Effect of Vasectomy on the Retinal Vasculature of Men

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Ophthalmoscopic examination of the retinal vasculature of 159 men over age 30 showed a significant increase in mild vascular changes in vasectomized as compared to nonvasectomized men. Although this preliminary study revealed no significant difference in blood pressures when the two groups were compared, vasectomized men age 40 and under had an increased frequency of arteriolar constriction in comparison with the control group. The authors suggest that this noninvasive method may be useful for future studies.

Key words: vasectomy, atherosclerosis, diffuse arteriolar sclerosis, hypertension, ophthalmoscope, retinopathy, sphygmomanometer, systolic blood pressure, diastolic blood pressure.

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Vasectomy has become widely accepted as a method of permanent birth control. The procedure is simple, inexpensive, and effective. However, numerous investigations have shown that an immune response to sperm antigens develops in half to two-thirds of vasectomized men (Ansbacher, 1971; Schulman et al, 1972; Alexander et al, 1974; Alexander, 1975; Samuel et al, 1975; Ansbacher et al, 1976).

Recent studies in both cynomolgus (*Macaca fascicularis*) and rhesus monkeys (*Macaca mulatta*) indicate that vasectomy may exacerbate the development of atherosclerosis (Alexander and Clarkson, 1978; Clarkson and Alexander, 1980). The basis for this vasectomy effect is considered to be immunologic injury to the arterial walls. In the studies in monkeys, tissues were taken at necropsy and evaluated morphologically, histologically, and with biochemical and immunological techniques. These findings suggest that vasectomy may increase risk of vascular disease.

The progression of vascular disease in man is difficult to evaluate by means of noninvasive techniques. However, the eye provides a unique chamber in which observation of the smaller vessels is possible. Normally, the retinal arterioles are almost transparent, so that the observer sees a column of blood with a central light reflex. This light streak is formed by the reflection of light from the convex surface of the blood column and the blood vessel wall (Newell and Ernest, 1974). Normal vessels appear to be gently undulating with arteries and veins crossing at oblique angles (Becker and Ley, 1967).

The ophthalmoscopic changes of hypertension usually relate to attenuation of arterioles. The earliest recognizable change is a diffuse constriction of the retinal arterioles. When this is more severe, the irregularities in caliber are superimposed upon diffuse narrowing. Many conditions, including hypertension and vasculitis, may cause vessel changes revealed as constrictions and, when more severe, may result in hemorrhage, exudates, and edema (Scheie and Albert, 1977; Rutstein et al, 1978).

The ophthalmoscopic signs of arteriolar sclerosis are often secondary to hypertension. Arteriolar sclerosis may be the anatomic reflection of

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a significant increase in blood pressure over a long period of time that results in thickening of the walls and narrowing of the lumina of arterioles in response to the hypertension. First, reflection of light from the arteriole wall increases, causing the streak of light to widen until it becomes so broad that it occupies most of the vessel, and the vessel has the appearance of a copper wire. In the advanced stage, the vessel wall becomes opaque and assumes the appearance of a silver wire (Scheie and Albert, 1977). Accompanying these arteriolar changes are changes occurring at the vessel crossing sites. Crossings tend to become right-angled, and defects in the venous column become apparent as depressions, notches, or humping of veins over thickened arterioles (Becker and Ley, 1967). In arteriolar sclerosis, the vascular involvement is generalized; therefore, all arterioles throughout the body are affected to a similar degree, in contrast to the discrete, plaque-like lesions of intimal atherosclerosis (Scheie and Albert, 1977).

Atherosclerosis manifests itself in the eye mainly by involvement of the central retinal artery within the optic nerve or in those branches immediately adjacent to the optic disk (Newell and Ernest, 1974). Atherosclerosis is characterized by focal necrosis and thickening of the intima, with intimal and subintimal lipid deposition associated with hyperplastic and degenerative changes in the arterial wall, particularly of the internal elastic lamina.

