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Research Article

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EFFECTS OF OXYGEN BREATHING ON THE HEART RATE, BLOOD PRESSURE, AND CARDIAC INDEX OF NORMAL MEN—RESTING, WITH REACTIVE HYPEREMIA, AND AFTER ATROPINE *

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Oxygen breathing has been used extensively to treat a wide variety of clinical disorders. An understanding of its effects on the normal circulation, at rest and under conditions of increased cardiac output, is fundamental to the understanding of the efficacy of oxygen therapy in clinical situations. Furthermore, interpretation of physiologic data concerning the effects of hyperoxia on the regional circulations requires definition of any changes in cardiac output or over-all peripheral circulation that occur during oxygen breathing.

This investigation was undertaken for two purposes: *1*) to evaluate the effects of oxygen breathing on the heart rate, systemic blood pressure, and cardiac index of normal men, resting, after atropine, and subjected to the circulatory stress of reactive hyperemia; and *2*) to study the higher ranges of oxygen-sensitive chemoreceptor activity in man.

METHODS

Fifteen normal male subjects, ages 21 to 32, were used in this study. Each rested supine 30 to 45 minutes prior to the beginning of measurements. Heart rates were recorded electrocardiographically. Electronically damped mean brachial arterial blood pressure was recorded from an indwelling no. 18 Cournand needle and P23D Statham strain gage.

Cardiac output was determined by an indocyanine green dilution method. Approximately 1 ml (5 mg per ml) of the dye was injected abruptly into a large intrathoracic vein, either superior vena cava or innominate vein, using a syringe-catheter system, calibrated to deliver a known quantity of dye ± 0.05 mg. All injections were made during the end-expiratory phase of respiration. A Harvard withdrawal pump was used to draw blood through a Waters XP-100A densitometer from the brachial arterial needle at a rate of 19.4 ml per minute. The needle through cuvet dead space of the system was 0.33 ml. Blood for calibration of the densitometer was obtained prior to the first dye injection and, at the conclusion of each experiment, serial dye dilutions were made using this blood. With the identical tubing and flow rate, these known blood-dye mixtures, with concentrations of 0, 0.19, 0.38, and 0.76 mg per 100 ml, were pumped through the densitometer. Calibration slopes obtained in this way were linear and were used in the calculation of the cardiac ouput. Preliminary observations with this densitometer, with concentrations from 0 to 2.5 mg per 100 ml, showed satisfactory linearity at concentrations below 1.0 mg per 100 ml. In only two of the experiments were concentrations above 0.76 mg per 100 ml observed. In further preliminary observations it was shown that calibration slopes in venous and arterial blood were the same. The change in cardiac output when subjects breathed oxygen was also observed when output was measured with an intermittent sampling technique, with spectrophotometric analysis of the serum concentrations of dye. Cardiac output was calculated by the Hamilton semilog replotting method (1). Duplicate determinations of cardiac output under similar conditions but often separated by as much as 60 minutes were reproducible with a mean difference of 5.0 per cent. In atropinized subjects, whose heart rates were less subject to variation, the mean difference was 3.3 per cent. Systemic resistance was calculated as the ratio of mean brachial arterial pressure to cardiac output, zero right atrial pressure assumed.

Artery-to-artery circulation time was recorded directly from the dye curves as peak-to-peak time. This circulation time is not a measure of any single or simple hemodynamic factor but is a useful and easily measured index of change of circulatory behavior. Mean circulation time and central blood volume were calculated as described by Hamilton, Moore, Kinsman and Spurling (2).

Using a low-resistance flutter valve, mouthpiece, and nose clip, all subjects breathed air and oxygen from Douglas bags. One of two sequences was used: either air, oxygen, air, oxygen; or oxygen, air, oxygen, air.

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† United States Public Health Service Postdoctoral Research Fellow.

TABLE I

Effects of 100 per cent oxygen breathing on resting heart rate, cardiac index, and stroke volume of normal men before and after atropine

