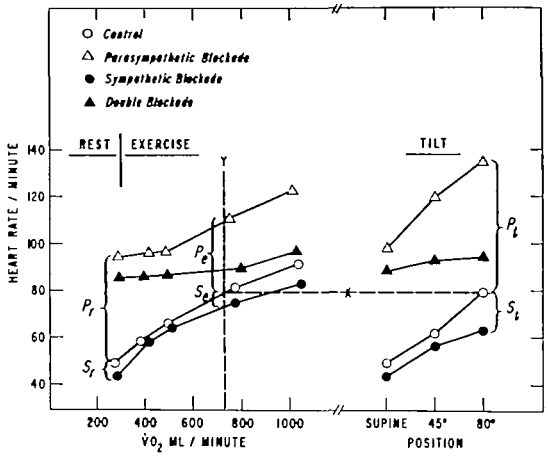

FIGURE 1

A comparison of the effects of various forms of autonomic blockade on the response of heart rate in subject RR to exercise when supine and to head-up tilt. The level of exercise in the control (no blockade) exercise study which would have produced a heart rate equal to that observed during the control 80° tilt is determined by interpolation (lines X and Y, see text). Effects of parasympathetic blockade on heart rate are indicated by P_r at rest, P_e during exercise, and P_t during tilting. Effects of sympathetic blockade are indicated by S_r, S_e and S_t.

B. Response to Tilting

The heart rate rose by an average of 29/min during the 80° head-up tilt in the control study with the subjects in the unblocked state (table 2, fig. 1). Following double blockade, the increase in rate induced by tilting was almost abolished and averaged only 5/min. During parasympathetic blockade, however, heart rate increased by an average of 36/min and during sympathetic blockade by 17/min. Thus, in contrast to light exercise in supine position, substantial speeding could still occur during tilting when the parasympathetic system was blocked.

The results were then analyzed to characterize in greater detail the differences between the mechanisms of cardiac speeding

TABLE 2

Effects of Autonomic Blockade on Heart Rate Response to Tilting

Subject	Tilt angle degrees	Control HR/min	Sympathetic blockade HR/min	Parasympathetic blockade HR/min	Double blockade HR/min
GM	0	61	57	96	88
	45	72	68	114	86
	80	88	75	130	92
RR	0	48	44	97	89
	45	61	56	119	92
	80	79	62	134	93
PY	0	50	46	116	108
	45	68	57	138	118
	80	79	67	151	114
RJ	0	53	44	96	84
	45	66	48	113	86
	80	80	57	134	90
Mean	0	53	48	101	92
	45	67	57	121	96
	80	82	65	137	97

Abbreviations as in table 1.

TABLE 3

Comparison of Effects of Sympathetic and Parasympathetic Blockade on Heart Rate Response to Supine Exercise and Tilting

Subject		Control HR/min	Sympathetic blockade HR/min	Sympathetic blockade ΔHR	Parasympathetic blockade HR/min	Parasympathetic blockade ΔHR
GM	Exercise	88	80	−8	110	+22
	80° tilt	88	75	−13	131	+43
RR	Exercise	79	74	−5	110	+31
	80° tilt	79	62	−17	134	+55
PY	Exercise	79	78	−1	111	+32
	80° tilt	79	67	−12	152	+73
RJ	Exercise	78	69	−9	103	+25
	80° tilt	78	56	−22	132	+54
Avg	Exercise			−6		+27
	80° tilt			−16		+56
	P			<.05		<.02

ΔHR = change in heart rate compared to control; Avg = average change in heart rate compared to control. Other abbreviations as in table 1.

