Chapter 4

Polyuria and polydipsia and disturbed vasopressin release in two dogs with secondary polycythaemia

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Abstract

In dogs, secondary polycythaemia (SP) may be associated with polyuria and polydipsia (PUPD). The pathogenesis of this PUPD has not yet been explained. We hypothesised that hyperviscosity and increased blood volume in SP might affect vasopressin (VP) release, resulting in PUPD. This hypothesis was tested in two dogs with SP caused by renal neoplasia, PUPD being the main presenting problem. Osmoregulation of VP release was studied by a water deprivation test and by investigating the VP response to hypertonic saline infusion.

Water deprivation test results were consistent with an inability to produce concentrated urine despite increasing plasma osmolality. During hypertonic saline infusion, the osmotic threshold of VP release was markedly increased in both dogs, resulting in a delayed VP response to increasing plasma osmolality. The sensitivity of VP release was low normal in both dogs. We conclude that blood hyperviscosity and increased blood volume led to impaired VP release and polyuria.
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Introduction

Polycythaemia is characterised by an increase in packed cell volume (PCV), red blood cell (RBC) count, and hemoglobin concentration (Brodsky 1980, Peterson and Randolph 1983). Based on its pathogenesis, polycythaemia can be classified as relative polycythaemia (RP), secondary polycythaemia (SP), or polycythaemia vera (PV).

Relative polycythaemia is the result of severe dehydration and disappears after correction of the fluid imbalance (Jain 1986, Drazner 1989, Giger 1992). Polycythaemia vera is a myeloproliferative disorder that results from proliferation of pluripotent stem cells in the bone marrow, leading to an increased red cell mass and variable increases in granulocytes and platelets (De Wolf et al. 1992). Secondary polycythaemia is the consequence of excessive production of erythropoietin (Epo) or other erythroid-stimulatory substances, such as androgens and adrenal steroids (Campbell 1990). Erythropoietin is produced primarily in the kidney, probably in interstitial or capillary endothelial cells. Increased production of Epo can be physiologically appropriate (i.e., the result of poor tissue oxygenation), or it can be physiologically inappropriate (Brodsky 1980, Peterson and Randolph 1983). Poor systemic tissue oxygenation may be caused by circulatory or respiratory diseases or hemoglobinopathies (Jain 1986, Drazner 1989). The most common cause of inappropriate SP in companion animal practice is the presence of space-occupying renal lesions such as cysts (Peterson and Randolph 1983, Drazner 1989), hydronephrotic lesions (Peterson and Randolph 1983, Drazner 1989), chronic pyelonephritis (Waters and Prueter 1988), or renal neoplasia (Scott and Patnaik 1972, Peterson and Zanjani 1981, Nelson et al. 1983, Gorse 1988, Waters and Prueter 1988, Crow et al. 1995). Renal tumours associated with SP in the dog include adenocarcinoma (Scott and Patnaik 1972, Peterson and Zanjani 1981, Waters and Prueter 1988, Crow et al. 1995), lymphosarcoma (Nelson et al. 1983), and fibrosarcoma (Gorse 1988). The space-occupying lesion causes local changes in renal blood flow, leading to a decrease in renal tissue oxygenation (Berk 1992, Cowgill 1992, Swinney et al. 1992). In addition, unregulated secretion of Epo may occur from a neoplasm (Berk 1992, Cowgill 1992, Swinney et al. 1992). In humans, polycythaemia also has been found to be associated with many non-renal tumours, including adrenal carcinoma, hepatoma, cerebellar hemangioblastoma, pheochromocytoma, and uterine leiomyoma (Golde et al. 1981, Conley 1987). In the dog, a nasal fibrosarcoma has been associated with SP (Couto et al. 1989).

In the veterinary literature, Epo assays have been reported to differentiate PV from SP (Jain 1986, Drazner 1989, Campbell 1990). The increased PCV and plasma Epo concentrations in dogs with SP due to renal neoplasia have decreased after removal of the neoplasm (Peterson and Zanjani 1981, Waters and Prueter
In humans (Erslev and Caro 1984, Conley 1987, De Wolf et al. 1992) and dogs (Cook and Lothrop 1994), there is considerable overlap of Epo concentrations among patients with SP and PV, and thus Epo assays have limited diagnostic value (De Wolf et al. 1992, Cook and Lothrop 1994).

