

Effects of Beta-Adrenergic Blockade on the Cardiac Response to Maximal and Submaximal Exercise in Man *

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Many of the changes in cardiac performance that take place during exercise resemble those that result from stimulation of the sympathetic nervous pathways to the heart. It has therefore been thought likely that an increase in sympathetic nervous activity occurs during exercise and is important in the mediation of the associated cardiac response. To test this hypothesis a variety of experimental approaches have been employed. Several investigators have studied the manner in which surgical denervation of the heart in the dog affects its performance during exercise (1-7), and others have examined the effects of a variety of antiadrenergic drugs on the response to exercise in man (8-12). The results have been conflicting, with some groups ascribing little, if any, importance to the sympathetic system in the over-all performance of the heart (1, 2, 4, 6, 7, 9-11), whereas others believe that the sympathetic nerves do play a major role (3, 5, 8).

The interpretation of these earlier studies is complicated. In several of the experiments utilizing surgical denervation, section of the sympathetic nerves was not confined to those innervating the heart (1-3, 5). In others, the parasympathetic innervation of the heart was also interrupted (4-7), and some experiments were performed under general anesthesia (3). Furthermore, it is quite unknown to what extent conclusions based on studies in the dog can be applied to exercising man. In previous investigations on human subjects in which guanethidine or syrosingopine was administered, the sympathetic blockade involved not only the heart but the venous and arterial beds as well (8, 12). The recent development of spe-

cific β -adrenergic blocking agents has made it possible to attack this problem with greater precision, since these drugs block adrenergic effects on the heart, while exerting little if any effect on the response of the peripheral circulation to sympathetic nervous stimulation (13, 14). Three groups of investigators (9-11) have examined the effects of β -blockade on the cardiac output response to exercise in man, but have not observed any consistent or significant changes. Implicit in the results of these investigations is the conclusion that sympathetic stimulation of the heart is not necessary for a normal response to exercise. Before accepting this proposition we felt it necessary to study the effects of β -adrenergic blockade in a variety of circumstances and under strictly controlled conditions. Accordingly, we have 1) compared the effects of exercise with and without β -blockade on the same day in each subject, 2) determined the effects of β -blockade both at maximal and submaximal levels of exercise, 3) determined the effects of acute blockade during a steady level of exercise by measuring mixed venous O_2 saturation with a system permitting continuous *in vivo* recording, and 4) studied both normal subjects and patients with heart disease.

Methods

Seven healthy male volunteers, ranging in age from 21 to 42 years, and nine patients, ranging from 14 to 48 years, were studied. The diagnoses in the patients are shown in Tables I and II; four of them were considered to be in functional Class I (as described by the New York Heart Association), four in Class II, and one in Class III.

Exercise was performed on a motor-driven treadmill at varying speeds and grades. Oxygen uptake ($\dot{V}O_2$) was recorded by means of a continuous flow system and paramagnetic O_2 analyzer, the details of which have previously been described (15). Two methods were utilized for measurement of the cardiac output. In the dye dilution technique, indocyanine green was used as the indicator and was injected through a PE no. 90 or 100 catheter

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TABLE I
Circulatory effects of maximal exercise

