Normal and Impaired Retinal Vascular Reactivity

By H. O. Sieker, M.D., and J. B. Hickam, M.D.

Normal retinal arteries and veins will constrict when the arterial blood oxygen tension is increased and dilate when it is lowered. A technic, employing fundus photography, is described for measuring this reaction. The amount of constriction on breathing oxygen, and its trend with age, have been measured in normal subjects. The arteries of persons with well-established hypertension and diabetes usually show marked impairment of this constrictor reaction, presumably because of sclerotic changes. It is suggested that measurements of this reaction may prove to be a useful, quantitative extension of present retinal vascular grading technics.

During life, vascular disease is evident mostly through the secondary effects of ischemia in various organs. These are late effects and there is need for the development of more direct and sensitive means of finding and quantitating degenerative vascular disease. Clinically, ophthalmoscopic examination has been valuable in estimating the condition of blood vessels, especially the arteries, because the vessels of the retina often show structural abnormalities in persons with generalized vascular disease. Attempts have been made to quantitate pathologic alterations in these vessels by various grading systems which depend upon visible changes.

In 1940, Cusick, Benson, and Boothby found that normal retinal vessels dilate when a subject breathes gas with a low oxygen tension and constrict when he breathes tank oxygen. The finding has been confirmed. This phenomenon must depend, in part at least, upon the presence of a mobile vessel wall. In view of the likelihood that this reaction would be impaired in persons with retinal vascular sclerosis, and the need for more quantitative estimates of vascular damage, the present study was undertaken. The purpose of this study was to establish the normal range of retinal vascular response to change in oxygen tension, and to determine to what extent the reaction may be altered in persons with known vascular disease.

Methods

Eye-ground photographs were made with a Bausch and Lomb fundus camera while the subjects breathed air, tank oxygen, and, in some cases, 10 per cent oxygen and 90 per cent nitrogen; or 5 per cent carbon dioxide, 21 per cent oxygen and 74 per cent nitrogen. The visible diameter of the larger vessels near the disc was measured from the photographs, using a low-power (9X) dissecting microscope having a scale in the ocular. The range of actual vessel diameter was in the order of 90 to 180 microns. The negative of a normal eye represents a magnification of approximately 3 diameters, and the photographs were 4 diameter enlargements.

As a standard procedure "retinal vascular reactivity" was measured as per cent shrinkage in vessel diameter when a subject breathed first air and then tank oxygen. In a normal subject there is considerable variation in the degree of shrinkage from vessel to vessel when the subject breathes oxygen. For this reason, multiple measurements are required. As a rule, measurements were made at identical points of all the larger vessels in each eye which were clearly defined in photographs made while the subject was breathing different gas mixtures. A given vessel usually shrinks uniformly between bifurcations, but the branches may show motility different from the parent vessel. In general, 6 to 12 measurements were made for both arteries and veins, and the results averaged. The reproducibility of the measurement method was studied on duplicate series of photographs. Estimates of over-all caliber change are reproducible within 2 per cent.

Trials on normal subjects indicate that retinal vascular constriction is substantially complete within five minutes after passing from breathing air to...
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breathing tank oxygen, and this was the standard
time used in the study.

A larger change in vascular diameter can be
produced in normal subjects by passing from 10
per cent oxygen to tank oxygen, but this method
has two disadvantages for general use. The low
oxygen mixture could be hazardous for subjects
with vascular disease. In addition, the arterial oxy-
gen tension on 10 per cent oxygen is quite variable.
Uniformity of stimulus would be hard to achieve
and would require oximetric control. Table 1 shows
the results obtained with 10 per cent oxygen and
99.6 per cent oxygen in a small series of normal
young subjects. On 10 per cent oxygen the per cent
oxygen saturation of brachial arterial blood ranged
from 50 to 84 per cent in this group.

<table>
<thead>
<tr>
<th>% O₂ Breathed</th>
<th>Arterial Reactivity*</th>
<th>Venous Reactivity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>99.6</td>
<td>13.6 ± 1.6†</td>
<td>15.0 ± 2.1</td>
</tr>
<tr>
<td>10</td>
<td>10.1 ± 1.1</td>
<td>10.0 ± 1.0</td>
</tr>
</tbody>
</table>

* Expressed as per cent change from vessel di-
diameter while breathing air.
† Standard error.

Parallel trials of the effects of breathing a mixture
of 5 per cent carbon dioxide, 21 per cent oxygen, and
74 per cent nitrogen, and of 99.6 per cent oxygen
have been made in 20 normal subjects and patients
with vascular disease. By the present method of
measurement, 5 per cent carbon dioxide has very
little effect on the larger retinal vessels, although it
is known to cause a considerable increase in cerebral
blood flow.

