The Relationship Between Impaired Retinal Vascular Reactivity and Renal Function in Patients with Degenerative Vascular Disease

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

In hypertension and diabetes retinal vascular changes which are evident on fundoscopic examination are usually accompanied by renal vascular changes which are evident on microscopic examination. It has been found that the retinal vessels of most patients with hypertension or diabetes fail to constrict normally when the blood oxygen tension is elevated. This investigation evaluates the clinical significance of decreased retinal vascular reactivity in patients with degenerative vascular disease by relating it to kidney function as measured by common clinical tests. The results of the study show that impairment of retinal arterial reactivity usually occurs in the course of degenerative vascular disease, particularly in hypertension, in advance of clinical evidence of altered kidney function. When clinical tests of renal function demonstrate renal damage, loss of retinal arterial and venous reactivity is marked.

Impairment of retinal vascular reactivity has been significantly correlated with a decrease in cerebral blood flow and cerebral vascular reactivity in arteriosclerotic patients. The purpose of the present study was to investigate further the clinical significance of retinal vessel reactivity by relating it to the state of the kidneys, as determined by common clinical tests, in normal individuals and patients with degenerative vascular disease.

METHODS

Observations were made in 97 hospital patients ranging in age from 12 to 76 years. This group includes 29 patients (the “control” group) without known renal disease, vascular disease or diabetes mellitus. The remaining patients had hypertension, diabetes, glomerulonephritis or pyelonephritis. The group did not include patients with congestive failure or prerenal azotemia which might cause transient changes in the tests by which the state of the kidney was evaluated.

Eyeground photographs were made under constant conditions with a Bausch and Lomb fundus camera while the patient breathed air and then tank oxygen. The visible diameter of the vessel was measured from the photograph with the aid of a low-power dissecting microscope containing a micrometric scale in the ocular. As described in a previous report, retinal vascular reactivity was expressed as the per cent shrinkage in vessel diameter resulting from the patient's changing from air-breathing to oxygen-breathing. For ready translation into familiar clinical terms commonly used kidney tests were chosen. These were: urinary

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TABLE 1.—Retinal Vascular Reactivity in Hospital Patients Without Known Renal Disease, Vascular Disease, or Diabetes

<table>
<thead>
<tr>
<th>No. Subjects</th>
<th>Arterial Reactivity (%)</th>
<th>Venous Reactivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
</tr>
<tr>
<td>29</td>
<td>10.1</td>
<td>4.4</td>
</tr>
</tbody>
</table>

protein by the sulfosalicylic acid method, graded as 1 to 4 plus; phenolsulfophthalein excretion and blood nonprotein nitrogen. The urine protein was estimated in all cases, the phenolsulfophthalein excretion in 40 and the nonprotein nitrogen in 55.

The data for each test of renal function were analyzed separately. For a given test, the subjects were divided into groups according to the degree of abnormality shown by the test. The groups were then examined with reference to the retinal vascular reactivity to determine the extent to which changes in this function were correlated with changes in renal function. This procedure was followed for the total group of subjects. In addition, to provide a more homogenous group which would be expected to show changes in both retinal vascular reactivity and renal function the same procedure was followed for the hypertensive group alone. Hypertension was defined as a blood pressure which is usually in excess of 150 mm. Hg systolic and 100 mm. Hg diastolic. Statistical significance was taken to begin at the level $P = .05$.

RESULTS

The retinal vascular reactivity of the 29 "control" hospital patients without vascular disease is presented in table 1. These figures are in good accord with those previously found in normal subjects.6

The relationship between proteinuria and retinal vascular reactivity for all subjects is presented in table 2. In the group without proteinuria, the reactivity is slightly below the "control" value because some patients with vascular disease are included. The difference, however, is not statistically significant. With the appearance of proteinuria (trace to 1 plus), the arterial reactivity shows a large, statistically significant decrease. At this point, venous reactivity is not significantly altered from the group without proteinuria, but with the appearance of massive proteinuria (2 to 4 plus), venous reactivity also falls markedly.