during exercise and tilting. The level of $\dot{V}O_2$ during exercise which would have produced the same degree of cardiac acceleration as that actually observed during the 80° tilt was determined by interpolation (fig. 1, lines X and Y). The effect of sympathetic and parasympathetic blockade on the heart rate at this level of $\dot{V}O_2$ was then estimated by determining the intercepts of line Y with the appropriate heart rate-$\dot{V}O_2$ relationship. The effects of autonomic blockade could then be compared under conditions of exercise and tilting which had identical effects upon the heart rate when the autonomic nervous system was functioning normally. If the mechanism of speeding had been identical during exercise and tilting, then the effects of autonomic blockade should also have been similar. In fact, the responses to sympathetic and to parasympathetic blockade were consistently different during the two interventions (fig. 1, table 3). During exercise, parasympathetic blockade increased heart rate by an average of 27/min (fig. 1, P_e), but the increase during tilting (P_t) was more than twice as great and averaged 56/min ($P < .02$). Similarly, during exercise, sympathetic blockade decreased the heart rate by an average of only 6/min (S_e), whereas the decrease during tilting (S_t) was significantly greater ($P < .05$), averaging 16/min. It is thus apparent that achievement of the same heart rate involved a different balance of autonomic activity, depending on whether the stimulus was provided by exercise in supine position or by tilting. Exercise resulted in a greater degree of parasympathetic withdrawal than did tilting as is shown by the lesser degree of speeding induced by atropine during exercise. Conversely, exercise produced a smaller degree of sympathetic stimulation than did tilting, as is shown by the lesser degree of slowing induced by β- adrenergic blockade. Thus, the cardiac acceleration in response to mild supine exercise in these subjects appeared to depend predominantly on parasympathetic withdrawal, whereas that produced by tilting involved a relatively greater degree of sympathetic stimulation.

2. EFFECTS OF EXERCISE ON CONTROL OF HEART RATE BY THE BARORECEPTOR MECHANISM

In these experiments, changes in heart rate were related to the changes in mean arterial pressure with which they were associated. It is appreciated that the use of mean arterial pressure as an index of baroreceptor stimulation ignores the possible influence of alterations in pulse pressure; however, since mean pressure and pulse pressure always changed in the same direction, the basic pattern of the results is unaffected by the fact that mean arterial pressure alone was considered. Although the relation between heart rate and mean arterial pressure was not a linear one, it was never-

theless found useful to express the results in terms of average values when making broad comparisons between different conditions.

At rest, graded elevations of mean arterial pressure in the six subjects studied caused progressive decreases in heart rate, while reductions of pressure uniformly resulted in increases of heart rate (table 4, fig. 2). On the average, a change of 40 mm Hg in mean arterial pressure was associated with an inverse change in rate of 50/min. During exercise, the heart rate was always higher at any given arterial pressure than it was at rest, but the absolute magnitude of changes in rate that followed alterations in pressure were similar to those observed at rest (fig.2); on the average, a change of 37 mm Hg in mean arterial pressure was associated with a change in rate of 42/min. One subject (GM) was studied at rest in both the sitting and standing positions, as well as at two levels of exercise; the relation between heart rate and mean arterial pressure could be expressed by four similar curves, each increase in stress leading to a further upward displacement of the entire curve (fig. 3).

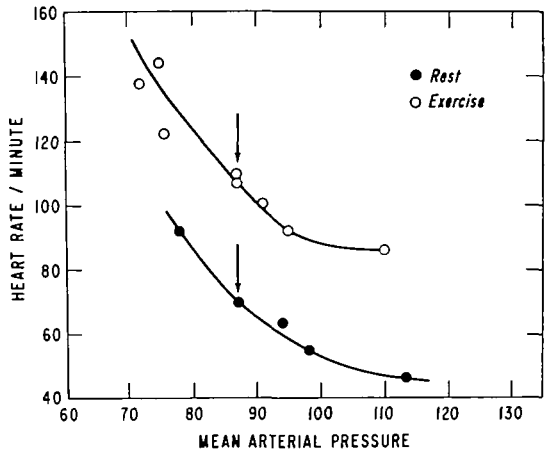

FIGURE 2

Relation between heart rate and mean arterial pressure in subject RR sitting at rest and during exercise in upright position. Arrows identify the baseline observations made before phenylephrine or nitroglycerin was given to modify arterial pressure. Slopes of the lines relating heart rate to mean arterial pressure are similar at rest and during exercise, but the heart rate is always greater at any given arterial pressure during exercise than it is at rest.