The clinical signs of PV and SP include erythema of mucous membranes, bleeding diatheses, and disturbances of the central nervous system (seizures, paraparesis, lethargy) (Gorse 1988, Crow et al. 1995). Many of these clinical manifestations are related to the increased RBC mass, which increases blood viscosity and expands blood volume (Peterson and Randolph 1983, Conley 1987). Hyperviscosity slows blood flow and expanded blood volume distends capillaries and small vessels, resulting in an increased risk of hypoxia, thrombosis, and rupture of these vessels (Peterson and Randolph 1983, Conley 1987). Another clinical sign reported in association with SP is polyuria/polydipsia (PUPD) (Scott and Patnaik 1972, Peterson and Zanjani 1981, Waters and Prueter 1988). It has been suggested that SP interferes with the ability of the kidneys to concentrate urine (Waters and Prueter 1988).

As hyperviscosity and expansion of blood volume may have consequences for the release of vasopressin (VP), we investigated the osmoregulation of VP release in two dogs with SP due to renal neoplasia by measuring the VP response to hypertonic saline infusion.

### Materials and methods

The VP response to hypertonic saline was investigated by intravenous infusion of 20% NaCl for 2 hours at a rate of 0.03 ml/kg body weight/min. Samples for measurement of plasma VP concentration, collected in EDTA-coated tubes placed in ice, and for plasma osmolality (Posm) were obtained from the jugular vein at 20-min intervals. Plasma osmolality was measured by freezing point depression immediately after collection of the samples. Plasma for measurement of VP was separated by centrifugation at 4°C and stored at -20°C until assayed for VP by radioimmunoassay (Biewenga et al. 1991). Nomograms for the relation between Posm and plasma VP have been described (Biewenga et al. 1987). The slope of the regression line was used to describe the sensitivity of the osmoregulatory system and the intercept with the 5 pmol/l line provided a measure of its threshold value (Biewenga et al. 1987).

A water deprivation test was performed as described by Mulnix et al. (1976). Glomerular filtration rate (GFR) was determined from the plasma clearance of $^{99m}$Tc-DTPA (Van den Brom
and Biewenga 1981). Renography was performed for 20 minutes after intravenous injection of $^{99m}$Tc-DTPA (Biewenga and Van den Brom 1985). Red cell mass (ml/kg body weight) was computed from the dilution of radioactivity, measured in a sample taken 1 hour after intravenous injection of $^{51}$Cr-labelled autologous erythrocytes (Sisson 1978).

**Case reports**

**Dog 1**

A 9½-year-old, castrated male Old English sheepdog weighing 43 kg was referred to the Department of Clinical Sciences of Companion Animals of Utrecht University because of PUPD which began suddenly 2½ months before and exercise intolerance for 6 months. According to the owner, the dog was less active and had signs of caudal weakness.

On physical examination the mucous membranes were noted to be brick red. No other abnormalities were observed. Laboratory findings included increased PCV, and slightly decreased plasma albumin concentration (Table 1). Urine specific gravity was 1.009. The diagnosis of absolute polycythaemia was confirmed by the finding of an increased red cell mass of 57 ml/kg (reference range 25-50 ml/kg). The glomerular filtration rate was normal. On ultrasonography of the abdomen, there was a hypoechoic mass approximately 15 mm in diameter in the caudal pole of the right kidney and a much larger hyperechoic mass in the cranial pole. Cytologic examination of the ultrasonography-guided biopsies of the mass in the cranial pole of the right kidney revealed poorly differentiated malignant cells, possibly of neuro-epithelial origin. There was no evidence of pulmonary metastasis on thoracic radiography.

During the water deprivation test, urine osmolality increased, but did not reach the level of normal concentrating capacity despite a marked loss of body weight (5%) and increase in Posm (from 310 to 320 mOsm/kg) (Figure 1). The VP response to hypertonic saline infusion was abnormal (Figure 2): The threshold value was 352 mOsm/kg (reference values 276-309 mOsm/kg), and the sensitivity of the VP response was 0.28 pmol/l per mOsm/kg (reference values 0.24-2.47 pmol/l per mOsm/kg). Euthanasia was performed at the owners request, but necropsy was not permitted.

**Dog 2**

A 9-year-old castrated male Labrador retriever weighing 37.5 kg was presented because of PUPD, lethargy, and weight loss for four weeks. The mucous
Table 1. Laboratory values of a 9.5-year-old Old English Sheepdog (dog 1), and a 9-year-old Labrador retriever (dog 2) on admission.

