

## 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 Courmand 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

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known quantity of dye  $\pm 0.05$  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 output. 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.

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*

| Subject | Cardiac index              |                |                            |                | Heart rate       |                |                  |                | Stroke index            |                |                         |                |
|---------|----------------------------|----------------|----------------------------|----------------|------------------|----------------|------------------|----------------|-------------------------|----------------|-------------------------|----------------|
|         | Before atropine            |                | After atropine             |                | Before atropine  |                | After atropine   |                | Before atropine         |                | After atropine          |                |
|         | Air                        | O <sub>2</sub> | Air                        | O <sub>2</sub> | Air              | O <sub>2</sub> | Air              | O <sub>2</sub> | Air                     | O <sub>2</sub> | Air                     | O <sub>2</sub> |
|         | <i>L/min/m<sup>2</sup></i> |                | <i>L/min/m<sup>2</sup></i> |                | <i>beats/min</i> |                | <i>beats/min</i> |                | <i>ml/m<sup>2</sup></i> |                | <i>ml/m<sup>2</sup></i> |                |
| 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*

| Subject | Mean blood pressure |                |                |                | Resistance         |                |                    |                | Artery-to-artery circulation time |                |                |                |
|---------|---------------------|----------------|----------------|----------------|--------------------|----------------|--------------------|----------------|-----------------------------------|----------------|----------------|----------------|
|         | Before atropine     |                | After atropine |                | Before atropine    |                | After atropine     |                | Before atropine                   |                | After atropine |                |
|         | Air                 | O <sub>2</sub> | Air            | O <sub>2</sub> | Air                | O <sub>2</sub> | Air                | O <sub>2</sub> | Air                               | O <sub>2</sub> | Air            | O <sub>2</sub> |
|         | <i>mm Hg</i>        |                | <i>mm Hg</i>   |                | <i>mm Hg/L/min</i> |                | <i>mm Hg/L/min</i> |                | <i>sec</i>                        |                | <i>sec</i>     |                |
| 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.



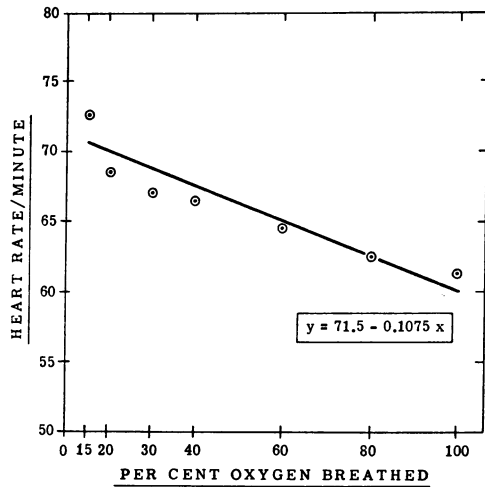


FIG. 1. EFFECTS OF BREATHING INCREASED OXYGEN CONCENTRATIONS ON THE HEART RATES OF TEN NORMAL RESTING MEN.

( $43 \pm 7$  to  $43 \pm 7$  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 ( $93.6 \pm 9.0$  to  $95.3 \pm 9.0$  mm Hg) as was over-all systemic resistance ( $16.3 \pm 4.6$  to  $18.5 \pm 2.9$  U), and artery-to-artery circulation time ( $18 \pm 3$  to  $21 \pm 3$  seconds). These effects of oxygen on systemic resistance and circulation time were not observed after atropine. Similarly, oxygen breathing increased the mean circulation time ( $19.4 \pm 3.3$  to  $21.5 \pm 4.0$  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

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.

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 ( $2.77 \pm 0.36$  to  $3.18 \pm 0.38$  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 ( $7.39 \pm 0.02$  to  $7.43 \pm 0.04$ ,  $p = 0.01$ ). 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,  $PCO_2$ , and oxygen saturation of 7 normal subjects

|                  | Air             | 30% $O_2$       | 60% $O_2$       | 100% $O_2$         |
|------------------|-----------------|-----------------|-----------------|--------------------|
| pH               | $7.39 \pm 0.02$ | $7.40 \pm 0.01$ | $7.39 \pm 0.02$ | $7.43 \pm 0.04^*$  |
| $PCO_2$ (mm Hg)  | $38 \pm 2$      | $42 \pm 3$      | $41 \pm 3$      | $39 \pm 3^\dagger$ |
| $O_2$ saturation | $95 \pm 3\%$    |                 |                 |                    |

\* pH during 100% oxygen breathing  $>$  pH during air, 30% or 60% oxygen breathing;  $p = 0.01$ .

†  $PCO_2$  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  $P_{O_2}$  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). Asmusen 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  $P_{O_2}$ '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  $P_{O_2}$  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 under-saturation, 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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