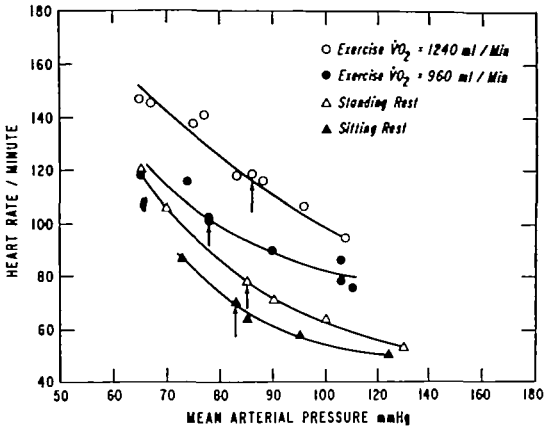

FIGURE 3

Relation between heart rate and mean arterial pressure in subject GM studied at rest, in the sitting and standing positions and at two levels of exercise in upright position. Arrows identify the baseline observations before arterial pressure was altered. Relations between heart rate and mean arterial pressure are similar under all four conditions, but the curve is displaced upward with the change from sitting to standing, and there is further upward displacement at each of the two levels of exercise.

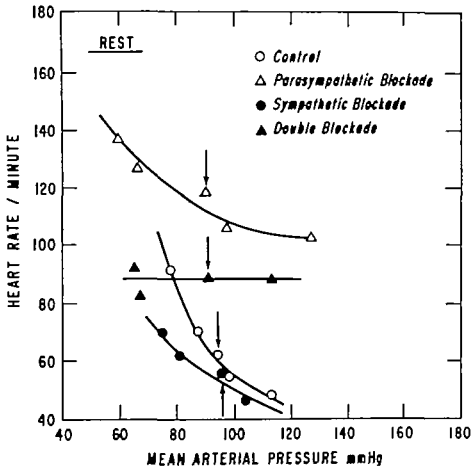

FIGURE 4

Effects of varying types of autonomic blockade on the relation between heart rate and mean arterial pressure in subject RR sitting at rest. Arrows denote the baseline observations before arterial pressure was modified under each circumstance. Heart rate continues to show some inverse variation in response to changes in mean arterial pressure when either division of the autonomic was blocked. When both divisions were blocked, changes in rate were almost completely prevented.

TABLE 4

Effects of Autonomic Blockade on Heart Rate Response to Changes in Arterial Pressure