Subject	BSA (Age)	Diagnosis	Heart rate				Cardiac output				
			R	E 3 min	E 4 min	E 5 min	R	E 3 min	E 4 min	E 5 min	
			beats/min				L/min				
A. Consecutive exercise											
T. D.	1.98 (21)	N'I	C ₁	91	180	180	186	4.61	19.20	20.12	19.52
			C ₂	96	176	182	184	4.56	18.90	20.71	20.61
G. H.	1.79 (25)	N'I	C ₁	94	176	178	180	4.38	21.65	22.97	21.06
			C ₂	104	178	182	182	3.87	21.00	20.39	24.25
D. B.	1.94 (21)	N'I	C ₁	94	184	189	192	5.41	25.18	23.80	23.03
			C ₂	101	184	189	194	4.65	22.81	22.50	22.53
E. S.	1.93 (42)	N'I	C ₁	78	149	154	160	5.45	17.79	18.53	21.92
			C ₂	95	154	154	160	5.84	18.19	19.16	19.38
		Mean	C ₁	89	172	175	180	4.96	20.96	21.36	21.38
			C ₂	99	173	177	180	4.73	20.23	20.69	21.69
B. Effects of β -blockade											
T. D.	1.98 (21)	N'I	C	92	180	182	188	4.58	19.95	18.72	21.07
			B	76	148	152	154	3.82	15.24	15.14	18.50
G. H.	1.79 (25)	N'I	C	90	171	175	180	3.70	18.87	20.14	22.62
			B	70	146	150	151	3.53	16.27	18.13	16.50
D. B.	1.94 (21)	N'I	C	79	190	196		4.62	18.94	20.78	
			B	82	137	144		3.92	16.79	16.71	
E. S.	1.93 (42)	N'I	C	79	152	156	159	5.16	16.04	16.70	18.68
			B	80	126	130	134	4.14	12.56	12.84	15.53
D. K.	2.16 (23)	N'I	C	75	176	177	183	6.57	31.50		
			B	71	137	139		6.33	19.68	22.50	
P. S.	1.96 (23)	N'I	C	93	171	174	176	5.14	22.69	21.29	23.21
			B	68	135	140	144	3.16	18.00	18.79	20.11
G. K.	1.80 (39)	N'I	C	63	140	146	151	4.72	16.88	16.55	18.50
			B	55	117	122	127	4.08	13.07	13.89	15.49
		Mean	C	82	169	172	171	4.93	20.70	19.03	20.82
			B	72	135	140	142	4.14	15.94	15.92	17.23
		p	NS	<0.01	<0.01	<0.01	<0.02	<0.01	<0.01	<0.01	<0.01
C. Effects of β -blockade											
C. H.	2.25 (42)	MS NSR	C	67	117	122	126	4.66	12.59	12.81	13.09
			B	58	88	90	90	4.27	9.16	9.18	9.28
J. L.	2.25 (28)	Post conv. NSR	C	94	150	152	155	6.86	29.02	27.63	
			B	61	108	110	112	4.76	17.87	17.35	17.30
W. S.	1.78 (38)	CM NSR	C	84	145	155	162	4.32	10.50	10.18	12.01
			B	78	110	114	114	3.24	9.52	8.58	9.10
G. S.	2.00 (48)	Post conv. NSR	C	94	155	158	160	4.00	14.63	15.15	15.73
			B	65	106	109	111	3.54	12.53	13.41	13.12
		Mean	C	85	142	147	151	4.96	16.69	16.44	13.61
			B	66	103	106	107	3.95	12.27	12.13	10.50

* N'I = normal subject; MS = mitral stenosis; NSR = sinus rhythm; Post conv. = idiopathic atrial fibrillation, post conversion; CM = cardiomyopathy; C₁ = first control study; C₂ = second control study; B = after propranolol; R = rest; E = exercise; TPR = total peripheral vascular resistance; LVMW = left ventricular minute work; Vo₂ = oxygen consumption; a-v O₂ = arteriovenous O₂ difference; NS = not significant (p > 0.05).

