The Relationship between the Arterial Oxygen Saturation and the Cardiovascular Response to Induced Anoxemia in Normal Young Adults

By Raymond Penneys, M.D., and Caroline Bedell Thomas, M.D.

The induced anoxemia test of cardiovascular function has been standardized according to the degree of anoxemia rather than the oxygen concentration of the gas mixture administered. The cardiovascular response of normal subjects at 80, 75 and 70 per cent arterial oxygen saturation is described. The changes can be closely correlated with the degree of anoxemia, as measured by the oximeter.

At the present time the most widely used method of studying the effect of induced anoxemia on the cardiovascular system consists of giving the subjects low oxygen gas (usually 10 per cent) inhalation for approximately twenty minutes and making observations during this period. In previous communications the variability of the degree of anoxemia, as measured by the blood arterial oxygen saturation, during inhalation of a gas of fixed low oxygen concentration was pointed out. The physiologic importance of standardizing the induced anoxemia test of cardiovascular function according to the level of the arterial oxygen saturation was discussed and a method of inducing and maintaining a constant degree of anoxemia by administering a gas of variable oxygen concentration was described. In one of these reports the nature of the cardiovascular response of a small group of young men at levels of 85, 80, and 75 per cent arterial oxygen saturation was presented. It is the purpose of this report to give a detailed description and analysis of the effect of anoxemia upon the heart rate, blood pressure, and electrocardiogram at levels of 80, 75, and 70 per cent arterial saturation in a substantial number of normal young adults.

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Method

Anoxemia was induced by the administration of mixtures of nitrogen and oxygen by means of a Heidbrink anesthesia machine. The arterial oxygen saturation was measured with the Millikan automatically-compensated oximeter. Details and modifications of the procedure have been reported elsewhere.

Each subject rested on a bed in a quiet room until his or her blood pressure and pulse rate became stabilized. Electrocardiograms were made with a Cambridge electrocardiograph and standardized to give a 10-mm. deflection with 1 millivolt. In measuring the height of the RS-T segment, the P-Q or P-R segment was selected as the isoelectric line according to the method followed by Katz, Malmström, and others. Blood pressure was taken by the auscultatory method with a Tyco manometer; the heart rate was obtained from the electrocardiogram. The blood pressure, pulse rate, and electrocardiogram were taken before, during, and after the period of anoxemia.

A total of 76 normal persons was studied. Seventy-two were medical students and the remainder were laboratory assistants. All but 3 of the subjects were men. Seventy-three of the subjects were between 22 and 28 years of age; the other 3 subjects were 16, 17, and 34 years old. All subjects were of the white race and were free from any cardiovascular disease as far as could be determined by a preliminary examination, which included a detailed medical history, physical examination, and electrocardiogram.

Eighty-one tests were performed on the 76 subjects. In most instances the arterial oxygen saturation was lowered in a "step-wise" manner so that a subject was studied at more than one level of saturation during the same test. The various readings (electrocardiogram, etc.) usually were taken at each level. If the saturation was maintained at only one level, readings were taken at the end of approximately ten and twenty minutes of anoxemia. The number of tests, according to the saturation at which
Table 1.—Changes in the Electrocardiogram (RS-T Segment, T Wave, and Heart Rate) and Blood Pressure at 80, 75, and 70 per cent Arterial Oxygen Saturation