	Cardiac index				Heart rate				Stroke index			
	Before atropine		After atropine		Before atropine		After atropine		Before atropine		After atropine	
Subject	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
	L/min/m²		*L/min/m²*		*beats/min*		*beats/min*		*ml/m²*		*ml/m²*	
JO	2.59	2.02			75	68			35	31		
DJ	2.91	2.66			70	56			42	48		
EP	2.43	2.08			74	67			32	30		
MP	3.98	3.36			74	68			49	53		
DL	2.49	2.43			59	53			42	46		
JH	2.89	2.76			63	58			47	48		
WM	3.36	3.27			79	74			43	44		
DC	2.98	2.43			58	55			52	44		
BR	2.76	2.65			81	78			35	33		
DF	3.12	2.65	2.93	2.84	67	63	72	73	47	42	35	34
CC	3.44	2.97	3.11	2.87	79	73	99	96	44	41	31	30
WM	2.38	2.25	3.35	3.33	59	55	86	86	40	41	39	39
DR	3.57	2.14	3.96	3.84	62	56	96	96	58	56	41	40
TS	3.83	3.33	4.15	4.07	84	78	99	98	46	44	42	42
KH	2.49	2.13	3.51	3.51	62	56	122	129	39	40	39	34
Mean	3.01	2.67	3.50	3.41	70	64	96	96	43	43	38	37
SD	0.52	0.47	0.47	0.50	8.7	8.9	16	17	7	7	3	4
p*	<0.001		0.10		<0.001		>0.5		0.5		0.2	

* Paired-comparison *t* test.

The two air and two oxygen values were averaged. After determination of resting values, 7 subjects were given 2.0 mg of atropine sulfate intramuscularly, and observations were repeated 1 hour later when typical atropine flush, dryness, and tachycardia had appeared. Six subjects, after preliminary measurements, had pneumatic thigh tourniquets inflated to 250 mm Hg abruptly. These tourniquets were left in place 20 minutes and then deflated suddenly. During the last 10 minutes of occlusion and 5 minutes after release, the sub-

TABLE II

Effects of 100 per cent oxygen breathing on resting mean brachial blood pressure, calculated systemic resistance, and artery-to-artery circulation time before and after atropine in normal subjects

	Mean blood pressure				Resistance				Artery-to-artery circulation time			
	Before atropine		After atropine		Before atropine		After atropine		Before atropine		After atropine	
Subject	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
	mm Hg		*mm Hg*		*mm Hg/L/min*		*mm Hg/L/min*		*sec*		*sec*	
EP	96	93			22.5	24.1			23	26		
DL	84	89			18.4	19.8			22	23		
JH	87	90			15.5	16.5			17	19		
DC	93	96			15.3	19.3						
DF	106	108	94	102	16.9	20.2	18.1	18.1	19	20	19	19
CC	90	94	110	115	13.5	16.3	18.4	20.7	16	19	17	17
DR	86	89	97	98	12.5	14.5	12.6	13.2	18	20	14	17
TS	110	109	114	120	14.3	16.4	13.8	14.6	17	18	15	15
KH	91	90	105	107	17.5	20.1	14.2	14.2	21	22	16	16
IS	80	83	102	104								
Mean	92	94	104	108	16.3	18.5	15.4	16.2	18	21	16	17
SD	9.0	9.0	8.5	9.1	4.6	2.9	2.6	3.1	3	3	2	
p*	0.05		0.025		<0.001		0.200		0.005		0.200	

* Paired-comparison *t* test.

TABLE III

Effects of 100 per cent oxygen breathing (1 atm) on mean circulation time and central blood volume of 12 normal resting men

	Mean circulation time		Central blood volume	
	Air	O_2	Air	O_2
	sec		*ml*	
Mean	19.4	21.5	1,800	1,790
SD	3.3	4.0	210	240
p*	<0.001		>0.5	

* Paired-comparison *t* test.

jects breathed either air or oxygen. After a rest period of 30 minutes the procedure was repeated with breathing of the opposite gas. Heart rate and cardiac output were measured 5 minutes before and 15 seconds after release of the tourniquets. Dye-dilution methods may not be wholly valid during the rapidly changing state following tourniquet release; however, provided the timing of injection is kept constant, the factors detracting from the validity of the method are random and would therefore only increase the variability of the results. During oxygen breathing the values obtained for cardiac output were regularly less, thus the decrease is statistically real, although the magnitude of decrease in a given instance is subject to considerable variability.

The heart rates of 10 normal male subjects, ages 21 to 32, were recorded while they breathed oxygen mixtures: 15, 21, 30, 40, 60, 80, and 100 per cent. Each gas cylinder was assigned a number, and the sequence of their use was determined from a random number table (3). In no case did the subjects know the sequence of mixtures to be used. The heart rate was counted from an electrocardiogram taken 7 to 10 minutes after the subject began to breathe the mixture from the Douglas bag system. Arterial blood was analyzed for pH and P_{CO_2} with glass electrodes at the end of the period of breathing air and 30, 60, and 100 per cent oxygen.[1] Oxygen saturation was determined after air and 100 per cent oxygen breathing by the method of Van Slyke.