TABLE I
with and without β -adrenergic blockade*

Central venous		Arterial		TPR		LVMW		$\dot{V}O_2$	a-v O_2
R	E	R	E	R	E	R	E	E	E
mm Hg		mm Hg		dyne-sec-cm ⁻⁵		kg-m		ml/min	ml/100 ml
studies without β -blockade									
2	3	91	122	1,542	487	5.71	32.39	3,087	15.81
1	1	87	106	1,507	407	5.40	29.71	2,860	13.88
0	2.5	94	115	1,715	427	5.60	32.94		
-0.5	0	81	118	1,683	389	4.26	38.92		
0	-2	75	127	1,108	448	5.52	39.78	3,953	17.16
0	-2	83	125	1,426	450	5.25	38.30	3,971	17.63
-2	1	67	108	1,012	390	4.97	32.20	2,535	11.56
-1	-1	68	105	944	437	5.40	27.67	2,589	13.34
0	1	82	118	1,344	438	5.45	34.33	3,192	14.84
0	-0.5	80	114	1,390	421	5.08	33.65	3,140	14.95
in normal subjects									
6.5	5.5	93	112	1,509	404	5.79	32.09	3,282	15.58
5	7.5	90	94	1,778	376	4.68	23.65	3,096	16.74
-2	-0.5	93	113	2,051	401	4.68	34.76	3,370	14.90
-0.5	0	87	105	1,981	508	4.18	23.56	3,087	17.03
1.5	4.5	73	115	1,130	473	5.12	29.22	2,697	14.44
	7	63	86	1,187	406	3.55	18.16	2,639	16.99
-3	3	99	117	1,240	289	8.85	50.12		
1	9	93	92	1,161	337	8.01	24.62		
0.5	1.5	90	116	1,391	394	6.29	36.62	3,495	15.06
0	4.5	85	108	2,149	411	3.65	29.54	3,192	15.87
		105	140	1,777	605	6.74	35.22	2,462	13.31
		107	120	2,095	619	5.94	25.28	2,406	15.53
0.5	2.8	92	119	1,516	428	6.25	36.34	3,061	14.66
1.4	5.6	88	101	1,725	443	5.00	24.14	2,884	16.43
NS	<0.05	<0.05	<0.01	NS	NS	<0.02	<0.01	<0.05	<0.01
in patients									
		84	110	1,440	671	5.32	19.58	2,272	17.36
		86	97	1,609	835	4.99	12.24	1,959	21.11
6	5	88	108	955	298	8.21	40.58		
8	5	75	89	1,125	387	4.86	21.00		
8	3.5	107	109	1,831	702	6.29	17.80	1,080	8.99
7.5	3	96	100	2,182	852	4.23	12.38	923	10.14
		82	107	1,638	544	4.46	22.89	2,537	16.13
		68	102	1,535	621	3.27	18.20	2,460	18.75
		90	109	1,466	554	6.07	25.21	1,963	14.16
		81	107	1,613	674	4.34	15.96	1,781	16.67

TABLE II
Effects of β -adrenergic blockade during submaximal exercise in patients*

Subject	BSA (Age)	Diagnosis		Heart rate	Cardiac output		Pulmonary arterial O ₂ saturation		V̇O ₂	
					Mean	(Range)	Mean	(Range)	Mean	(Range)
					L/min		%		ml/min	
A. H.	2.07 (48)	LVH	C	84	10.56	(10.39-10.75)	40	(40-41)	1,058	(1,045-1,061)
		NSR	B	76	8.77	(8.55- 8.83)	30	(29-30)	1,055	(1,045-1,061)
W. Q.	1.78 (35)	MR	C	110	7.22	(6.96- 7.53)	55	(54-55)	555	(546- 577)
		AF	B	90	6.43	(6.22- 6.54)	48	(46-44)	577	(569- 585)
J. L.	2.25 (28)	Post conv.	C	112	24.55	(24.31-24.89)	56	(55-56)	1,771	(1,760-1,783)
		NSR	B	89	16.66	(16.52-16.79)	39	(39-40)	1,648	(1,645-1,652)
J. K.	2.03 (44)	IHD	C	130	14.32	(14.25-14.49)	62	(62-62)	876	(872- 887)
		NSR	B	102	12.28	(11.90-12.63)	57	(56-58)	838	(833- 841)
M. S.	1.63 (45)	MS	C	128	10.18†		48		843	
		NSR	B	86	8.08	(7.97- 8.11)	38	(37-38)	824	(824- 824)
R. P.	1.66 (14)	FM	C	145	15.34	(14.98-15.70)	42.5	(42-43)	1,646	(1,607-1,685)
		NSR	B	111	13.42	(13.34-13.57)	36	(36-37)	1,615	(1,599-1,630)
		Mean	C	118	13.70		50.6		1,125	
			B	92	10.94		41.3		1,093	
		p		<0.01	<0.05		<0.01		NS	

* LVH = left ventricular hypertrophy (unknown cause); MR = mitral regurgitation; AF = atrial fibrillation; IHD = ischemic heart disease; FM = functional murmur; mean = average of five observations at half-minute intervals. Other abbreviations as in Table I.