<table>
<thead>
<tr>
<th>Changes in Arterial Oxygen Saturation (%)</th>
<th>(1) 80</th>
<th>(2) 75</th>
<th>(3) 70</th>
<th>(4) 80 to 75</th>
<th>(5) 75 to 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>M</td>
<td>R</td>
<td>σ</td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
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<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>RS-T Dev. (mm.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>64</td>
<td>-0.68</td>
<td>-2 to +5</td>
<td>-0.52</td>
<td>67</td>
</tr>
<tr>
<td>II</td>
<td>64</td>
<td>-1.04</td>
<td>-3.7 to +0.2</td>
<td>-0.7</td>
<td>67</td>
</tr>
<tr>
<td>III</td>
<td>64</td>
<td>-0.37</td>
<td>-1.5 to +0.8</td>
<td>-0.66</td>
<td>67</td>
</tr>
<tr>
<td>IV</td>
<td>64</td>
<td>-0.75</td>
<td>-2.9 to +3.3</td>
<td>-0.96</td>
<td>67</td>
</tr>
<tr>
<td>T Wave (mm.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (per minute)</td>
<td>69</td>
<td>14.0</td>
<td>+1 to +33</td>
<td>6.9</td>
<td>73</td>
</tr>
<tr>
<td>Blood Pressure (mm. Hg.)</td>
<td>Syst</td>
<td>67</td>
<td>4.1</td>
<td>-11 to +23</td>
<td>6.5</td>
</tr>
<tr>
<td>Diast</td>
<td>67</td>
<td>-1.9</td>
<td>-12 to +13</td>
<td>5.2</td>
<td>70</td>
</tr>
</tbody>
</table>

(1) to (5) at top of columns indicate “column number” referred to in text. In (1), (2), and (3) changes from room air (approx. 95 per cent) to 80, 75, or 70 per cent are listed; in (4) changes from 80 to 75 per cent and in (5) 75 to 70 per cent are given.

N = number of observations. “N” for “heart rate” and “blood pressure” is slightly larger than that for “RS-T” and “T Wave” for the same group of subjects since occasionally electrocardiograms were not obtained either for technical reasons or because of abrupt termination of the test.

M = mean difference.

R = range of differences.

σ = standard deviation of the mean differences.

P = (probability that difference is due to chance) values are <0.005 in all instances except where ( ) are placed around “M” in which P is > 0.005 but < 0.05 or where [ ] is placed around “M” indicating P > 0.05.

RS-T Deviation — indicates total for all four leads regardless of direction of change from the control electrocardiogram.
readings were taken, are as follows: eleven at 80 per cent; thirty-two at 80 and 75 per cent; fourteen at 80, 75, and 70 per cent; eight at 75 per cent; sixteen at 75 and 70 per cent.

All subjects, therefore, were not studied at the same levels of anoxemia. To determine the effect of anoxemia at a particular level, such as 80 per cent saturation, all readings at 80 per cent were totalled and compared to the readings obtained on the same subjects during the control period. The difference was then expressed arithmetically. In columns 1, 2, and 3 of table 1, the differences between 80, 75, and 70 per cent saturation and the control readings on room air (before the anoxemia period) are presented. The differences in taking a group of subjects from 80 to 75 per cent are given in column 4 and from 75 to 70 per cent in column 5.

**OBSERVATIONS**

**Cardiovascular Response at 80, 75, and 70 per cent Arterial Oxygen Saturation**

The changes in heart rate, blood pressure, and electrocardiogram noted at these three levels are given in table 1. Graphic presentation shows that there is a progressive increase in certain values with lowering of the arterial oxygen saturation (fig. 1) which are consistent in the same individual at different levels of anoxemia (fig. 2). The nature and degree of these changes are described in detail below.

**Electrocardiographic Changes.** Changes in RS-T segment, T wave, P wave, and heart rhythm,

![Diagram of Arterial Oxygen Saturation (‰)](http://circ.ahajournals.org/)

**ARTERIAL OXYGEN SATURATION (‰)**

Fig. 1.—Changes with Progressive Lowering of the Arterial Oxygen Saturation. Heart rate change (○) in beats per minute; T-wave lowering (●) in Lead II in tenths of mm.; RS-T deviation (▲) in Leads I-IV inclusive in tenths of mm.; systolic blood pressure (▲) in mm. Hg.

and evidence of coronary disease were noted as follows:

RS-T Segment: The total RS-T deviation for Leads I to IV (CF4), inclusive, increased slightly with progressive anoxemia. It did not exceed 2.5 mm. at 80, 75, and 70 per cent saturation in any individual. The distribution of RS-T changes for each lead at each level of arterial saturation is given in table 2. It can be seen that when a change did occur it usually was a depression of 0.5 mm. and was more com-
monly found in Lead II than in the other leads. A total of 37 out of the 76 subjects showed this type of change at one level or another.