When the comparison is made for hypertensive subjects (table 3), the arterial reactivity is significantly decreased below the control level just by virtue of the subjects being hypertensive even without proteinuria. As the proteinuria becomes massive, the arterial reactivity is further decreased. Venous reactivity, while not significantly decreased in the group without proteinuria, falls markedly with the appearance of protein in the urine. To view the picture in reverse, of the 18 hypertensive subjects who showed proteinuria only, two had

*Significantly less than “control” subjects without vascular or renal disease (table 1).
† Significantly less than the mean of the category just above.
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TABLE 5.—Relation Between Proteinuria, Phenolsulfonphthalein Excretion, and Retinal Vascular Reactivity

<table>
<thead>
<tr>
<th>Degree of Proteinuria</th>
<th>No. of Subjects</th>
<th>% PSP Excretion in 2 Hours</th>
<th>Arterial Reactivity (%)</th>
<th>Venous Reactivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>62 ± 16</td>
<td>5.4* (5.0)</td>
<td>11.9 (5.9)</td>
</tr>
<tr>
<td>trace−1+</td>
<td>17</td>
<td>55 ± 19</td>
<td>5.0 (5.4)</td>
<td>11.0 (4.4)</td>
</tr>
<tr>
<td>2−4+</td>
<td>9</td>
<td>41 ± 26†</td>
<td>3.3 (5.0†)</td>
<td>36.0+</td>
</tr>
</tbody>
</table>

* Significantly less than “control” group (table 1).
† Significantly less than mean of category just above.
‡ Significantly less than PSP excretion of subjects with 0 proteinuria.

arterial reactivity within the normal range (8.1 and 19.5 per cent).

In general it appears that retinal arterial reactivity can easily be diminished without the appearance of proteinuria in hypertensive subjects. In all the subjects, the appearance of proteinuria indicates, to a high degree of probability, that retinal arterial reactivity is considerably reduced, and with massive proteinuria it tends to be further reduced. Venous reactivity follows the same general course, but the change is more gradual.

The test of phenolsulfonphthalein excretion was not done on subjects with a normal urine and nothing to suggest the possibility of renal disease. Consequently, the patients in whom it was performed constituted a specially selected group which proved to have a significant reduction below “control” values in both retinal arterial and venous reactivity. Several group-

TABLE 6.—Relation Between Serum Nonprotein Nitrogen and Retinal Vascular Reactivity: All Subjects

<table>
<thead>
<tr>
<th>Serum NPN (Mg. %)</th>
<th>No. of Subjects</th>
<th>Arterial Reactivity (%)</th>
<th>Venous Reactivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean  S.D.</td>
<td>Mean</td>
</tr>
<tr>
<td>20−30</td>
<td>13</td>
<td>6.0†</td>
<td>4.8</td>
</tr>
<tr>
<td>30−40</td>
<td>27</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Above 40</td>
<td>15</td>
<td>3.7</td>
<td>3.5</td>
</tr>
</tbody>
</table>

* Significantly different from “control” group (table 1).
† Significantly less than mean in category just above.

lings of these subjects were made on the basis of different levels of phenolsulfonphthalein excretion, but no significant difference in arterial or venous reactivity of these groups was observed. The results for the hypertensive patients are presented in table 4. The subjects were divided into two groups; one with a normal two hour phenolsulfonphthalein excretion and the other with a reduced excretion. In both groups the retinal vascular reactivity was altered and it changed little as the phenolsulfonphthalein excretion declined. In the reverse view, of the 15 hypertensive subjects with a subnormal phenolsulfonphthalein excretion only two had arterial reactivity within the normal range (8.1 and 19.5 per cent). These were the same patients who had proteinuria and normal reactivity.

In order to provide a better picture of the material on which this study was conducted, phenolsulfonphthalein excretion was compared with the level of proteinuria. The patients were divided according to the degree of proteinuria with the results presented in table 5. There is an apparent overall tendency for increasing proteinuria, decreasing phenolsulfonphthalein excretion and decreasing vascular reactivity to be associated.

