Hypertension

Laboratory Studies

Decreased Intraocular Pressure in Dogs with One-Kidney, One Wrapped Hypertension

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SUMMARY We examined the relationship of intraocular pressure and the development of one-kidney, one wrapped (perinephritic) hypertension in the dog. Conscious femoral arterial pressure (direct arterial puncture) and intraocular pressure (Schiotz tonometer) were measured weekly before and after the surgical induction of hypertension in 11 healthy male mongrel dogs and before and after unilateral nephrectomy in 15 normotensive control dogs. Preoperative mean arterial pressure (102 ± 5 vs 99 ± 8 [SD] mm Hg, hypertensive vs control dogs) and intraocular pressure (18.1 ± 2.5 vs 17.7 ± 2.1 mm Hg, hypertensive vs control dogs) were similar in both groups. In normotensive control dogs, mean arterial pressure and intraocular pressure averaged over the postoperative period (4-8 weeks) did not differ significantly from preoperative values. In contrast, during the same period arterial pressure significantly increased and intraocular pressure significantly decreased in hypertensive dogs (arterial pressure, 163 ± 8 mm Hg; intraocular pressure, 11.9 ± 4.0 mm Hg; p < 0.001 for both values compared with corresponding values in control dogs). Intraocular pressure was inversely related to arterial pressure in hypertensive dogs (r = 0.56, p < 0.01). These observations indicate that intraocular pressure decreases with the development of canine one-kidney, one wrapped hypertension. The mechanism of this decrease may be related to abnormalities in Na⁺,K⁺-adenosine triphosphatase activity found in this form of hypertension. (Hypertension 10: 152-156, 1987)

KEY WORDS • blood pressure • aqueous humor • Na⁺,K⁺-adenosine triphosphatase

THERE is evidence for a circulating inhibitor of the Na⁺,K⁺ pump in dogs with chronic one-kidney, one wrapped (1K1W; perinephritic) hypertension.1,2 Because inhibition of Na⁺,K⁺-adenosine triphosphatase (Na⁺,K⁺-ATPase) has been associated with decreases in intraocular pressure,3,4 we measured intraocular pressure during the development of perinephritic hypertension in dogs.

Materials and Methods

Our techniques were similar to those we have used previously.1,5 Briefly, we trained healthy male mongrel pound dogs weighing between 20 and 32 kg and maintained on standard dog chow and water ad libitum to lie quietly for measurements of baseline arterial and intraocular pressure (IOP). We measured IOP with a Schiotz tonometer after corneal anesthesia with proparacaine hydrochloride (Opthaine, 0.5%; E.R. Squibb & Sons, Princeton, NJ, USA). At each session, IOP was measured at least twice in each eye and the mean value was converted to millimeters of mercury (conversion table provided with the tonometer). We measured intraocular pressure during the development of perinephritic hypertension in dogs.

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Received December 18, 1986; accepted March 9, 1987.
DECREASED INTRAOCULAR PRESSURE IN HYPERTENSIVE DOGS/Bell et al.

Pfizer, New York, NY, USA), for 5 successive days. We measured femoral arterial pressure, IOP, body weight, and hematocrit weekly in all dogs and carefully monitored general health postoperatively.

After 4 to 8 weeks of sustained hypertension (mean arterial pressure > 140 mm Hg) in 1K1W dogs and at a similar time period in the 1K control animals, we prepared the dogs for a terminal experiment reported elsewhere. At necropsy, we measured plasma Na⁺ and K⁺ by flame photometry (Instrumentation Laboratory, Lexington, MA, USA), plasma creatinine (Creatinine Determination Kit; Sigma Chemical Corp., St. Louis, MO, USA), urine blood and protein (Multistix: Ames Division, Miles Laboratories, Elkhart, IN, USA), as well as heart and kidney weights. We examined other organs for gross abnormalities. We did not use data from dogs that, at the terminal procedure, had a greater than 10% decrease in body weight or hematocrit or that had retinal hemorrhages, detachment, or both; intestinal bleeding; hematuria or proteinuria; or plasma Na⁺, K⁺, or creatinine concentrations outside two standard deviations from mean values in control dogs. Procedures followed in dogs throughout the study were in accordance with institutional guidelines.

Data in text and figures are expressed as means ± SD. Mean values between groups were compared with the unpaired two-tailed Student's t test; a paired test was used for within-group comparisons. The null hypothesis was rejected at a p<0.05. Regression analysis was used to compare IOP and mean femoral arterial pressure.