A paired comparison *t* test, analysis of variance, and estimation of deviation from linearity were used in the statistical analysis of the data obtained (3). With the paired comparison test it is possible to detect small systematic changes in an experimental method having a relatively large variability. Thus the dye-dilution method, with a 5 per cent mean variation in our hands, may be used to detect a change in cardiac output which is not much larger, because the inherent variability of the method is random while the change induced by oxygen breathing is not.

RESULTS

One hundred per cent oxygen breathing decreased the heart rate (70 ± 8.7 to 64 ± 8.9 beats per minute) and cardiac index (3.01 ± 0.52 to 2.67 ± 0.47 L per minute per m^2) of the resting normal subjects without a change in stroke index

[1] Instrumentation Laboratories, Inc., Boston, Mass.

TABLE IV

Effects of 100 per cent oxygen breathing on the circulatory response to tourniquet hyperemia

	Cardiac index						Heart rate						Artery-to-artery circulation time					
	Air			Oxygen			Air			Oxygen			Air			Oxygen		
Subject	R*	T on†	T off‡	R	T on	T off	R	T on	T off	R	T on	T off	R	T on	T off	R	T on	T off
	L/min/m²						*beats/min*						*sec*			*sec*		
JO	2.59	2.49	3.54	2.02	1.92	2.03	75	70	92	66	62	78	14	22	18	24	25	20
DJ	2.91	3.35	4.61	2.66	3.06	3.21	70	73	84	56	60	72	18	18	18	23	22	21
EP	2.43	3.20	5.51	2.08	2.44	5.09	74	73	76	67	62	78						
DL	2.49	3.15	4.77	2.43	2.29	3.25	59	56	75	53	56	64	22	21	14	23	28	24
JA	2.89	3.21	4.60	2.78	3.24	4.81	63	64	82	58	58	84	17	17	14	19	17	16
WM	3.36	3.66	4.52	3.27		4.08	79	80	100	74		86	15	17	14	17		20
BF							63	66	80	56	56	84	18	18	18	23	22	21
Mean	2.77	3.18	4.59	2.54	2.59	3.74	69	69	86	61	59	75	17	18	16	21	22	21
SD	0.36	0.38	0.63	0.47	0.23	1.14	6	8	10	7	5	9	3	3	2	3	4	3
p§	0.02		0.01		>0.5	0.01		0.01			>0.5	0.005	0.4	0.05			>0.5	0.05
p§ (air-O_2)	0.025						0.025						0.001					
	0.025						0.025						0.005					
	0.01						0.01						0.025					

* Resting.
† Tourniquet inflated 15 minutes.
‡ During phase of reactive hyperemia.
§ Paired-comparison *t* test.

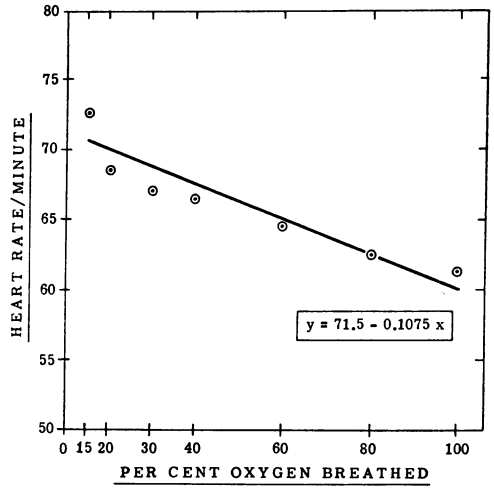

FIG. 1. EFFECTS OF BREATHING INCREASED OXYGEN CONCENTRATIONS ON THE HEART RATES OF TEN NORMAL RESTING MEN.

TABLE V

Effects of breathing increased oxygen concentrations on the heart rates of 10 normal resting men *

Subject	15%†	21%	30%	40%	60%	80%	100%
16	69.4	68.0	70.7	67.1	66.6	65.2	62.8
17	68.0	63.5	62.0	61.0	55.6	53.8	54.2
18	73.0	72.6	72.0	70.8	68.8	68.0	68.8
19	68.6	66.8	75.0	76.8	69.0	67.4	68.4
20	73.4	62.0	55.6	57.0	57.0	54.0	51.5
21	60.6	65.5	57.6	64.6	56.5	56.5	54.0
22	91.5	86.0	83.0	83.4	80.4	80.4	79.8
23	77.0	62.4	64.2	63.3	61.6	60.5	58.7
24	79.0	71.4	68.4	68.0	71.1	69.0	65.4
25	62.6	61.6	62.4	55.6	57.6	52.2	51.6
Mean	72.3	68.2	67.1	66.8	64.5	62.7	61.5
SD	8.8	7.3	8.4	8.6	8.3	8.9	9.2

* Probability that heart rates at 21 and 100% are the same $=< 0.001$. Probability that relationship of heart rate to oxygen concentration over 15 to 100% range deviates from linearity = 0.025.
† % O_2 in inspired gas mixture.