† Two measurements only.

that had been introduced percutaneously into a forearm vein and advanced to the superior vena cava or right atrium. Brachial arterial blood was sampled through an indwelling polyvinyl catheter by a motor-driven syringe. The details of the method used for measurement of cardiac output, including the technique for calibration of the cuvette densitometer, have been described elsewhere (12). The second method employed the Fick principle; V̇O₂ was recorded continuously as described above, and arterial blood was sampled intermittently in order to ensure that the O₂ saturation and content remained stable. Mixed venous O₂ saturation was recorded with an oximeter catheter the tip of which was located in the pulmonary artery, and the cardiac output was calculated at half-minute intervals. The fiberoptic oximeter catheter has been described in detail elsewhere (16). Briefly, a beam of light from an external source is transmitted through a bundle of glass fibers and reflected by the red blood cells onto a second bundle, which carries it to an external detector. After passage through a light chopper and appropriate filters the light impinges on a phototube, and the final output of the instrument is a linear function of O₂ saturation.

Systemic arterial and venous mean pressures were recorded by means of Statham pressure transducers, with zero pressure at the level of the mid-right atrium. The electrocardiogram, mean pressures, and indicator-dilution curves were recorded on an Electronics for Medicine recorder. Arterial O₂ content and capacity were estimated by the method of Van Slyke and Neill (17).

Left ventricular minute work in kilogram-meters was calculated as the product of cardiac output (liters per minute) and mean arterial pressure (centimeters H₂O), divided by 100. Peripheral resistance was calculated as the product of 1,332 and the difference between mean ar-

terial and venous pressures (millimeters Hg) divided by the cardiac output (milliliters per second).

All studies were performed with subjects in the post-absorptive state. They were trained regularly on the treadmill at various levels of activity for about a week before any of the definitive measurements were made. Beta-adrenergic blockade was produced by the intravenous administration of propranolol,¹ 0.15 mg per kg. This drug has been shown to be an effective β -adrenergic blocking agent both in experimental animals and in man (18). In the present study it was shown in eight subjects that the dose used produced a degree of blockade that caused at least a tenfold reduction in the sensitivity to infused isoproterenol. McNerny, Gilmour, and Blinks have shown *in vitro* that the dose of propranolol required to produce complete β -blockade is several orders of magnitude less than that required to produce direct depression of the contractile state of the myocardium (19).

Exercise endurance. The conditions of exercise that produced total exhaustion after 3 to 6 minutes were determined by repeated trial. This level of exercise was then performed twice on each of 2 days with a 45-minute rest between each run; the time at which the subject signaled he could no longer continue was recorded and was taken as the "endurance time." The first run of each pair was regarded as the control. On the first experimental day, 5 minutes before the second period of exercise, the subject was given either propranolol, 0.15 mg per kg iv, or an equal volume of saline, without being aware which he was receiving. On the second day he was given whichever preparation he had not received on the previous occasion. The endurance time for the second bout of exer-

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

cise was expressed as the percentage change from the control run for that day.

Maximal exercise. The conditions of work that would produce total exhaustion in $5\frac{1}{2}$ to 6 minutes after β -adrenergic blockade were determined in each subject, and these conditions were used for the definitive investigation. The study began with a warm-up at a submaximal level of work. The cardiac output was then determined in duplicate by the dye-dilution method with the subject standing at rest. The value presented in the results is the mean of the two determinations; the second of the paired measurements differed from the first by an average of 7.6%. Single determinations of cardiac output were made after 3, 4, and 5 minutes of maximal exercise. $\dot{V}O_2$ was recorded continuously during exercise, and mean arterial and central venous pressures were recorded except when cardiac output was being determined. After completion of exercise and a 45-minute rest period, either propranolol (all of the seven subjects) or placebo (four of the seven subjects) was administered, and measurements were repeated at rest and during an identical bout of exercise.