RESULTS

1. Normal Retinal Vascular Reactivity

Measurements of retinal vascular reactivity,
as average per cent decrease in vessel diameter
on passing from air to tank oxygen, were
made in 31 normal subjects. There were 26
males and five females. The mean age was 37.4
years (standard deviation 17.8), with the
extremes being 17 and 83 years. The subjects
were medical students and hospital patients.
None showed evidence of vascular disease by
history and physical examination.

The mean arterial reactivity was 11.5 per
cent (standard error 0.8), and the mean
venous reactivity was 14.0 per cent (S.E. 1.0).
The regression of arterial reactivity on age is
presented in figure 1. There is a significant
negative correlation between arterial reactivity
and age (r = -.381, t = 2.215, .02 < p < .05).
The tendency is to lose reactivity at about
the rate of 1 per cent every 10 years. In this
group, no subject below the age of 55 had an
arterial reactivity under 6.0 per cent. The
correlation between age and venous reactivity
is not at a significant level. There is, however,
a significant positive correlation between
arterial reactivity and venous reactivity for
the group as a whole (r = .565, t = 3.68,

p < .01). That is, there is a tendency for a
high order of arterial reactivity to be associated
with a high order of venous reactivity, and
vice versa.

An example of normal reactivity is shown in
figure 2.

2. Retinal Vascular Reactivity in Hypertension

Measurements of reactivity were made in
29 hypertensive subjects. The criteria for
hypertension were a systolic pressure usually
over 150 or a diastolic pressure usually over
90 mm. Hg. These limits were ordinarily
considerably exceeded. There were 23 males
and six females. The mean age was 49.7 years
(S.D. 10.0). The mean arterial reactivity was
3.2 per cent (S.E. 0.8). This is significantly
different from normal (t = 7.390, p < .01).
The three best reactivities in the group were

![Regression of retinal arterial reactivity on age in 31 normal subjects.](http://circ.ahajournals.org/Downloaded from)
7.0 per cent (male, age 48, blood pressure 162/95), 15.8 per cent (male, age 45, blood pressure 218/128) and 20.2 per cent (male, age 35, blood pressure 174/120). Venous reactivity was much less impaired. The mean venous reactivity was 10.9 per cent (S.E. 0.9). This is still significantly different from normal ($t = 2.318, .02 < p < .05$).

As a group, these patients were severe hypertensives. Several of them had had cerebral vascular accidents or myocardial infarctions.

40.4 years (S.D. 15.4). The mean arterial reactivity was 3.0 per cent (S.E. 0.9). This is significantly different from normal ($t = 6.750, p < .01$). Many members of this group had severe diabetes, with complications such as retinopathy, neuropathy, hypertension, and coronary or peripheral arterial insufficiency. Three subjects, who were nonhypertensive, had arterial reactivities within the normal range. The venous reactivity of the group was 9.2 per cent (S.E. 1.4). This is also significantly different from normal ($t = 2.824, p < .01$).

### Table 2.—Retinal Vascular Reactivity in Hypertensives on the Rice Diet

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>State</th>
<th>B.P.</th>
<th>Arterial Reactivity</th>
<th>Venous Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.S.</td>
<td>51</td>
<td>Before diet</td>
<td>190/122</td>
<td>2.7</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>On diet 4 mo.</td>
<td>135/90</td>
<td>1.2</td>
<td>11.3</td>
</tr>
<tr>
<td>M.R.</td>
<td>41</td>
<td>Before</td>
<td>181/128</td>
<td>0.5</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>On diet 4 mo.</td>
<td>109/81</td>
<td>5.1</td>
<td>15.0</td>
</tr>
<tr>
<td>R.H.</td>
<td>64</td>
<td>Before</td>
<td>190/100</td>
<td>2.6</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>On diet 4 mo.</td>
<td>110/82</td>
<td>3.8</td>
<td>13.1</td>
</tr>
<tr>
<td>B.C.</td>
<td>53</td>
<td>Before</td>
<td>180/110</td>
<td>3.4</td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>On diet 4 mo.</td>
<td>142/77</td>
<td>4.0</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Through the courtesy of Dr. Walter Kempner, four patients were studied before and after four months on the rice diet. These patients had a substantial reduction in blood pressure but no pronounced change in arterial reactivity. The data are presented in Table 2. This result is pertinent because it demonstrates that loss of arterial reactivity in hypertension is not caused simply by a high internal distending pressure which mechanically resists constriction.