The purpose of this preliminary study is to examine in man the relationship between vasectomy and vascular damage of the retinal arterioles. Ophthalmoscopic observation of retinal fundi is regarded as a good index of the process of hypertension and arteriolar sclerotic vascular changes (Yamori et al, 1977). Therefore, we used an ophthalmoscopic approach to determine whether vasectomy is linked to increased risk of vascular disease.

Methods

One hundred fifty-nine volunteer male subjects, consisting largely of college faculty and scientists, were drawn from three different academic centers. Bilateral ophthalmoscopic examination, blood pressure measurements, and case histories were obtained, in that sequence, to ensure that evaluations were done without bias. Thus, the investigator recorded the results of the ophthalmoscopic examination with no knowledge of whether the individual had had a vasectomy.

Retinal arterioles of both fundi were examined for evidence of hypertension and arteriolar sclerosis. Vein nicking, tapering, deviation, or sheathing of arterioles was recorded. Retinopathy was classified according to a modified Keith-Wagener (K-W) four stage grading system (Table 1) (Vaughan and Asbury, 1977; Wagener and Keith, 1939). All ophthalmoscopic examinations were performed by the same observer two to three disk diam-

TABLE 1. A Classification of Hypertensive Retinopathy and Arteriolarsclerotic Retinopathy (modified after Keith and Wagener)

Stage	Ophthalmoscopic Appearance	Clinical Classifications
0	A/V ratio > 1/2. R/A ratio 1/4–1/3.	Normal.
I	A/V ratio < 1/2. R/A ratio > 1/3. Minimal narrowing or sclerosis of arterioles. Some focal constrictions.	
II	A/V ratio < 1/2. R/A ratio > 1/3. Thickening and dulling of vessel reflection (copper-wire appearance). Many focal constrictions. Generalized narrowing of arterioles. Changes at arteriovenous crossings (A/V nicking). Scattered round or flame-shaped hemorrhages. Vascular occlusion may be present. Very small exudates.	"Essential" hypertension (chronic, benign, "arteriosclerotic").
III	Sclerotic changes may not be marked. "Angiospastic retinopathy": Localized arteriolar spasm, hemorrhages, exudates, "cotton wool patches," retinal edema. Sheathing of arterioles. Silver wire appearance of vessels.	Accelerated hypertension.
IV	Same as III, plus edema of optic disk.	

A/V = arteriovenous ratio (hypertensive retinopathy).
R/A = reflex to artery ratio (arteriolarsclerotic retinopathy).

eters from the optic disk; a mydriatic agent was not used. Ophthalmoscopic examination was followed by systolic and diastolic blood pressure measurements from the seated subject. Systolic and both the diastolic muffle and fade were recorded using a mercury column sphygmomanometer and a stethoscope; diastolic muffle readings were used for analysis. Blood pressure readings were repeated 5 minutes later and, if one value was elevated, it was discarded and the normal value was recorded.

A case history also was obtained to determine age, weight, height, occupation, presence of cardiovascular diseases, renal disease, hypertension, and whether vasectomized, and if vasectomized, time since the vasectomy. Inquiries were also made concerning the subject's general health, ocular history, familial history, medications used, allergies, and whether or not the subjects were smokers.

Statistical analysis focused on the inter-relationship of ophthalmoscopic evaluation, systolic blood pressure, diastolic blood pressure, age, smoking habit, the presence of vasectomy, and the length of time since vasectomy. All other data were taken to confound the subjects and were not analyzed. Multiway contingency tables were constructed for the following dichotomous variables and analyzed with the *G* test of independence (Sokal and Rohlf, 1969): K-W score greater than 0, presence of vasectomy, presence of smoking habit, and age greater than 40 years.

For this analysis, either a two-stage regression model or a single-stage multiple regression model could be used. We chose the two-stage structured multiple regression (Li, 1975) to take full advantage of the detailed ophthalmoscopic, age, and blood pressure data. In the first stage, systolic and diastolic blood pressures were treated as dependent variables with age, smoking habit, and vasectomy as independent variables. The residual blood pressures (ie, those parts of the blood pressures not explained by the independent variables) were then used as independent variables in stage II along with age, smoking habit, and vasectomy. Square roots of the ophthalmoscopic K-W scores fit the regression model better than did the raw scores.