Submaximal exercise. The subjects performed treadmill exercise of mild to moderate intensity, and propranolol was administered intravenously after a steady state had been reached. In the six patients in whom pulmonary arterial O_2 saturation was recorded with the fiberoptic oximeter catheter, the attainment of a steady state could be checked directly by observation of $\dot{V}O_2$, mixed venous O_2 saturation, and heart rate. When these values had been constant for at least 5 minutes, the drug was given and the recordings were continued until a new steady state had been reached and maintained for several minutes. In the three normal subjects in whom the dye dilution technique was employed, cardiac output was measured during the fifth and seventh minutes after the start of exercise, at which time a steady state had been reached, so far as could be determined from the $\dot{V}O_2$, heart rate, and mean arterial pressure. As exercise continued at the same level, propranolol was administered, and after an interval of at least 5 minutes the cardiac output was again determined in duplicate. The values for cardiac output presented in the Results are the averages of the duplicate determinations.

Results

Exercise endurance. In the five normal subjects and four patients who were studied, administration of a placebo did not consistently or significantly alter the endurance time, which was 5% less on the average after saline than during the control run on the same day. After propranolol, however, there was a consistent fall in the endurance time, which was 40% less on the average than the control. The differences in the effects of propranolol and placebo on the endurance time were statistically significant ($p < 0.01$, Figure 1).

Maximal exercise. In four of the normal subjects, control studies were performed in which the first exercise period was followed by a second without the administration of propranolol. There were no consistent or significant differences between the circulatory measurements during the two successive periods of exercise (Table IA).

In the seven normal subjects in whom the action of propranolol was studied, the resting values of cardiac output, mean arterial pressure, and left ventricular minute work were significantly reduced after the drug (Table IB). When the values during the second period of exercise were compared to those of the first, it was noted that the drug caused significant reductions of heart rate (average, -19%), cardiac output (-22%), mean arterial pressure (-15%), left ventricular minute work (-34%), and maximal $\dot{V}O_2$ (-6%), but increased the calculated arteriovenous O_2 difference (+12%) and the central venous pressure (+2.8 mm Hg) (Table IB, Figure 2). In the four patients with heart disease studied at maximal levels of exercise, the effects of propranolol on circulatory dynamics were similar to those noted in the seven normal subjects, both at rest and during exercise. However, the absolute levels of $\dot{V}O_2$ and cardiac output achieved during exercise were usually lower than in the normal subjects (Table IC).

Submaximal exercise. When propranolol was given to six patients during the course of submaximal exercise, a depression of the circulatory response commenced 1 to 2 minutes after the injection, and a new steady state was achieved within 5

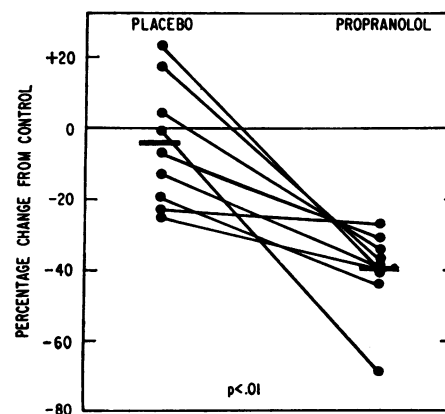


FIG. 1. THE EFFECT OF PROPRANOLOL AND PLACEBO ON THE ENDURANCE TIME FOR MAXIMAL EXERCISE.