Results

All animals remained in good health throughout the study, and necropsy revealed no gross abnormalities other than perinephritis. Plasma Na⁺ (143 ± 6 vs 142 ± 6 mEq/L), K⁺ (4.94 ± 0.58 vs 4.50 ± 0.41 mEq/L), creatinine (1.40 ± 0.70 vs 1.49 ± 0.41 mg/dl), and urinalysis values remained within normal limits in 1K1W versus 1K control dogs. Kidney weight and the ratio of kidney weight to body weight did not differ in the two groups of dogs, but the ratio of heart weight to body weight was elevated in 1K1W dogs compared with that in 1K dogs (6.23 ± 0.70 vs 6.84 ± 0.56 g/kg; p<0.001).

Postoperatively, hematocrit decreased significantly (p<0.05) in 1K1W dogs, but not in 1K dogs. In 1K1W dogs, mean preoperative hematocrit was 43.6 ± 3.2%, decreasing to 40.1 ± 4.9% after the first operation and to 38.6 ± 2.9% after the second operation. However, beginning 3 weeks postoperatively, hematocrits in 1K1W dogs and 1K dogs were similar.

The results of weekly measurements of mean arterial pressure and IOP are shown in Figure 1. All dogs were studied for at least 4 postoperative weeks, some for as long as 8 weeks. Preoperative mean arterial pressure and IOP were similar in hypertensive 1K1W dogs and 1K control dogs (mean arterial pressure, 102 ± 5 vs 99 ± 8 mm Hg; mean IOP, 18.1 ± 2.5 vs 17.7 ± 2.1 mm Hg). During the 4- to 8-week postoperative period mean arterial pressure and IOP in the 1K dogs did not change significantly (108 ± 7 and 17.3 ± 2.6 mm Hg, respectively). In contrast to these normotensive dogs, blood pressure in 1K1W dogs increased during the postoperative period. During the week following wrapping mean arterial pressure rose 12 ± 9 mm Hg (p<0.05 vs preoperative control values), and a further rise of 23 ± 16 mm Hg occurred following nephrectomy.

In 1K1W dogs a trend for reduction in IOP during the week following wrapping was not statistically significant. However, in this hypertensive group IOP was reduced by an average of 4.8 mm Hg within 1 week after nephrectomy (p<0.01). Mean arterial pressure and IOP in 1K1W dogs averaged over the entire postoperative period were 163 ± 8 and 11.9 ± 4.0 mm Hg, respectively. Both of these values were significantly different (p<0.001) from corresponding values in 1K dogs.

FIGURE 1. Time course of mean arterial pressure and intraocular pressure in one-kidney, one wrapped hypertensive (1K1W; ○) and one-kidney control normotensive (1K; □) dogs. All values are means ± SD. Preop = preoperative control period; first op = left kidney wrapped in silk (1K1W) or left kidney dissected free of its fat pad (1K); second op = right nephrectomy. Numbers in parentheses represent number of dogs observed at that time point; occasionally, measurement of arterial pressure or intraocular pressure was unsuccessful in a given dog, as reflected by differences in these numbers.
There was a significant inverse linear relationship between IOP and arterial pressure in the hypertensive dogs \((r = 0.56, p < 0.01; \text{Figure 2})\), but not in normotensive control dogs.

**Discussion**

The results of this study indicate that IOP is significantly reduced in dogs with perinephritic hypertension as compared with normotensive control dogs. The hypertensive dogs studied were in good health with no evidence of azotemia or dehydration. The reduction in IOP occurred within the first 2 weeks of hypertension, paralleled the rise in blood pressure, and was proportional to the level of hypertension.

There have been few previous studies of the relationship between IOP and experimental hypertension. Acute increases in arterial pressure in response to intravenous infusion of epinephrine or vasopressin elevate, rather than reduce, IOP.\(^8\) We could find only one other study of IOP in chronic experimental hypertension. Funk et al.\(^9\) reported that IOP is decreased in stroke-prone spontaneously hypertensive rats compared with that in normotensive Wistar-Kyoto controls and found a negative correlation between IOP and blood pressure in hypertensive rats. They suggested that a reduced compliance of intraocular vessels may have been responsible. Their measurements of IOP were made in pentobarbital-anesthetized rats; barbiturates decrease IOP\(^{10}\) and may have differential effects in hypertensive and normotensive animals. Nevertheless, their findings in genetic hypertension in rats resemble ours in canine perinephritic hypertension.

