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LABORATORY STUDY

Absence of Hypertension in Dogs with Renal Insufficiency

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ABSTRACT

Dogs have provided classic models of induced hypertension. This paper shows that despite being susceptible to hypertension, they are naturally resistant to its development even when renal function is severely compromised. The proportion of hypertensive dogs was almost as low among those with reduced glomerular filtration rate (GFR) (9%) as those with normal GFR (6%). Dogs with GFR less than 33% of the normal lower limit (with an average GFR equivalent to 10 mL min^{-1} in a 70-kg patient) had arterial pressures not significantly above normal. Only dogs with a GFR 33–75% of the lower limit of normal had significantly elevated systolic pressure, though none was actually hypertensive. Since there was no correlation between arterial pressure and GFR below 33% of lower limit, the dogs in the 33–75% range may be showing an effect of increased pressure, rather than a cause. In humans with GFR less than 33% of normal, the majority are hypertensive. Since various aspects of canine cardiovascular and renal function are comparable with humans, the question is why dogs, despite being capable of developing hypertension, are resistant to it, even when they have chronic renal insufficiency.

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INTRODUCTION

The dog has always been at the center of the comparative medicine of hypertension. Hales made the first direct measurements of canine arterial pressure and, expressed in conventional units, these averaged 112 ± 9 mm Hg (± SEM) in animals weighing from 3 to 24 kg (1). The original Goldblatt model of hypertension was in dogs. Yet clinically, canine hypertension has always seemed likely to be rare despite the fact that dogs seldom have routine measurements of their blood pressure. The canine ocular fundus is frequently examined and if hypertension were prevalent the typical lesions (2–5) would be seen more frequently—indeed, blindness is regarded as a common presenting sign of canine hypertension. A remarkable screening study of 1000 dogs (6) found less than 1% with a pressure above "normal" (148 ± 8 mm Hg). An earlier study of "street dogs" subject to a femoral artery puncture found hypertension in only 2% (7). While these suggested a low prevalence, they were colored by the use of invasive measurements in untrained animals; hence the inevitable elevation of the "normal" values (8). Spangler et al. (9) also found a low prevalence, this time with noninvasive measurements, but, like the Katz study (6), the data were exclusively from young dogs.

A low prevalence of hypertension, compared with humans, need mean no more than the virtual absence of essential hypertension. Michell (10) noted evidence, however, that dogs are also resistant to the induction of hypertension and the effects of salt loading. Specifically, they appeared resistant to hypertension even when they had chronic renal failure (CRF) whereas in humans renal parenchymal disease is a major cause of secondary hypertension (11). If so, the reasons for this resistance deserve specific investigation since dogs, like humans, customarily have at least ten times the dietary sodium intake needed to meet their nutritional requirement (12) and show the associated age-related rise in blood pressure (1,13). First, however, it was necessary to confirm the hypothesis that dogs are resistant to hypertension even when they have chronic renal insufficiency (10). This required two studies. The first (13,14) established that in a population of 1900 dogs, hypertension was unusual, although certain breeds had "normal" pressures which were remarkably high. Among the diseases associated with higher pressures, chronic renal failure was not a striking cause of secondary hypertension.

The second study, described here, examined blood pressure and glomerular filtration rate in some 130 pet dogs referred to us because of symptoms that might indicate CRF (e.g., polydipsia, polyuria) or because of established elevation of blood pressure or a familial history of renal disease.

METHODS

Arterial pressure was measured noninvasively using a tail cuff of the appropriate size and an oscillometric monitor (Dinamap 1846); this method has been validated in both conscious and anesthetised dogs (15,16). Glomerular filtration rate (GFR) was measured by the plasma clearance of Tc-DTPA and the result expressed as GFR/ECFV (extracellular fluid volume); the lower limit of normal (0.01 min^{-1}) corresponds to approximately 2 mL min^{-1} kg^{-} (17,18). This corresponds to the plasma clearance of Tc-DTPA observed in normal dogs by Klopper et al. (19). We compared blood pressures in dogs below (n = 66) and above (n = 68) this limit, the latter group being regarded as "normals" and the former as "subnormals" for this study. Means ± SE are given unless otherwise stated. "High

pressure" breeds [i.e., greyhounds, deerhounds, lurchers, afghans, etc. (13)] were excluded from both groups.

RESULTS

Systolic blood pressure in the normals was 131.5 ± 21.5 mm Hg (*SD*) giving an upper normal limit (mean ± 2 *SD*) of 175 mm Hg. This mean (like that for diastolic pressure) was within 0.2 of that for 1267 normal dogs in our population study (13). The proportions of the groups with pressures above the limit were 6% (normals) and 9% (subnormals). Correspondingly, for diastolic pressure, the mean for normals was 74.0 ± 18.3 mm Hg (*SD*), giving an upper limit of 111 mm Hg. The proportion of dogs with normal GFR and higher diastolic pressures was 4%, whereas 8% of dogs with subnormal GFR had higher pressures. Mean systolic pressure for the subnormal GFR group was not statistically different (135.3 ± 3.5 mm Hg); the same was true for diastolic pressure (78.6 ± 2.7 mm Hg; means ± *SE*).