Further evidence that the RS-T deviation increases with lowering of the arterial saturation is found in the increasing frequency of depression or elevation amounting to 1 mm., in any lead, in passing from 80 to 70 per cent saturation (table 2). Whereas, only 6 per cent of the subjects studied at 80 per cent showed that degree of deviation, 22 per cent of the subjects studied at 75 per cent and 43 per cent of the subjects studied at 70 per cent saturation showed such changes. In contrast, the percentage of subjects with no RS-T change in any lead decreased with lowering of the saturation. At 80 per cent saturation 38 per cent of

![Graph of Arterial Oxygen Saturation and Heart Rate and Blood Pressure Changes](https://example.com/arterial-oxygen-saturation-graph.png)

**Fig. 2.**—The Response of the Same Subjects to Different Degrees of Anoxemia. Each point represents comparison of changes noted in one subject at the arterial oxygen saturations indicated along the abscissa and ordinate. Reference lines are drawn at 45 degrees to indicate identical values at the two levels of arterial saturation. (Figure continued on facing page.)

the subjects showed no change, while at 75 per cent the percentage of subjects decreased to 28 per cent and at 70 per cent saturation to 25 per cent.

T Wave: In practically every test the T wave was progressively lowered with diminishing arterial oxygen saturation. Statistical analysis of
the T-wave changes showed that the degree of lowering was closely correlated with the level of the arterial oxygen saturation. More striking evidence that the degree of T-wave lowering was related to the level of the arterial saturation was demonstrated in those tests where upright T waves became diphasic or inverted with progressive anoxemia (table 3). In all but one instance these directional changes of the T wave took place in Leads III or IV. The various types of T wave changes with progressive anoxemia are illustrated in figure 3.

P Wave: Ten subjects showed elevation of the P wave with anoxemia. The increase in height ranged from 0.5 to 3 mm. and was most pronounced in Leads II or III. The most striking example of elevation of the P wave with anoxemia is illustrated in figure 4. In this instance marked increase in P2 and P3 occurred upon decreasing the arterial oxygen to 75 per cent saturation, and there was no further increase at 70 per cent saturation. It may also be noted that P1 decreased very slightly in amplitude, and the P wave in Lead IV became inverted.

Rhythm: The heart rhythm remained regular during anoxemia; no transitory ectopic rhythms were noted. In two of three instances in which sinus arrhythmia was present during the control period, the rhythm became regular.
Fig. 3.—Different types of T-Wave Changes with Progressive Anoxemia. Subject A (49M26) shows lowering of the T wave, B (49M20) flattening, and C (48M56) inversion.
with anoxemia. In both tests this conversion of sinus arrhythmia into normal sinus rhythm was associated with a concomitant increase in the heart rate, amounting to 25 beats per minute.

Table 2.—RS-T Deviations According to Lead of Electrocardiogram and Arterial Oxygen Saturation

<table>
<thead>
<tr>
<th>RS-T Dev. (mm.)</th>
<th>Changes in Arterial Oxygen Saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95 (approx) to</td>
</tr>
<tr>
<td></td>
<td>80</td>
</tr>
<tr>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>+0.5</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-0.5</td>
<td>0</td>
</tr>
<tr>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>

Total No. of Electrocardiograms ........ 64 67 28

Numbers in blocks indicate number of electrocardiograms with indicated deviation. “Deviation” refers to arithmetic change from control value of RS-T segment on room air (before the period of anoxemia).