	Subject		Control		Sympathetic blockade		Parasympathetic blockade		Double blockade	
			MAP mm Hg	HR/min	MAP mm Hg	HR/min	MAP mm Hg	HR/min	MAP mm Hg	HR/min
GM	Rest	B	83	71	75	67	95	110	82	87
		P	95	58	85	63	132	94	98	84
			112	50	100	49	138	96	142	88
		N	48	104	68	67	75	108	60	84
					66	73	65	132		
	Exercise	B	85	118	84	96	82	131	63	102
	$\dot{V}o_2 =$ 960	P	88	116	90	86	99	118	83	100
			96	106	110	83	97	116	112	98
			104	94	121	78	127	108		
		B								
		N	65	146	62	96	59	139	52	104
RR	Rest	B	87	70	96	56	90	118	91	89
		P	94	62	104	46	97	106	113	88
			98	55			127	103		
			113	48						
		N	78	92	81	62	66	126	67	83
					75	70	60	137	65	92
	Exercise	B	86	110	84	88	73	141	77	100
	$\dot{V}o_2 = 1430$	P	87	108	87	86	83	134	97	97
			91	101	92	83	88	120	126	90
			95	92	103	80	100	119		
			110	86						
		B			79	86			76	103
		N	72	138	75	94	68	178	70	108
			75	144	73	95			62	118
PY	Rest	B	83	54	83	49	75	140	80	99
		P	90	47	91	43	87	120	83	99
			95	40	95	38	112	116	105	99
			98	38					118	101
			103	36						
		N	76	69	72	63	60	141	57	97
			71	80						
	Exercise	B	81	123	84	95	84	165	69	120
	$\dot{V}o_2 = 1950$	P	85	116	87	94	100	142	75	120
			90	109	100	88	128	136	89	115
			104	106	109	85			107	109
		B	78	146	90	100	65	163	67	121
		N	71	156	70	102	61	181	55	126
RJ	Rest	B	83	55	85	46	81	110	58	84
		P	91	51	92	44	92	94	103	93
			105	44	105	39	126	101	122	91
			118	43						
		N	75	76	76	51	48	114	58	87
			70	98	75	64			52	91
	Exercise	B	93	97	84	84	62	120	78	101
	$\dot{V}o_2 = 1406$	P	98	94	95	79	97	104	92	98
			110	92	105	78	112	105	105	96
			120	90	115	78	122	114	118	96
		B	97	108	87	78	52	128	77	104
		N	75	130	84	88	50	142	74	110
			75	136						
JW	Rest	B	80	75						
		P	88	72						
			98	65						

(Table 4, continued on next page.)

3. RELATIVE ROLES OF PARASYMPATHETIC AND SYMPATHETIC EFFERENTS IN MEDIATING BARORECEPTOR-INDUCED ALTERATIONS IN RATE

A. Rest

In the 4 subjects studied, a change of 41 mm Hg in arterial pressure in the unblocked state was associated on average with change in rate of 49/min (table 4, fig. 4). Following double blockade, the heart rate at rest remained essentially constant when arterial pressure was altered (fig. 4), a change of 65 mm Hg in mean arterial pressure being associated with an inverse change in heart rate of only 7/min; autonomic stimuli resulting from changes in pressure would therefore appear to have been effectively inhibited by the drugs used. When the parasympathetic system alone was blocked, substantial changes in heart rate occurred in response to changes in arterial pressure, but tended to be less than during the control period; on the average, a change of 63 mm Hg in mean arterial pressure was associated with a change in heart rate of 29/min. During parasympathetic blockade, when rate was controlled primarily by the sympathetic system, the heart not only speeded when arterial pressure was reduced below control, but also slowed as the pressure was elevated; this indicates that in a resting, sitting subject the heart rate can be changed reflexly by either increase or decrease in the activity of the sympathetic nervous system.

When the sympathetic system alone was blocked, the heart rate continued to vary inversely with arterial pressure, a change of 29 mm Hg being associated with an average change in heart rate of 25/min. During sympathetic blockade, when rate was controlled primarily by the parasympathetic system, rate could not only be slowed by an intensification of vagal restraint as pressure was elevated, but could also be speeded by a decrease in vagal activity when pressure was decreased below control.

B. Exercise

In the four subjects in whom the effects of autonomic blockade on the response to baroreceptor stimulation were studied during exercise in upright position, an average change in arterial pressure of 40 mm Hg was associated with a change in heart rate of 52/min during the control studies (table 4, fig. 5). In the same subjects, parasympathetic blockade caused only a slight impairment of the rate response, an average change in arterial pressure of 60 mm Hg being associated with a

TABLE 4 continued

Subject			Control MAP mm Hg	Control HR/min	Sympathetic blockade MAP mm Hg	Sympathetic blockade HR/min	Parasympathetic blockade MAP mm Hg	Parasympathetic blockade HR/min	Double blockade MAP mm Hg	Double blockade HR/min
			116	56						
		N	80	88						
			75	96						
	Exercise	B	91	105						
		P	96	103						
			120	94						
		B	80	100						
		N	75	106						
AS	Rest	B	66	81						
		P	73	69						
			80	50						
		N	67	98						
			60	113						
	Exercise	B	74	94						
		P	75	85						
			85	68						
		B	70	95						
		N	65	103						

MAP = mean arterial pressure; B = baseline; P = phenylephrine given in increasing doses; N = nitroglycerine. Other abbreviations as in table 1.