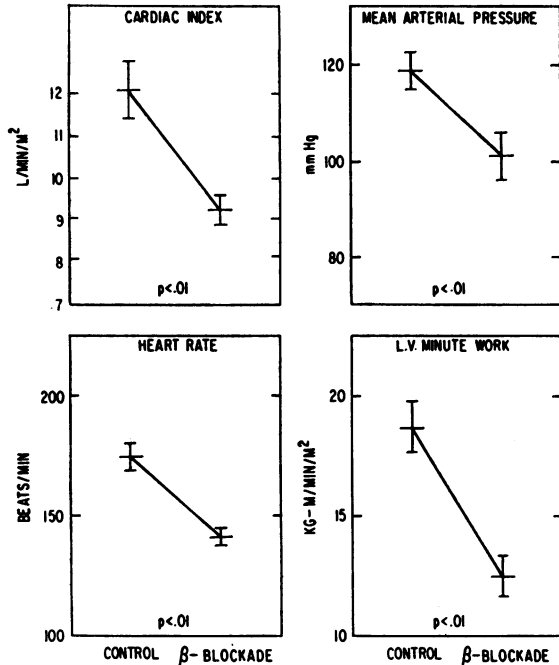


FIG. 2. THE EFFECTS OF β -BLOCKADE ON FOUR CIRCULATORY VARIABLES DURING MAXIMAL EXERCISE IN NORMAL SUBJECTS. The mean values (\pm standard error of the mean) are shown for each variable; for cardiac index and heart rate $n = 7$, and for mean arterial pressure and left ventricular minute work $n = 6$. The values from which the means were calculated are those for the last minute of exercise in which determinations were made.

minutes. In all patients a decrease occurred in heart rate (average, -21%), and pulmonary arterial O_2 saturation fell from an average level of 50.6% to 41.3% ; $\dot{V}O_2$ and arterial O_2 saturation and content were not significantly changed. When a new steady state had been reached, the cardiac output, calculated by the Fick method, was found to have stabilized at a level that averaged 18% below control (Table II, Figure 3).

When propranolol was given to three normal subjects during submaximal exertion, cardiac output measured by the dye-dilution method declined in every case (average, -16%), as did heart rate (-21%), mean arterial pressure (-7%), and left ventricular minute work (-22%). Central venous pressure remained constant throughout the control period, but always rose by a small amount after the drug (2 to 3 mm Hg) to reach a new steady level (Table III).

Discussion

The results of this investigation indicate that the acute induction of β -adrenergic blockade impairs the circulatory response to exercise. Heart rate, cardiac output, and mean arterial pressure were slightly, although consistently, reduced in normal subjects and in patients with cardiac disorders, and