As with the phenolsulfonphthalein excretion, the serum nonprotein nitrogen was determined in a selected group of patients whose overall picture indicated that it might be elevated. In consequence, the arterial reactivity of the group (table 6) is significantly below the “control” group even in the subgroup with a normal nonprotein nitrogen. In the first group venous reactivity is normal, but with the progressive increase in nonprotein nitrogen venous
reactivity shows a progressive and significant decline below normal values. When the analysis is confined to hypertensive subjects (table 7), retinal vascular reactivity is much reduced in the whole group with no significant difference between the groups with normal or elevated nonprotein nitrogen. Of the 12 patients with an elevated nonprotein nitrogen only two had normal retinal arterial reactivity. These were the same patients who also showed proteinuria and diminished phenolsulfonphthalein excretion with normal vascular reactivity.

**Discussion**

In a correlative investigation of this kind, interpretation of the results must, of course, be limited by the types of subjects used. This study included two general groups; one composed of hospital patients thought to be free of diseases which would affect the blood vessels or the kidneys and the other composed of patients with illnesses which are known to involve both systems. These were chronic illnesses, mostly hypertension, but included diabetes mellitus and chronic nephritis. In this group reactivity of the retinal arteries begins to be affected in advance of renal changes which produce marked proteinuria, diminished phenol sulfonphthalein excretion and increased nonprotein nitrogen. In the hypertensive patients severe impairment of retinal arterial reactivity occurred considerably in advance of evidence of renal damage. This functional evaluation is similar to the experience previously reported by Wendland on the basis of grading retinal and renal vascular disease by anatomical changes. By the time evidences of renal damage are definitely established, retinal arterial reactivity is nearly uniformly decreased and retinal venous reactivity is impaired.

In the hypertensive group of 35 patients, only two had the combination of vascular reactivity within the normal range and impaired renal function. Previous pathological studies have shown that marked renal impairment without retinopathy suggests a renal basis for the vascular disease. The clinical impression in these two patients was hypertensive cardiovascular disease and there was no evidence to suggest a primary renal basis for the hypertension. Four patients in the series were clinically diagnosed as having chronic renal disease, either glomerulonephritis or pyelonephritis; all had hypertension and all showed markedly impaired retinal vascular reactivity.

Account should be taken of the possibility that the retinal arteries of a hypertensive person might fail to constrict well in response to oxygen because they were already partially constricted or because constriction was opposed by the high intravascular pressure and not because of sclerotic changes in the wall. If the vessels were potentially motile but were already partly constricted, they should dilate relatively well in response to the proper stimulus. Retinal hypoxia will cause dilation of retinal arteries in both normal and hypertensive subjects, but the hypertensive vessels dilate less than the normal. The wall of the hypertensive artery shows less motility than the normal in either direction. Reduction of high intravascular pressures by the rice diet in a small group of hypertensives did not cause an immediate increase in arterial reactivity. It is concluded that decreased retinal arterial reactivity in hypertensive subjects is not an artifact but depends upon pathological changes in the vessel wall.

This investigation, it is believed, has presented an objective method for assessing degenerative vascular changes, at least in the retinal vessels, and correlating that change with renal function in the living patient. The results emphasize that changes in the retinal arteries precede more overt evidence of impaired kidney function in degenerative vascular diseases, particularly hypertension. When overt signs of renal damage are manifest the retinal veins are also involved.

**Conclusion**

Impairment of retinal arterial reactivity usually occurs in the course of chronic degenerative vascular disease, and particularly in hypertension, in advance of clinical evidence of altered kidney function. When renal damage is apparent, loss of retinal arterial and venous reactivity is usually far advanced.
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SUMMARIO IN INTERLINGUA

In hypertension e diabete il es un observation commun que le alterationes del vasos retinal, que es evidente sub le examine fundoscopic, es accompaniante per alterationes del vasos renal, que es evidente sub le examine microscopic. Il ha essite constatate que le vasos retinal del majoritade de patientes de hypertension o diabete non reage per un constriction normal al augmento del nivello oxygenic del sanguine. Le presente investigation provide un evaluation del significacion clinic del reducite reactivitate del vasos retinal in patientes con morbo vascular degenerative per poner lo in relation con le function del renes, mesurate per methodos clinic usual. Le resultatos del studio indica que defectuositate del reactivitate del vasos retinal occurre usualmente in le curso del morbo vascular degenerative, specialmente in hypertension, ante omne signo clinic de alterate functiones renal. Quando essayos clinic del functiones renal demonstra un lesion renal, le perdita del reactivitate retinal arterial e venose es semper multo avantiate.

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