(43 ± 7 to 43 ± 7 ml per m^2). After administration of atropine the effects of oxygen breathing on heart rate and cardiac index were eliminated (Table I). Mean blood pressure (Table II) was increased after oxygen breathing (93.6 ± 9.0 to 95.3 ± 9.0 mm Hg) as was over-all systemic resistance (16.3 ± 4.6 to 18.5 ± 2.9 U), and artery-to-artery cirulation time (18 ± 3 to 21 ± 3 seconds). These effects of oxygen on systemic resistance and circulation time were not observed after atropine. Similarly, oxygen breathing increased the mean circulation time (19.4 ± 3.3 to 21.5 ± 4.0 seconds) and produced no change in central blood volume (Table III).

Observations of the changes after release of arterial thigh tourniquets confirm the data of Stead and Warren: there is a very rapid increase in cardiac output, heart rate, stroke volume, and decrease in circulation time after the release of the tourniquets (4). As shown in Table IV, these changes were greatly decreased by oxygen breathing. The stroke index, as calculated from the data in Table IV, was not affected by oxygen breathing. After inflation of the tourniquets, air breathing was associated with a slight increase in cardiac index (2.77 ± 0.36 to 3.18 ± 0.38 L per minute per m^2, $p = 0.02$). This change was not observed during oxygen breathing.

Figure 1 and Table V show the effects of hyperoxic breathing on the heart rates of normal resting men. Over the range of 15 to 100 per cent oxygen inspired, a progressively decreasing heart rate occurred. Statistically, this is a linear relationship ($p = 0.025$).

A slight increase in arterial pH was observed when the subjects breathed 100 per cent oxygen (7.39 ± 0.02 to 7.43 ± 0.04, $p = 0.01$). This change is probably related to the slight hyperventilation that occurs when normal subjects breathe 100 per cent oxygen (5). No large change in P_{CO_2} was observed, and the mean arterial oxygen saturation during air breathing was 95 per cent (Table VI).

TABLE VI

Effects of oxygen breathing on arterial pH, P_{CO_2}, and oxygen saturation of 7 normal subjects

	Air	30% O_2	60% O_2	100% O_2
pH	7.39 ± 0.02	7.40 ± 0.01	7.39 ± 0.02	7.43 ± 0.04*
P_{CO_2} (*mm Hg*)	38 ± 2	42 ± 3	41 ± 3	39 ± 3†
O_2 saturation	95 ± 3%			

* pH during 100% oxygen breathing > pH during air, 30% or 60% oxygen breathing; $p = 0.01$.
† P_{CO_2} not significantly different; $p = 0.2$.

DISCUSSION

Careful studies of the circulatory effects of oxygen breathing in normal man began with Parkinson, in 1912, who showed a slight but consistent decrease in the resting heart rate of normal men breathing oxygen (6). This was subsequently confirmed by numerous other workers (7–10). Alella and Meda, in 1948, reported that this effect on heart rate was not present in atropinized subjects (11). They found that it did not appear until the alveolar Po_2 exceeded 300 mm Hg, obtained by breathing an oxygen concentration of approximately 50 per cent (12). Benedict and Higgins, in 1911, observed that breathing oxygen concentrations above 40 per cent decreased the resting heart rate of normal men (13). Asmussen and Neilsen were able to detect a decrease in heart rate when normal, strenuously exercising men breathed oxygen (14). Cullen, Weir and Cook found decrease in heart rate when oxygen breathing was added to artificial-fever therapy (15). In animal experiments, Whitehorn and Bean showed an early chronotropic effect of hyperoxia in decerebrate dogs only if the vagi were intact (16). The same workers reported a decrease in frequency of contraction of the isolated frog heart exposed to high oxygen concentrations, but only after 3 to 6 hours (17). The effect in normal men occurs almost immediately (18).