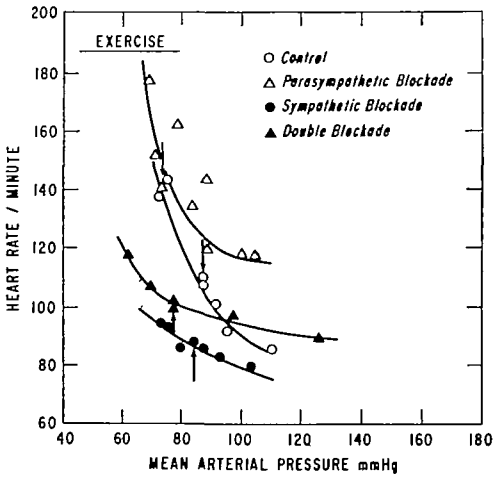

FIGURE 5

Effects of varying types of autonomic blockade on the relation between heart rate and mean arterial pressure during exercise in subject RR. Arrows denote the baseline observations for each. Response of heart rate to alterations of arterial pressure is only slightly reduced after parasympathetic blockade, but it is markedly impaired following sympathetic blockade and double blockade.

change in rate of 43/min. This finding suggests that during exercise the alterations in rate as a consequence of changing arterial pressure took place largely as a result of variations in sympathetic activity. This conclusion is supported by the finding that when the sympathetic system alone was blocked, the heart rate response to changes in arterial pressure was much impaired, a change of 40 mm Hg being associated with an average change in rate of only 15/min. Moreover, when sympathetic blockade was added to parasympathetic blockade, the rate response that had been observed during parasympathetic blockade alone was markedly attenuated; during double blockade a change in pressure of 55 mm Hg was associated with an average change in rate of 15/min.

At the levels of exercise employed, changes in the degree of sympathetic stimulation of the heart thus appeared to play a more important role in mediating baroreceptor induced increases and decreases in heart rate than did changes in parasympathetic activity. At rest, on the other hand, the roles of the sympathetic and parasympathetic systems in mediating baroreceptor reflexes appeared to be more nearly equal.

Discussion

Interest in the mechanism of exercise-induced tachycardia dates to 1914 when Gasser and Meek observed in the dog that after vagotomy little augmentation of heart rate occurred during exercise, although stellate ganglionectomy did not greatly impair the rate response.[4] Bruce et al., on the other hand, studying anesthetized dogs, observed that the cardioacceleration produced by electrically induced muscular contraction was abolished not only by vagotomy, but also by excision of the upper thoracic sympathetic ganglia.[5] Donald and Shepherd, however, reported that even after total cardiac denervation, animals exhibited a large, though subnormal increase in heart rate during running.[6] Relatively little information is available concerning the relative roles of the two components of the autonomic nervous system in effecting the tachycardia of exercise in man. S. Robinson et al.[7] observed that at maximal levels of exercise atropine did not elevate heart rate, suggesting that vagal restraint is normally totally withdrawn at this level of activity. It is generally agreed that sympathetic blockade lowers the heart rate during exercise, a finding which suggests that sympathetic stimulation contributes to cardiac acceleration.[2, 8-10] No information is available, however, on the interplay between the two divisions of the autonomic nervous system during exercise, and the relative importance of each at varying levels of exercise has not previously been defined.