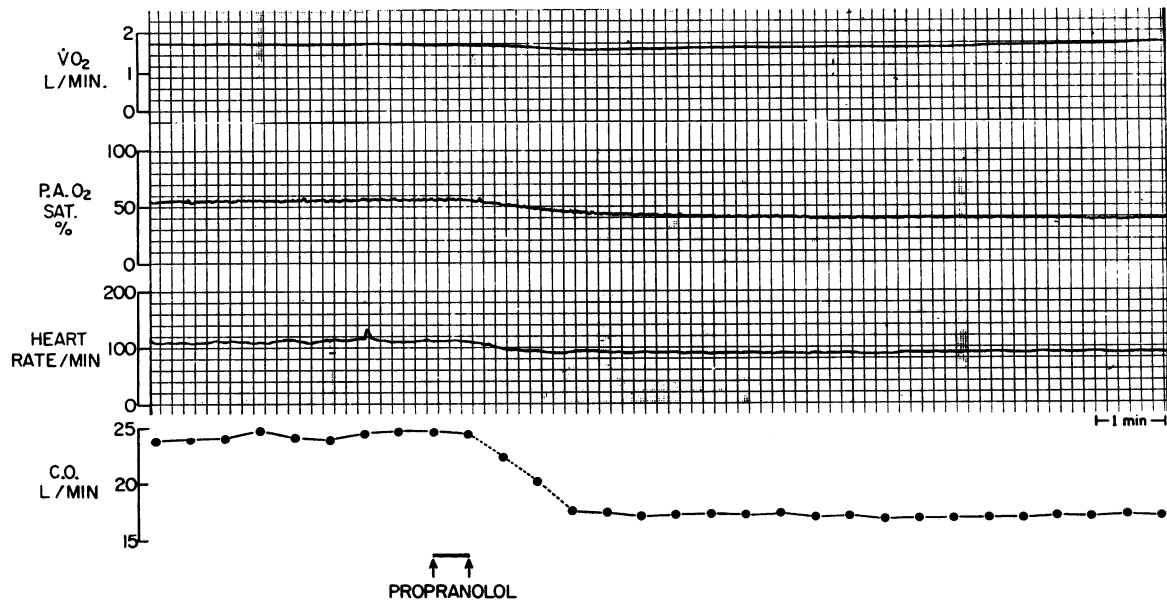


FIG. 3. THE CIRCULATORY EFFECTS OF ACUTE INDUCTION OF β -ADRENERGIC BLOCKADE DURING STEADY SUBMAXIMAL EXERCISE. Recording obtained from patient J.L., showing from above downwards: oxygen uptake (tracing has been shifted 1 minute to the left to allow for instrumental delay); pulmonary arterial O_2 saturation; heart rate; cardiac output (calculated by the Fick principle).

the changes were observed at both maximal and submaximal levels of work. The reliability of the results is substantiated by the finding of comparable reductions of cardiac output utilizing two different methods of measurement, the indicator-dilution technique and the direct Fick method. The possibility that simple repetition of a bout of exercise was responsible for the reduced circulatory response after propranolol can be excluded, since there were no consistent differences in the circulatory response when two consecutive bouts of maximal exercise were carried out without β -blockade. Moreover, when propranolol was injected in the course of steady-state levels of exercise, a small but unequivocal fall in cardiac output was always observed.

The decline in mean arterial pressure that was seen after propranolol at rest and during exercise can be accounted for almost entirely by the reduction of cardiac output, since calculated systemic vascular resistance was not consistently altered. These findings are not in agreement with those of Schröder and Werkö, who noted little effect of β -blockade on cardiac output and attributed the fall in arterial pressure observed during exercise to a reduction of systemic vascular resistance (11).

The effect of propranolol on O_2 uptake during exercise was a function of the intensity of the muscular effort. At submaximal levels of work, $\dot{V}O_2$ was unchanged, the fall in cardiac output after β -adrenergic blockade being fully compensated for by an increase in the arteriovenous O_2 difference. At maximal levels of work, the fall in cardiac output was incompletely compensated for, and the maximal $\dot{V}O_2$ achieved was therefore reduced. The reduction in O_2 uptake, and therefore in the O_2 delivery to the tissues during maximal exercise, presumably accounts for the striking reductions in the endurance times for maximal exercise that were produced by β -blockade, although other peripheral effects cannot be excluded. In this connection it is of interest that Donald, Milburn, and Shepherd observed that chronic cardiac denervation did not impair the racing speed of greyhounds (6). However, the duration of the sprints was relatively short (less than 36 seconds), and it seems possible that the running speed that can be achieved during such a brief bout of exercise may not be critically dependent on O_2 delivery to the tissues (20-22).

The finding that propranolol resulted in a small but significant reduction of cardiac output at rest indicates that sympathetic nervous stimulation of the heart is of some importance in maintaining cardiac output even in the resting state, at least when the subject is upright. The reduction of cardiac output during exercise appears to be due to interference with two fundamental mechanisms. First, the increase in heart rate is less after β -adrenergic blockade, and second, the normal augmentation of myocardial contractility is almost certainly prevented. Evidence for the latter effect has been obtained from other studies in this laboratory (23), in which propranolol was shown to abolish the shift of the myocardial force-velocity curve normally induced by exercise in man; changes due to alterations in heart rate were avoided by atrial pacing.