Table 3.—Change in the Direction of the T Wave According to the Degree of Anoxemia

<table>
<thead>
<tr>
<th>Subject's Study No.</th>
<th>Arterial Oxygen Saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95 (approx) to</td>
</tr>
<tr>
<td></td>
<td>80</td>
</tr>
<tr>
<td>49M10</td>
<td>III upright</td>
</tr>
<tr>
<td></td>
<td>IV upright</td>
</tr>
<tr>
<td>F.J.</td>
<td>IV upright</td>
</tr>
<tr>
<td>48M56</td>
<td>III upright</td>
</tr>
<tr>
<td>48M33</td>
<td>III upright</td>
</tr>
<tr>
<td>48W03</td>
<td>III upright</td>
</tr>
<tr>
<td>48M81</td>
<td>III upright</td>
</tr>
<tr>
<td>51M28</td>
<td>III upright</td>
</tr>
<tr>
<td>49M45</td>
<td>III diphasic</td>
</tr>
<tr>
<td>49M19</td>
<td>III upright</td>
</tr>
<tr>
<td>49W11</td>
<td>III upright</td>
</tr>
</tbody>
</table>

— indicates no electrocardiogram made.

Heart Rate: Increase in the heart rate with anoxemia occurred in almost every instance. The mean increase of the heart rate for the entire group of subjects was 14 beats per minute at 80 per cent saturation, 18 beats at 75 per cent, and 23 beats at 70 per cent saturation (table 1, columns 1–3). This progressive increase in heart rate with decreasing oxygen saturation is also demonstrated by the observations made in those subjects who were studied at more than one level of anoxemia (columns 4 and 5). It should be noted that while none of those tested had a slower heart rate during anoxemia than on room air, there were some individual decreases in rate when passing from 80 to 75 per cent and from 75 to 70 per cent, as is shown in figure 2.

Blood Pressure: The changes in blood pressure are also shown in table 1. There was an increase of 4 mm. in the mean systolic blood pressure at 80 and 75 per cent and of 6 mm. at 70 per cent over that obtained in the same individuals on room air (columns 1–3). Although these mean changes are small, they are statistically significant. The mean change in diastolic blood pressure at the same three levels, however, was slight (less than 1 mm.) and not statistically significant. These changes in the systolic and diastolic blood pressure resulted in a slight increase of the mean pulse pressure with anoxemia.

In contrast to these small changes of the mean blood pressure values, the individual responses to the same degree of anoxemia were often quite different, as is reflected in the ranges tabulated in table 1. Anoxemia produced a fall in systolic blood pressure in some subjects, and a rise in others; the diastolic pressures varied both concordantly and discordantly with the systolic readings. As a result, the pulse pressure changes were quite variable. The blood pressure changes were very consistent in the same subject at three different levels of anoxemia, however, regardless of the direction and degree of the change (fig. 2).

Pulse Quality: The quality of the pulse was kept under constant observation by palpation of the superficial temporal artery. In most
Fig. 4.—Elevation of the P Wave with Anoxemia (Subject 40381). Records in Lead IV are mounted in their full width in order to include the entire QRS complex, 1 mv. = 10 mm.
persons there was an increase in the fullness and forcefulness of the pulse with the lowering of the arterial oxygen saturation. In a few instances, however, the pulse suddenly became weak with progressive anoxemia although there was no associated drop in the blood pressure. In one test this occurred at 80 per cent, in two at 70 per cent. When this happened the test was terminated because the change in pulse quality was interpreted as a sign of the individual's inability to adjust to anoxemia at that time.

Relationship of the Heart Rate, Blood Pressure, and Electrocardiographic Changes to Each Other. All the readings of the blood pressure, heart rate and electrocardiogram at one level of arterial saturation, 75 per cent, to which most of the subjects were taken, were tabulated and the following relationships studied:

Heart Rate Change and RS-T Depression: It has been reported that RS-T depression noted during anoxemia may be due to tachycardia alone, which is also produced by anoxemia. Our data show that the degree of depression of the RS-T segment was not related to the degree of heart rate increase.

Heart Rate Change and T-wave Lowering: The degree of lowering of the T wave (in Lead II) was found to bear no statistical relationship to the degree of heart rate change. This observation, therefore, does not support the statement that tachycardia itself lowers the height of the T wave.*

Heart Rate Change and Pulse Pressure Change: The degree of heart rate change was found to bear no definite relationship, either direct or inverse, to the pulse pressure change at 75 per cent arterial saturation. Some subjects showed very little change in either the heart rate or the pulse pressure, while others showed marked changes in one or the other, or in both.