Dogs with more extreme renal insufficiency were selected by choosing those with a GFR of 33% or less of the lower limit of normal. Mean GFR in this group was 0.00171 ± 0.00015 (*SE*) min^{-1} compared with 0.0134 ± 0.0027 min^{-1} in the normal group; average GFR in the renal insufficiency (chronic renal failure: CRF) group was merely 13% of that in the normal group and their lowest GFRs, assuming 20 kg body weight of which 20% is ECFV, correspond approximately to 10 mL/min in a 70-kg patient. Yet there was no significant difference between the normals and the CRF group in either systolic (131.5 ± 2.6, 143.6 ± 7.6) or diastolic pressure (74.0 ± 2.2, 83.8 ± 6.1 mm Hg). The mean GFR in the normal group corresponds to 2.68 mL min^{-1} kg^{-1}, exactly the same figure as that found with Tc-DTPA in 9 normal dogs by Moe and Heine (20).

There was a negative correlation between systolic pressure and GFR in dogs where the latter was below the normal limit ($r = -0.345$, $p < 0.01$) but no significant correlation for dogs with GFR less than 33% of normal ($r = 0.021$, $p > 0.9$) or for all dogs throughout the range of GFR ($r = -0.122$, $p > 0.16$). Dogs in the range of GFR 33–75% of the lower limit of normal had a mean systolic pressure of 144.8 ± 5.9, significantly above the normal group ($p < 0.05$). Diastolic pressure was also significantly above normal (68.3 ± 2.4 mm Hg, $p < 0.025$). Dogs between 75% and 100% of the lower limit of GFR had a mean systolic pressure (121.6 ± 3.7) below the normal group ($p < 0.05$) but no significant difference in diastolic pressure (68.3 ± 2.4 mm Hg). There was no significant difference in pulse pressure between normals (57.5 ± 1.4), subnormals (56.7 ± 1.3), and dogs with more extreme renal insufficiency (59.7 ± 2.7 mm Hg).

The absence of a relationship between reduced GFR and increased arterial pressure is clear in Figure 1 (systolic) and Figure 2 (diastolic). Thus, while there was a tendency for some dogs with renal insufficiency to have higher pressures, the trend was very slight and the differences were not statistically significant, even when renal insufficiency was substantial.

DISCUSSION

We are not the first to observe that dogs may be more interesting in the comparative medicine of hypertension because they differ from humans, rather than because they resemble them. Stamler et al. (21) noted that "canine chronic benign blood pressure does

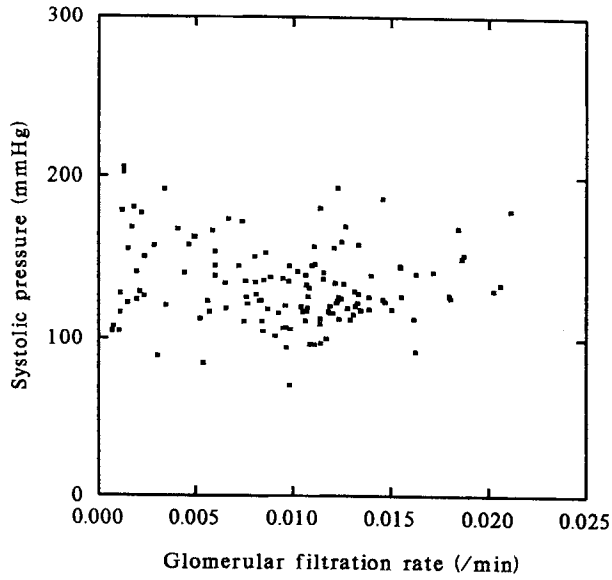

Figure 1. Scatterplot of data for systolic pressure (mm Hg) and GFR/ECFV (lower limit of normal = 0.010).

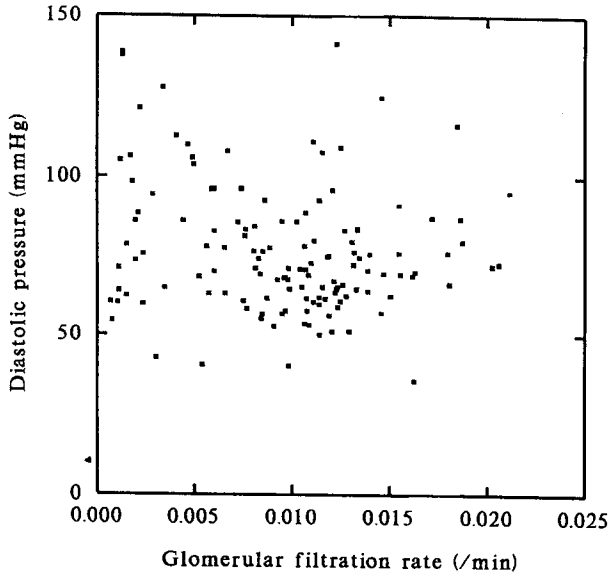

Figure 2. Scatterplot of data for diastolic pressure (mm Hg) and GFR/ECFV (lower limit of normal = 0.010).