### 3. Retinal Vascular Reactivity in Diabetes

Reactivity was measured in 16 subjects, 11 males and five females. The mean age was
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In order to distinguish the effect of diabetes, per se, from that of hypertension, reactivities were calculated separately for those diabetics who had never had hypertension, so far as could be determined. There were 10 of these, having a mean age of 41.4 years (S.E. 16.0). The arterial reactivity was 4.2 per cent (S.E. 1.4), significantly different from normal ($t = 4.710, p < .01$). The venous reactivity was 10.6 per cent (S.E. 1.6), which is not significantly different from normal.

The results obtained on normal, hypertensive and diabetic subjects are summarized in table 3.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Number</th>
<th>Age</th>
<th>Arterial Reactivity</th>
<th>Venous Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal . . . . . .</td>
<td>31</td>
<td>37.4</td>
<td>11.5±0.8</td>
<td>14.0±1.0</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>29</td>
<td>49.7</td>
<td>3.2±0.8*</td>
<td>10.9±0.9*</td>
</tr>
<tr>
<td>Diabetic . . . . .</td>
<td>16</td>
<td>40.4</td>
<td>3.0±0.9*</td>
<td>9.2±1.4*</td>
</tr>
<tr>
<td>Nonhypertensive diabetic . . . .</td>
<td>10</td>
<td>41.4</td>
<td>4.2±1.4*</td>
<td>10.6±1.6</td>
</tr>
</tbody>
</table>

* Significantly different from normal.

**DISCUSSION**

The means of expressing retinal vascular reactivity deserves some comment. The functional result of vessel motility is to regulate flow, and it would be desirable to express retinal vascular reactivity directly in terms of resultant flow changes. However, it is only changes in internal diameter of the larger retinal vessels which can be measured at present, and it would be hazardous to attempt to translate diameter changes in the measurable arteries into terms of vascular resistance and thence into flow. In defense of the present method, it can be said that per cent decrease in diameter is directly related to per cent decrease in circumference, and the measurement, for arteries at least, is a direct expression of constrictor activity of the vessel wall at the point where the measurement is made.

The observations on the effect of altered oxygen tension in normal man are in agreement with those of Cusick, Benson and Boothby$^1$ and of later investigators, $^2, ^3$ but the changes, by the present technic, are somewhat smaller than those originally described.$^1$ We do not confirm the finding of Huerkamp and Rittinghaus$^4$ that carbon dioxide causes a dilatation of the retinal vessels.

There is strong presumptive evidence that the loss of arterial reactivity which occurs in hypertensives and diabetics results from sclerosis of the retinal arteries. Retinal arteriosclerosis, as well as generalized arteriosclerosis, is extremely common in these disorders. It is more difficult to ascribe loss of venous reactivity simply to vessel wall changes, although retinal venous sclerosis is common in hypertensives and diabetics.$^5$ It is possible that venous caliber changes may be dependent in part upon changing pressure and flow, and that failure of veins to change size is simply a reflection of failure to change flow rate through the arterial system.

As would be expected, there is a rough relationship between clinical grading of arteriosclerotic changes by ophthalmoscopic examination and the impairment of retinal arterial reactivity. Marked "sclerotic" changes are nearly always associated with marked loss of reactivity. However, there have been several instances of marked reduction in arterial reactivity in which the vessels appeared only slightly altered on examination by an experienced internist.

It is probable that measurement of arterial reactivity would be a useful extension of present retinal arterial grading technics from the viewpoints of both sensitivity and quantitation.

**SUMMARY**

1. "Retinal vascular reactivity" is defined as the average per cent decrease of diameter of visible vessel which occurs when a subject passes from breathing air to breathing tank oxygen. A technic is described for measuring this change by fundus photography.

2. Measurements of retinal vascular reactivity have been made in 31 normal people. There is a slight but statistically significant decline in arterial reactivity with age.

3. Retinal vascular reactivity was measured in 29 hypertensive and 16 diabetic patients.
In both of these groups arterial reactivity was greatly diminished below normal. A few subjects in each group showed reactivity within the normal range.

4. It is believed that the decrease in arterial reactivity of hypertensive and diabetic persons is the result of sclerotic changes in the retinal arteries.

5. Measurement of retinal vascular reactivity may prove to be a useful extension of present retinal vascular grading techniques.

**SUMARIO Español**

Las arterias y venas retinales se contraen cuando la tensión de oxígeno arterial es aumentada y se dilatan cuando disminuye. Una técnica para medir el cambio mediante fotografía del fondo se describe. La cantidad de contracción a la inhalación de oxígeno y el cambio que ocurre con el entorno se ha determinado en sujetos normales. Las arterias de personas con hipertensión establecida y diabetis usualmente muestran deterioro de esta reacción de contracción, presumiblemente debido a cambios escleróticos. Se sugiere que determinaciones de esta reacción pueden probar provechosas como una extensión cuantitativa de las técnicas presentes para la gradación vascular retinal.

**REFERENCES**


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