Degree of Cardiovascular Change at 75 per cent Arterial Saturation versus the Control Value (on room air): Larsen? has stated that the amount of T-wave lowering with anoxemia is proportionate to the height of the T wave on room air. Analysis of the degree of lowering of the T wave at 75 per cent saturation, in general, agreed with his statement. The degree of heart rate increase at 75 per cent saturation, on the other hand, bore no definite relationship to the absolute value of the heart rate in the control period. Also, the systolic blood pressure increase at 75 per cent saturation was not found to be related in any way to the absolute height of the systolic blood pressure on room air.

Combination of Unusual Responses: The tests of all subjects showing a marked response in any single feature (e.g., heart rate) were examined to determine whether these tests were unusual in other ways as well. All tests in which any of the following changes occurred were tabulated as “unusual”: (1) heart rate increase greater than 25 beats per minute (5 subjects), (2) blood pressure change greater than 15 mm. systolic or 10 mm. diastolic (6 subjects), (3) RS-T deviation (Leads I-IV inclusive) 2 mm. or more (3 subjects), (4) T-wave inversion (in any lead) (7 subjects), (5) P-wave increase greater than 0.5 mm. (8 subjects). At 75 per cent arterial saturation, a total of twenty-nine unusual responses was shown by 22 different subjects. No consistent combination of unusual responses was noted in those 5 subjects with more than one such response.

Duration of Anoxemia

In the seventeen tests in which the arterial saturation was maintained at only one level (80 or 75 per cent) during the test, readings of the electrocardiogram and blood pressure were approximately the same at the end of ten and twenty minutes; no consistent difference could be found between the ten- and twenty-minute readings. Also, the pulse rate and quality, constantly observed throughout the test, usually showed no systematic change with increase in the duration of anoxemia, provided the level of arterial saturation was kept constant.

Symptoms

Only a few of the subjects could distinguish between breathing room air and the low oxygen gas regardless of the degree of anoxemia. This may have been related to the fact that induction to each level was gradual.

In two instances respiratory distress required early termination of the test. Both subjects manifested labored breathing and hyperventilation at the beginning of the test while still at a saturation of approximately 85 per cent.
Seven persons complained of mild frontal headache. This seemed definitely related to the degree of anoxemia. Five of these subjects noted the headache as soon as they reached 75 per cent arterial saturation and the other two on reaching the 70 per cent level. The headache was usually relieved by the inhalation of pure oxygen at the end of the test.

One subject, a medical student, who became excited and started to hyperventilate as soon as the nose clip and mouthpiece were in place, complained of “precordial pain radiating down the left arm” approximately one minute after he began to breathe the low oxygen gas, although the arterial oxygen saturation was still 95 per cent. No unusual changes occurred in the heart rate, blood pressure, or electrocardiogram. Prompt termination of the test resulted in immediate disappearance of the “pain.”

**DISCUSSION**

The cardiovascular response of 76 normal young adults to the stress of anoxemia at 80, 75, and 70 per cent arterial saturation has been presented. These three standardized levels of physiologic stress were obtained by means of an oximeter-controlled method of inducing anoxemia which has been previously described.\(^1\) The electrocardiogram, heart rate, and blood pressure showed increasing changes at successively lower levels of arterial saturation. These changes were quantitatively progressive, the response at 70 per cent saturation differing only in degree from that at 75 and 80 per cent. This indicates that at these levels of anoxemia, normal subjects can still compensate for the increasing stress by means of an increased physiologic response,\(^8\) and are therefore still in the “pre-crisis” state of anoxemia. The absence of any *abrupt* change in the cardiovascular response as the arterial saturation was lowered to 70 per cent gives evidence that the “post-crisis” state of anoxemia, with impending collapse, was not reached in any of the 30 subjects carried to that level.