It is of interest that even when the heart is deprived of its normal sympathetic stimulation, the cardiac output is still able to rise substantially during exercise. Thus, although our findings indicate that sympathetic stimulation of the heart contributes to the response to exercise, its importance in increasing the cardiac output appears to be relatively small, at least in normal subjects, or in those with mild impairment of cardiovascular reserve. However, even if nervous control of the heart is not of major importance in increasing the output during exercise, it may be of significance in allowing the heart to make rapid adjustments to changes in demand. Donald and Shepherd have shown that in dogs subjected to cardiac denervation both the heart rate and cardiac output increase more slowly than normal as exercise is begun, even though the final cardiac output achieved does not appear to be significantly reduced (7). A number of possible explanations for the increase in cardiac output during exercise after β -adrenergic blockade may be invoked. First, the blockade of endogenous sympathetic nerve stimuli may be less than that to infused catecholamines. Second, several mechanisms may serve to mitigate the loss of sympathetic stimulation of the heart. Withdrawal of vagal impulses may be responsible in part for the increase in heart rate that still occurs on exercise after β -blockade. In addition, an increase in venous return to the heart can still occur as a result of systemic venoconstriction and the pumping action of the skeletal muscles; it is thus possible

TABLE III
*Effects of β -adrenergic blockade during submaximal exercise in normal subjects**

Subject	BSA (Age)	Diagnosis		Heart rate	Cardiac output	Mean pressure					a-v O ₂
						Central venous	Arterial	TPR	LVMW	Vo ₂	
	m ² (years)			beats/ min	L/min	mm Hg	dyne-sec- cm ⁻⁵	kg-m	ml/min	ml/100 ml	
G. H.	1.79 (25)	N'I	C	119	8.81	1.5	89	794	10.66		
			B	95	6.31	3.5	79	956	6.78		
D. B.	1.94 (21)	N'I	C	139	10.41	2	89	668	12.60	1,240	11.91
			B	102	9.55	5	85	669	11.04	1,240	12.98
E. S.	1.93 (42)	N'I	C	106	9.53	-2	64	553	8.29	750	7.87
			B	90	8.30	0.5	60	573	6.77	750	9.04
		Mean	C	121	9.58	0.5	81	672	10.52		
			B	96	8.05	3	75	733	8.20		

* Abbreviations as in Table I.

that the contractile activity of the sympathetically denervated heart is augmented by an increase in end-diastolic filling pressure and fiber length, i.e., through the operation of the Frank-Starling mechanism. This mechanism may indeed be operative, since in all six normal subjects in whom central venous pressure was measured during exercise (Tables IB and III), an increase of 2 to 3 mm Hg occurred after β -adrenergic blockade. Finally, the metabolic vasodilatation that lowers peripheral resistance during exercise and tends to augment cardiac output still occurs after sympathetic blockade.

In conclusion, this investigation has shown that although sympathetic stimulation of the heart plays a significant role in the circulatory response to exercise, its contribution is not very great quantitatively, and it would appear that sympathetic stimulation of the heart is only one of a number of mechanisms by which the cardiac output is augmented during exercise.

Summary

The effect of β -adrenergic blockade on the circulatory response to maximal and submaximal exercise was studied in seven normal subjects and in nine patients with cardiac disorders. Beta-adrenergic blockade invariably caused a reduction in heart rate, cardiac output, mean arterial pressure, and left ventricular minute work; arteriovenous O₂ difference increased and there was a small rise in central venous pressure. As an apparent consequence of the impaired circulatory re-

sponse to exercise both maximal Vo₂ and capacity for strenuous exertion were reduced. However, even after β -adrenergic blockade, cardiac output still rose substantially during exercise. We conclude that sympathetic nervous stimulation of the heart plays a significant, although quantitatively limited, role in mediating the normal response to exercise in man.

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ERRATUM

In the paper entitled, "Alterations of Ventilation to Perfusion Ratios Distribution Associated with Successive Clinical Stages of Pulmonary Emphysema," by Claude Lenfant and William R. Pace, Jr., published in the September issue (page 1566), the following corrections should be noted:

On page 1569 in the fourth paragraph of the "Calculations," read $\dot{V}_{A1}/V_{L1} = 2.3/M$ rather than $V_{A1}/V_{L1} = M/2.3$.

On page 1577 in Table V under column " \dot{V}_{A1}/\dot{Q}_1 ," read 7.71 rather than 1.71. Under column "Range \dot{V}_A/\dot{Q} ," the numbers should be 2.00, 1.48, 1.56, and 7.40.

On page 1579 in the second paragraph, the reference number should be 14 rather than 12.