Alveryd and Brody, in 1948, reported a 5.7 per cent increase in diastolic pressure in normal subjects breathing oxygen (18). Barratt-Boyes and Wood found a 4 per cent increase in mean radial pressure and a 10 per cent increase in over-all systemic resistance in a group of normal subjects breathing pure oxygen but no change in cardiac output as measured by the Fick technique (10). Grollman earlier had found no change in cardiac output as measured with his acetylene method (19). At least three independent groups reported decreases in cardiac output in normal subjects breathing oxygen as estimated by ballistocardiograph—decreases averaging 8 to 10 per cent and largely due to decreased heart rate (5, 8, 20). Using a roentgenkymographic technique, Keys, Stapp and Violante reported a 10 per cent decrease in cardiac output under similar conditions (9). In a group of patients with ventricular septal defect, Marshall, Swan, Burchell and Wood have reported that 100 per cent oxygen breathing decreased cardiac output as measured by an indicator-dilution method (21).

Nevertheless, it is commonly assumed that hyperoxia—that is, oxygen tensions above those obtained when one breathes air—has little effect on chemoreceptors (22). This concept is supported by direct observations of action potentials in the carotid body nerves of the cat by von Euler, Liljestrand and Zotterman, who found no evidence of chemoreceptor activity when arterial oxygen saturations were above 97 per cent (23). Witzleb, Bartels, Budde and Mochizuki, using a somewhat similar technique, found no evidence of oxygen-sensitive chemoreceptor activity at arterial Po_2's above 110 mm Hg (24).

The results of the present study demonstrate that breathing concentrations of oxygen above 21 per cent produces a vagus-dependent decrease in heart rate and a rate-dependent decrease in cardiac index. The possibility of a lesser direct myocardial effect of hyperoxia is not excluded. Furthermore, 100 per cent oxygen breathing produces an increase in mean arterial blood pressure and systemic resistance which is, at least in part, related to the decrease in cardiac output, although direct or reflex vascular effect of hyperoxia is not excluded, since the blood pressure of the atropinized subjects rose substantially during oxygen breathing. The observed changes in circulation times probably reflect the composite effect of decreased cardiac output and increased systemic resistance.

That these effects are not due to the relief of unrecognized hypoxia is shown by: *1*) arterial oxygen saturations during air-breathing were normal; *2*) the oxygen effect was not confined to the range of concentrations closest to air but was progressive over the 21 to 100 per cent range. These data provide evidence that oxygen, or the lack of it, is an effective chemoreceptor stimulus in man—far above the Po_2 range inferred from the work of von Euler and co-workers and of Witzleb and associates in cats. This discrepancy may be the result of experimental differences, or species differences, but it also suggests that some chemosensitive area other than the carotid body may be involved.

The circulatory responses to tourniquet hyperemia have been investigated previously by

Stead and Warren (4). Using the ballistocardiographic techniques they found a sudden increase in cardiac output after release of arterial tourniquets and likened this effect to a sudden opening of an A-V fistula. The present study demonstrated a decreased change in heart rate and cardiac output in subjects breathing oxygen during the phase of reactive hyperemia. Since the circulation to the legs is occluded during the period of oxygen breathing, this effect of oxygen must either be the result of a very rapid metabolic change after tourniquet release, or is a neurogenic effect. The fact that changes associated with oxygen breathing appeared after only 15 seconds of exposure of the legs to hyperoxic tensions argues against any other than reflex effect of hyperoxia.

Inflation of thigh tourniquets to a pressure sufficient to occlude the arterial circulation produced a slight increase in heart rate and cardiac index, possibly related to the associated discomfort and anxiety. When the subjects breathed oxygen these changes were not observed. It may be that oxygen breathing decreases the circulatory response to such a stimulus.

The effects of oxygen breathing on the normal circulation are of intrinsic physiologic interest and are of importance in considering the responses of the regional circulations to hyperoxia. These observations suggest that the efficacy of oxygen breathing in clinical situations, such as myocardial infarction or heart failure without arterial undersaturation, may depend upon a decrease in cardiac output and an associated decrease in external cardiac work.

SUMMARY

1. Oxygen breathing in normal subjects causes a small decrease in heart rate abolished by atropine (probably vagal) and a comparable rate-dependent decrease in cardiac output.

2. Oxygen breathing increases systemic resistance and blood pressure.

3. The oxygen effect on cardiac output, heart rate, and circulation time persists in the circulatory response to reactive hyperemia.

4. The effect of hyperoxia on heart rate of normal subjects is progressive with increasing concentrations of inspired oxygen from 15 to 100 per cent.

5. A far higher range of chemoreceptor activity is suggested than has previously been generally recognized.

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