In general, the degree of cardiovascular response to induced anoxemia showed a close statistical correlation with the level of arterial oxygen saturation of the blood. From this it follows that any precise evaluation of cardiovascular function during anoxemia should preferably be based upon a form of anoxemia test in which the level of arterial oxygen saturation, rather than the oxygen concentration of the inspired gas, should be standardized, since there is no fixed relationship between the oxygen content of the inspired gas and the oxygen saturation of the blood.

The data on our 76 normal subjects gives information of direct clinical value concerning the present criteria for a “positive” reaction to the anoxemia test for coronary artery disease. The *maximal* electrocardiographic changes noted in our group of subjects at 80, 75, and 70 per cent arterial saturation do not overlap the criteria for a positive reaction to the test as set forth by Patterson, Clark, and Levy.\(^4\) Using 10 per cent oxygen to induce anoxemia, these authors classify a reaction as positive when any one of the following changes is found: (1) The arithmetic sum of the RS-T deviations in all four leads (1–IVF inclusive) is greater by 3 mm. or more, than in the control record. (2) Partial or complete reversal of the direction of the T wave in Lead I, accompanied by an RS-T deviation of 1 mm., or more, in this lead. (3) Complete reversal of the direction of the T wave in Lead IVF, regardless of any associated RS-T deviation in this lead. Not only were none of these “positive” criteria found in the electrocardiographic records of our subjects at 80, 75, and 70 per cent arterial saturation, but between the upper limit of our normal range and the lower limit of their “positive” criteria there remains a definite small gap, into which records with the following characteristics would fall: (1) Partial or complete reversal of the direction of the T wave in Lead I in the absence of any RS-T deviation in this lead. (2) An RS-T deviation greater than 1 mm. in any lead.

The significance of such records is still uncertain; they have not been considered “positive” heretofore, yet they do not fall within the normal range in this present series. Until observations made on a larger number of normal subjects have conclusively demonstrated that the changes listed above actually do occur in normal individuals, it seems justified to regard them as probably abnormal, and therefore
a “doubtful positive” reaction to the electrocardiographic test for coronary artery disease.

Oximeter-controlled induced anoxemia should not only help to establish the electrocardiographic criteria for a positive reaction to the test, but should also help to evaluate the subject’s symptomatic response to inhalation of the low oxygen gas. When “precordial pain radiating down the left arm” is associated with nearly normal arterial oxygen saturation, as occurred in one of our subjects, it seems unlikely that the symptoms could be directly attributable to anoxemia. Without the oximeter reading, however, the reaction to this test would have to be considered as “presumptively positive.”

Finally, the oximeter-controlled method of producing standardized degrees of cardiovascular stress through the use of comparable levels of anoxemia provides us with an excellent means of studying the individual patterns of response. The gross differentiation between the various types of response to induced anoxemia in different subjects could be made at relatively high levels of arterial saturation. The responses of the same subject at subsequent lower levels of anoxemia were similar save for slight gradual intensification in some instances, indicating that these cardiovascular patterns are highly characteristic of the individual.

SUMMARY

1. By the use of oximeter-controlled induced anoxemia, the cardiovascular response of 76 normal young adults was studied at levels of 80, 75, and 70 per cent arterial oxygen saturation.

2. There was an increase in the response with progressive lowering of the saturation.

3. The degree of cardiovascular response was closely correlated with the level of the arterial saturation.

4. Maximal electrocardiographic changes observed in our group were smaller than the minimal criteria established by Patterson, Clark, and Levy for persons with coronary artery disease.

5. A possible intermediate zone of electrocardiographic changes indicating a “doubtful positive” reaction to the test was delineated.

6. The importance of knowing the arterial oxygen saturation in evaluating “presumptively” positive reactions to the test was pointed out.

7. The type of cardiovascular response of the same subject was similar at different levels of anoxemia.

8. The cardiovascular pattern of response to anoxemia varied considerably from subject to subject.

ACKNOWLEDGMENTS

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