not result in any progressive impairment of renal function," and despite the limitations of their data, their conclusion is interesting. Dogs are also resistant to the adverse effects of excessive sodium intake unless it is combined with stress or obesity (1). Moreover, hyperinsulinemia does not cause hypertension in dogs in a variety of situations (22) and diabetes mellitus is not a prominent cause of canine hypertension, especially when allowance is made for age (13). Together with the low prevalence of hypertension, this could explain the fact that diabetic nephropathy is seldom recognized in dogs, though some may develop proteinuria (1). An important factor in diabetic nephropathy is afferent arteriolar relaxation which exposes the glomeruli to damaging hypertension even when systemic pressure is only mildly elevated. It could, of course, be missed, and it could require longer to develop than the usual life span of diabetic dogs. This seems unlikely, however, since induced diabetes mellitus does cause lesions, and dogs with diabetes do have reduced afferent arteriolar tone (1).

The difference between dogs and humans could lie in the nature of their renal disease; thus in humans there is a view that glomerular disease is more likely than tubulointerstitial disease to cause hypertension (11,23,24), though there are clear exceptions and also those who reject this view (12,25). The picture is complicated by patients who may have confirmed renal lesions, yet no detectable proteinuria (26). Kheder et al. (27) found a prevalence of hypertension of 42% among patients with chronic glomerulonephritis confirmed by biopsy. Hypertension can develop in glomerular disease even before the onset of renal insufficiency (11,28), though it should be emphasized that the latter may be missed if proteinuria is the screening test, and also that GFR may increase in the early stages of glomerulonephritis (29). It is important that the effect of renal insufficiency on arterial pressure is examined in studies where the patients are initially normotensive because systemic hypertension accelerates the progression of renal disease (11,24).

Renal failure occurs with increasing prevalence as dogs age; 1.25% at age 7–10, 2.4% age 10–15 and 5.7% in older dogs (30). Glomerular disease is generally regarded as uncommon, though not rare, in dogs, and since awareness of its importance has only emerged during the last 25 years it may be underdiagnosed (31–33). Proteinuria is an insensitive test for canine renal insufficiency; the latter frequently occurs without it (34). Familial glomerulonephritis in young spaniels causes hypertension (35). Samoyeds provide a model of hereditary glomerulonephritis (36) but, as yet, data on their arterial pressure have not appeared.

In humans, nearly 90% of those with advanced CRF are hypertensive (37) and where renal disease and hypertension coexist, the latter is likely to be the consequence (38), though it is not always clear which is the chicken and which the egg (28). Thus the data of the recent "MRFIT" study show that systolic hypertension is a major risk factor in causing end-stage CRF but cannot exclude the possibility that, at least in some cases, renal insufficiency preceded the onset of hypertension (39). Moreover, if, as Zucchelli and Zuccala (40) suggest, the underlying reason why a minority of "primary" hypertensives succumb to progressive renal disease is actually renovascular atheroma, they are, in fact, victims of secondary hypertension due to renal arterial stenosis.

The dogs in the subgroup with GFR 33–75% of the lower limit of normal are interesting because they underlie the negative correlation between GFR and arterial pressure in the subnormal dogs; dogs with GFR below 33% showed no such correlation, and subnormal dogs with GFR above 75% did not have elevated pressures. Yet none of the dogs in the 33–75% subgroup were hypertensive; that is, all had systolic pressures below 175 mm Hg. It is, therefore, possible that their slightly higher pressures accelerated the progression of their

renal insufficiency rather than resulting from it, since greater loss of renal function did not cause a greater rise in pressure. It is worth emphasizing that among dogs between 33% and 100% of the lower limit of normal GFR, none was hypertensive, whereas even among dogs with normal GFR, 6% were.

The data of Danielsen et al. (41), who examined 310 cases of human chronic glomerulonephritis, in which 97% did not have hypertension before their renal disease, showed a majority with hypertension by the time GFR was 33% of normal. This could be an underestimate since the anemia of CRF may conceal some cases by reducing PCV and blood viscosity: such cases become hypertensive when their PCV is increased by erythropoietin (11). Clearly no such tendency exists in dogs, confirming our hypothesis. This goes beyond a trite species difference. The point is that dogs, despite being capable of developing hypertension, are resistant to it even when they have chronic renal insufficiency. Since they experience a routine excess of dietary sodium comparable to humans and since both species show an age-related rise in arterial blood pressure (13), the reasons for this difference now warrant further investigation. It also appears that certain breeds, with average pressures in the borderline hypertensive range for humans, are resistant to the adverse effect of arterial pressure (13). This needs to be confirmed in a longitudinal study and, if so, the biological basis for this resistance warrants investigation. Whether the high pressures prove adaptive or maladaptive, an important question is the extent to which these dogs could be regarded as having primary hypertension analogous to essential hypertension in humans. The answer requires comparisons of genetic, biochemical, and hormonal markers; such studies are now in hand.

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