In the present investigation we examined the response to exercise in the supine position, since only in this way could the effects of exercise be separated from the effects of the upright position with its associated alterations in the background of autonomic activity. The results, presented schematically in figure 6, indicate that the speeding of heart rate at relatively mild exercise ($\dot{V}O_2$ up to 500 ml/min) is effected primarily by a withdrawal of parasympathetic restraint on the sinoatrial

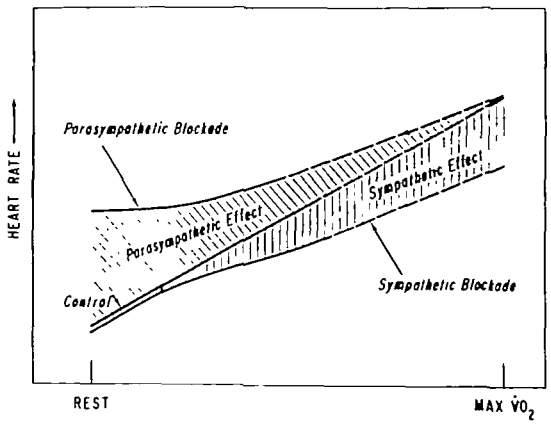

FIGURE 6

Schematic diagram showing the relative contributions of the sympathetic and parasympathetic systems to cardioacceleration at various levels of exercise. Broken lines are extrapolations based on published[2, 7] and unpublished data. Comparisons are between control (no blockade) state and parasympathetic or sympathetic blockade.

node. At higher levels of work, further withdrawal of parasympathetic restraint occurs, but increases in sympathetic activity become progressively more important in accelerating the cardiac rate. This interpretation is derived from a comparison of the rate responses at varying levels of exercise in the control study with those observed after either sympathetic or parasympathetic blockade; comparison of the rate response after blocking one division of the autonomic with the response after double blockade leads to a similar conclusion (fig. 7).

The possibility cannot be excluded that interference with the activity of one division of the autonomic nervous system might lead to compensatory changes in the other that would obscure to some extent the relative contribution of each of the two components. Interpretation of the results could also be complicated if the degree of blockade of either system was incomplete. This did not appear to be the case in the present experiments, however, since heart rate was constant, or increased only slightly at the higher levels of exercise during double blockade. It must be borne in mind that the autonomic nervous system is probably not the only mechanism concerned in speeding the heart during severe exertion. As already mentioned, the heart rate of dogs continues to increase substantially during heavy exercise even after complete cardiac denervation,[6] and the increases in rate seen in man during maximum exertion after double blockade (our laboratory, unpublished observations) may be due at least partly to nonautonomic influences.

In contrast to the mechanism of speeding during mild exercise, the increase in heart rate induced by upright tilting involved a significantly greater degree of sympathetic stimulation. This finding is relevant to the underlying mechanism responsible for the tachycardia of exercise. It has been suggested that this tachycardia is mediated primarily through the baroreceptor system.[11, 12] Since arterial pressure does not normally fall in man during exercise, this hypothesis in its simplest form appears to be untenable. It could be argued, however, that the baroreceptor system is 'reset' during exercise and responds as if the blood pressure were reduced. If this were the case, it might be expected that the tachycardia of exercise would be mediated by a balance of autonomic activity similar to that observed during tilting. The observation

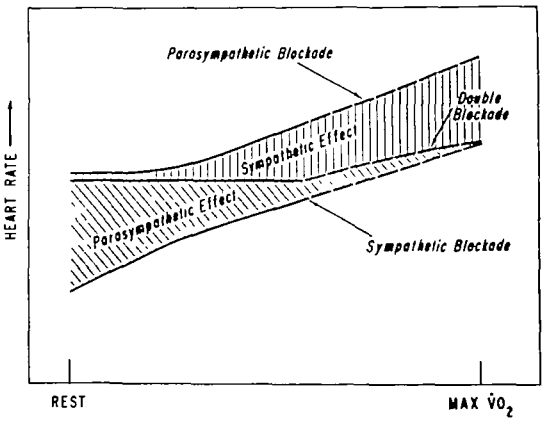

FIGURE 7

Schematic diagram showing the relative contributions of the sympathetic and parasympathetic systems to cardioacceleration at various levels of exercise. Broken lines are extrapolations based on published[2, 7] and unpublished data. Comparisons are between double blocked state and parasympathetic or sympathetic blockade alone.