Results

The study group was confined to men over 30 years old. Since none of the vasectomized group and only six of the nonvasectomized group were older than 60 years, these six subjects were not included in the subsequent multiway contingency analysis. A summary of the data from subjects in the study with stage 0, I, or II K-W changes is shown in Table 2. None of the men studied had stage III or IV K-W type retinal vascular changes, nor were Hollenhorst plaques or lesions observed.

We determined whether retinal vascular change, age, vasectomy, and smoking were mutually independent of each other. Since the number of smokers in some categories was insufficient for us to perform a *G* test of independence, smokers were lumped with nonsmokers. The prevalence of smoking appeared to be independent of all factors except to show an increase with age. The analysis of the remaining factors is shown in Table 3. Retinal vascular change, age, and vasectomy were not mutually independent ($P < 0.01$). Age and retinal changes were inter-related; the incidence of K-W scores greater than 0 increased after 40 years of age. Overall, the vasectomized group did not differ from the nonvasectomized group in age or retinal damage. However, the significant ($P < 0.05$) interaction among K-W score, age, and vasectomy indicates a complex relationship among the three variables. Examination of Table 2 shows that in men 40 years old or younger, vasectomy was associated with an increase in frequency of K-W score greater than 0 (adjusted *G* statistic = 3.921, 1 *df*, $P < 0.05$). However, vasectomized and nonvasectomized men older than 40 years did not differ significantly in frequency of K-W scores greater than 0.

The first stage of the regression analysis determined the relationship between dependent variables, systolic and diastolic blood pressures, and the independent variables, age, vasectomy, smoking, and all two- and three-way interactions among these variables. Smoking and all interac-

TABLE 2. Multiway Contingency Table for Stage of Hypertensive and Arteriolarsclerotic Retinopathy in Vasectomized and Normal Men with Respect to Age

	Vasectomized Men			Nonvasectomized Men			
	Age (yr)		Sub-	Age (yr)		Sub-	
	≤40	>40	totals	≤40	>40	totals	Totals
K-W stage 0	7	12	19	28	35	63	82
K-W stage greater than 0	8	14	22	7	42	49	71
Column sums	15	26	41	35	77	112	153*

* Six men over 60 years old from the nonvasectomized group were not included.

TABLE 3. G Test of Independence for Table 2 Data

Hypothesis Tested	Degrees of Freedom	G Statistic
K-W score × age independence	1	8.224*
K-W score × vasectomy independence	1	1.183
Vasectomy × age independence	1	0.384
K-W score × age × vasectomy interaction	1	4.150†
K-W score × age × vasectomy independence	4	13.944*

* $P \leq 0.01$.
† $P \leq 0.05$.

tions between smoking and the other variables had no apparent effect on either blood pressure and were dropped from the model. The analysis was then equivalent to the analysis of covariance of the effect of vasectomy on blood pressure with age as a covariate. The results show that both blood pressures increased significantly ($P < 0.05$) with age, the systolic increasing by 0.4 per year (SE = 0.17, 154 *df*) and the diastolic increasing by 0.2 per year (SE = 0.1, 154 *df*). Vasectomized and nonvasectomized individuals did not differ significantly in either of the mean blood pressures or in the rates of change of the blood pressures with age.

Age, vasectomy, and smoking may produce retinal vascular changes directly or through their effects on either blood pressure variable. The mechanisms may be separated by using residual blood pressures from the analyses of covariance as independent variables instead of raw blood pressure values. Therefore, the second stage of the regression analysis consisted of the eight independent variables, age, vasectomy, smoking, residual systolic blood pressure, residual diastolic blood pressure, and all two-way interactions among age, vasectomy, and smoking. A preliminary examination of the fit of the K-W scores to the regression data showed that transforming the raw K-W scores to square roots gave a better fit to the regression model. This transformation, in effect, modified the K-W scale to bring scores of 2, 3, and 4 closer to 1. Modified scores were used for the final analysis. Nonsignificant independent variables were deleted stepwise until the error mean square reached a minimum with age, vasectomy, and residual diastolic blood pressure remaining in the model. Table 4 shows that only age explained a significant ($P < 0.01$) part of the variation in retinal damage, increasing the square root K-W score by 0.015 per year (SE = 0.005, 154 *df*). Vasectomized individuals had a square root K-W score 0.17 higher (SE = 0.109, 154 *df*) than nonvasectomized men, but this value was not significantly different from zero ($0.10 < P < 0.25$). There is no evidence in this study that either systolic or diastolic blood pressure is an important intermediate variable linking age to retinal vascular damage.