In clinical studies, Williams et al.\(^{11,12}\) reported no differences in mean daily IOP between hypertensive and normotensive patients. Williams and Ledingham\(^13\) later reported that morning, but not afternoon, measurements of IOP were increased in hypertensive patients. In these studies the hypertensive patients were not subdivided on the basis of etiology of their disease, so that abnormalities in subgroups (e.g., renovascular hypertensive subjects) may have been undetected. We find no reported studies of IOP in patients with renovascular hypertension. Bullett\(^{14}\) reported a weak positive correlation between arterial and intraocular pressures in elderly patients; however, interpretation of this finding is complicated by the fact that IOP and blood pressure both rise with age.\(^{15}\) A correlation has also been reported between the occurrence of hypertension and glaucoma.\(^{16}\) Watson and Greenwood\(^{17}\) and Gafter et al.\(^{18}\) reported slightly elevated arterial pressure and low IOP in azotemic patients that did not change with hemodialysis. Low IOP has also been reported in azotemic dogs; blood pressure was not measured.\(^{19}\)

Several possible mechanisms may account for the decreased IOP we observed in this study in dogs with renal hypertension. The reduced IOP may have been an effect of the hypertension. In this regard, blood pressure rose significantly during the week after renal wrapping, but trends toward decreases in IOP did not reach statistical significance until after nephrectomy. However, this apparent time lag may well be explained by the greater experimental variation in measurements of IOP.

Alternatively, the decrease in IOP may have reflected underlying disease mechanisms. Changes in IOP occur in response to several variables that may be deranged in hypertension: 1) a positive relationship between IOP and body fluid volumes,\(^{16-22}\) 2) complex effects of autonomic influences on IOP, and 3) a positive relationship between IOP and the activity of \(\text{Na}^+,\text{K}^+-\text{ATPase}.\)^\(^{4,22}\)

Regarding fluid volumes, plasma \(\text{Na}^+\) concentration in our hypertensive dogs in this and previous\(^{23}\) studies remained within normal ranges. Furthermore, in the early stages of 1K1W hypertension when IOP is falling, body fluid volumes are probably increasing.\(^{24}\) This change may be reflected in our study by the decrease in hematocrit in hypertensive dogs 1 and 2 weeks postoperatively. Ferrario and Page\(^{25}\) have shown that plasma and extracellular fluid volumes are normal later in the course of canine perinephritic hypertension. Therefore, it is unlikely that decreases in body fluid volumes or increases in osmolality account for the reduced IOP we observed in our perinephritic hypertensive dogs.

Enhanced sympathetic nerve activity has been reported in some forms of hypertension.\(^{26}\) Both the production and drainage of aqueous humor are under autonomic control.\(^{27,28}\) Although specific effects of autonomic stimulation, denervation, or blockade on IOP are controversial,\(^ {20,21,28-37}\) such autonomic effects certainly could be involved in the decreased IOP we observed in canine perinephritic hypertension.

Finally, active transport of \(\text{Na}^+\) into the anterior chamber is a function of ciliary \(\text{Na}^+,\text{K}^+-\text{ATPase}\) and serves as a major determinant of the production of aqueous humor and, hence, of IOP.\(^2\) Inhibition of ciliary \(\text{Na}^+\) transport reduces secretion of aqueous hu-
DECREASED INTRACULAR PRESSURE IN HYPERTENSIVE DOGS/Bell et al. 155

mor38, 29 and the level of IOP. 4, 16, 35, 38, 40 For example, intravenously administered digitalis in the cat or intravitreal or corneal application of ouabain in the rabbit decreases IOP. Ciliarectomy and parasympathectomy also decrease formation of aqueous humor by reducing ciliary Na<sup>+</sup>,K<sup>+</sup>-ATPase activity. 29

Azotemia is associated with humoral inhibition of Na<sup>+</sup>+,K<sup>+</sup>-ATPase 41 and a reduction in IOP, 17 but our dogs were not azotemic. On the other hand, we have provided evidence for a circulating inhibitor of Na<sup>+</sup>+,K<sup>+</sup>-ATPase in similarly prepared dogs in the chronic benign stages of I1W hypertension, 1, 5 a finding that has been more recently confirmed. 2 Recently, we have found evidence that this inhibitor is also present in very early stages of the hypertension, when IOP falls (Overbeck et al., unpublished observations, 1987). Such a humoral inhibitor may decrease ciliary active transport of Na<sup>+</sup> into the anterior chamber. Additionally, the inhibitor may reduce Na<sup>+</sup>+,K<sup>+</sup>-ATPase activity by inhibiting autonomic supply to the ciliary body. Thus, the reduced IOP we observed may reflect the direct and indirect actions of the circulating Na<sup>+</sup>+,K<sup>+</sup>-ATPase inhibitor in this form of hypertension. Further work is required to test this possibility, including careful assessment of temporal relationships.

Although our present studies do not further define underlying mechanisms, investigation of the reduced IOP we have observed in perinephritic hypertensive dogs may lead to further understanding of basic disease mechanisms and may prove useful in identifying certain subtypes of human hypertension.

Acknowledgment

We acknowledge the excellent technical support of Robert E. Blackmon.

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Hypertension. 1987;10:152-156
doi: 10.1161/01.HYP.10.2.152

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/10/2/152

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