that the mechanisms of speeding are in fact quite different suggests that the speeding of the heart during exercise is not mediated primarily through the baroreceptor system, but depends, at least partly, on some other mechanism.

Interest in the control of heart rate by the baroreceptor system dates back to the work of Marey, who in 1859 demonstrated the inverse relation between arterial pressure and heart rate.[13] Subsequent attempts to define the mechanisms involved in the efferent limb of this reflex more precisely have yielded conflicting results. Several investigations carried out in experimental animals demonstrated a reciprocal relation between the sympathetic and parasympathetic nervous systems in response to changes in arterial pressure.[14–16] However, on the basis of studies carried out in this laboratory, primarily on anesthetized dogs, it was concluded that when arterial pressure rises above control, the slowing of heart rate results from an increase in parasympathetic restraint, while when pressure falls below control levels, the resultant increase in heart rate is mediated primarily by the sympathetic nervous system.[3] The results of the present investigation seem to resolve this apparent discrepancy. One of the major differences in the experimental conditions between the investigations in which a reciprocal relation was demonstrated and the study in which it was not was the level of background sympathetic tone present. It has been demonstrated in this study that the background autonomic activity existing prior to the induced change in arterial pressure profoundly influences the results. In the sitting position, sympathetic activity is apparently of sufficient magnitude to permit slight cardiac slowing by withdrawal of sympathetic stimulation as pressure is raised. In contrast, in the supine position sympathetic activity appears to be minimal, since slowing does not occur consistently when arterial pressure is elevated after parasympathetic blockade.[3] On the other hand, during exercise in the upright position, when sympathetic activity is at a much higher level and parasympathetic activity is lessened, cardiac slowing consequent upon increases in arterial pressure results predominantly from reduction in sympathetic tone; increase in parasympathetic activity plays a relatively minor role.

The observations on the effects of exercise on the relation between arterial pressure and heart rate (figs. 2 and 3) are relevant to the question of the sensitivity of the baroreceptor mechanism under differing conditions. It has been suggested that the baroreceptor reflexes are suppressed during static muscular exercise.[17] On the other hand, Bevegard and Shepherd[18] recently observed similar decreases in heart rate at rest and during exercise when the baroreceptors were stimulated by application of subatmospheric pressure to the neck. Our findings are in accord with theirs and indicate further that similar responses occur at rest and during exercise when arterial pressure is decreased. It thus appears that the sensitivity of the baroreceptor system to induced changes of pressure does not undergo any substantial alteration in the transition from rest to exercise: at any given level of arterial pressure, the heart rate during exercise is higher than at rest, but when arterial pressure is changed, the magnitude of the alteration in heart rate is similar under both conditions.

Since the baroreceptor system remains active during exercise, it undoubtedly continues to play a modifying role in determining the heart rate, and presumably it also influences the level of inotropic stimulation of the myocardium. It might therefore be expected that if the level of cardiac stimulation became excessive, the resultant increase in output and arterial pressure would lead to a reflex reduction in sympathetic stimulation of the heart which would tend to lower the rate and contractile state to more appropriate levels. In this way, the baroreceptor system might be visualized as providing the feedback necessary for adjusting the cardiac performance during exercise so that the output was precisely adjusted to the fall in peripheral resistance, and so to the metabolic demand. Thus, even though the primary drive to in-

creased cardiac activity during exercise arose by some mechanism that was quite independent, the baroreceptor system might still be of crucial importance in determining the final level of cardiac stimulation attained.

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