Discussion

The retinal changes observed in all subjects in this study were relatively mild; systolic and diastolic blood pressures did not exceed 164 mmHg and 114 mmHg, respectively. Although systolic and diastolic blood pressures increased significantly with age in both groups, vasectomized and nonvasectomized individuals did not differ significantly in systolic or diastolic blood pressures or in the rate of change of blood pressures with age. In this study, there is no evidence that systolic or diastolic blood pressures are important variables linking age to retinal vascular damage. Smoking appeared to be independent of all factors, except that the incidence of smoking increases with age. Our study was a preliminary one

TABLE 4. Analysis of Variance for Multiple Regression of Square Roots of K-W Scores on Age, Presence of Vasectomy, and Residual Diastolic Blood Pressure

Source of Variation	Degrees of Freedom	Sum of Squares	*F* Statistic
Total	157	56.482	
Multiple regression model	3	4.003	3.916*
Age	1	3.206	9.407*
Vasectomy	1	0.875	2.567
Residual diastolic blood pressure	1	0.373	1.094
Residual error	154	52.478	

* $P < 0.01$.

and did not take into consideration the possible contributions of numerous other factors known to affect vascular changes (eg, stress, exercise, personality type, serum cholesterol levels, and genetic predisposition to vascular disease).

Age and retinal changes were inter-related. As expected, there was an increase in frequency of hypertensive vascular changes with increasing age in both vasectomized and nonvasectomized men. However, there was a significant interaction between retinal changes, age, and vasectomy. Vasectomized men under 40 years old showed an increased proportion of arteriolar changes as compared to nonvasectomized men of the same age group. However, arteriolar changes in vasectomized and nonvasectomized men over 40 years old did not differ significantly. That the arteriolar changes might manifest themselves within the average five years after vasectomy could be considered surprising. The rapidity of onset and the degree of arteriolar changes depend on both the duration and severity of their causes. We suggest that the changes reflected in the significantly increased incidence of K-W I and II values among the vasectomized group under age 40 as compared to the control group of the same age may be attributed to possible circulating immune complexes that may result in vascular changes after vasectomy (Alexander and Anderson, 1979). We assume that vascular changes could be similar to those previously reported in monkeys (Alexander and Clarkson, 1978; Clarkson and Alexander, 1980). However, the studies in monkeys showed atherosclerotic changes in the aortic system and in the large arteries of the body (retinal vasculature was not examined). Since atherosclerosis by definition affects arteries but not arterioles, we would not expect to see an effect on the retinal vasculature, which is by definition composed of arterioles, with the exception of the central retinal artery (Hollenhorst, 1966). Whether immune complex vasculitis does indeed occur in some vasectomized men requires further studies.

Our data, although drawn from a small sample from the academic community, suggest that vasectomy may cause vascular changes in men. Since our study group showed mild vascular changes in the form of constriction and arteriolar sclerotic changes (no lesions or Hollenhorst plaques were observed), our findings cannot be said to be a barometer of generalized vascular disease (Hollenhorst, 1966; Greenberg and May, 1978) in man due to vasectomy, although the results may indicate that vasectomy could be regarded as a suspect event.

We suggest that this noninvasive method may prove useful for future studies on the effect of vasectomy on vascular changes. Complete studies using photographic analysis by several independent observers on a larger sample of individuals are necessary to validate this preliminary experiment. We propose that further research through the use of sequential evaluations of a group of vasectomized and control men would be appropriate.

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