<table>
<thead>
<tr>
<th>Unit</th>
<th>Reference ranges</th>
<th>Dog 1</th>
<th>Dog 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed cell volume</td>
<td>l/l</td>
<td>0.42 - 0.57</td>
<td>0.77</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>10^9/l</td>
<td>5.9 - 13.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Platelets</td>
<td>10^9/l</td>
<td>150 - 400</td>
<td>256</td>
</tr>
<tr>
<td>Urea</td>
<td>mmol/l</td>
<td>3.0 - 12.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Creatinine</td>
<td>µmol/l</td>
<td>&lt;60 + 1.2xBW</td>
<td>94</td>
</tr>
<tr>
<td>Glucose</td>
<td>mmol/l</td>
<td>3.9 - 5.0</td>
<td>ND</td>
</tr>
<tr>
<td>Sodium</td>
<td>mmol/l</td>
<td>141 - 149</td>
<td>145</td>
</tr>
<tr>
<td>Potassium</td>
<td>mmol/l</td>
<td>3.6 - 5.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Calcium</td>
<td>mmol/l</td>
<td>2.2 - 3.0</td>
<td>2.70</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>U/l</td>
<td>25 - 117</td>
<td>21</td>
</tr>
<tr>
<td>Bile acids</td>
<td>µmol/l</td>
<td>&lt;8</td>
<td>ND</td>
</tr>
<tr>
<td>Total protein</td>
<td>g/l</td>
<td>54 - 70</td>
<td>69</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/l</td>
<td>25 - 37</td>
<td>23</td>
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<tr>
<td>Plasma osmolality</td>
<td>mOsm/kg</td>
<td>295 - 320</td>
<td>316</td>
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<tr>
<td>Urinary total protein</td>
<td>g/l</td>
<td>0 - 0.56</td>
<td>0.12</td>
</tr>
<tr>
<td>Urinary corticoid/creatinine ratio</td>
<td>x 10^6</td>
<td>&lt;10</td>
<td>3.7</td>
</tr>
<tr>
<td>λ₀</td>
<td></td>
<td>0.0162 - 0.0238</td>
<td>0.0213</td>
</tr>
</tbody>
</table>

ND=not done; BW=body weight; λ₀=rate constant of fractional turnover of ⁹⁹ᵐTc-DTPA (⁹⁹ᵐtechnetium-diethylenetriaminepenta-acetate)

membranes and skin were hyperemic and the abdomen was tense. Laboratory findings included increased PCV, decreased plasma albumin concentration, and slightly increased plasma creatinine concentration (Table 1). Urine specific gravity was 1.008 and proteinuria was present. Ultrasonography of the abdomen disclosed a mass in the caudal pole of the right kidney. There was no evidence of pulmonary lesions on thoracic radiography.

The animal was hospitalised for additional studies. Initial treatment consisted of reduction of the PCV to 51 % by three phlebotomies and replacement of 1365 ml of blood by lactated Ringer's solution. During the following days, the PCV increased again to 64 %. There were no signs of dehydration and Posm and plasma concentrations of creatinine, sodium, and potassium were within the reference range. Urine specific gravity was 1.005 and urine osmolality was 142 mOsm/kg. The VP response to a hypertonic saline infusion was abnormal (Figure 2): The threshold value was 336 mOsm/kg and the sensitivity of the response was 0.28 pmol/l per mOsm/kg. Plasma clearance of ⁹⁹ᵐTc-DTPA was slightly decreased, but the fractional turnover of ⁹⁹ᵐTc-DTPA was normal indicating
normal GFR. The renogram revealed equal excretion of $^{99m}$Tc-DTPA by both kidneys.

After removal of the right kidney the dog recovered without complications. The tumour mass consisted of white lobulated, solid tissue and was well defined. A renal cell carcinoma with tubular, solid, and papillary growth patterns was observed on histological examination. By the day after surgery, the PCV had decreased to 53 % and remained at this level until the dog was discharged from the clinic one week later. Eight months postoperatively, the dog continued to do well without evidence of recurrence of the renal tumour or associated polycythaemia and PUPD.

**Figure 1.** Urine osmolality (Uosm) during a 12-hour water deprivation test in a 9.5-year-old castrated male Old English sheepdog with polyuria and polydipsia and secondary polycythaemia due to a renal neoplasm.

**Figure 2.** Relation between plasma vasopressin (VP) concentration and osmolality (Posm) in a 9-year-old castrated male Labrador retriever (dotted line) and a 9.5-year-old castrated male Old English sheepdog (uninterrupted line) with polyuria and polydipsia and secondary polycythaemia due to renal neoplasia. The outlined area represents the range of responses to infusion of hypertonic saline in 11 healthy dogs (Biewenga et al. 1987).
Discussion

This paper describes two dogs with SP due to renal neoplasia. In both dogs, PUPD was the main reason for the owners to seek veterinary help. In addition, there was loss of endurance. Only the condition of dog 2 required phlebotomy. Nevertheless, three days later when the additional studies were done the PCV was again abnormally high. In dog 2 red cell mass was not measured, but RP was considered unlikely because of the absence of clinical signs and laboratory features of dehydration. The remission of polycythaemia after nephrectomy provided evidence that the polycythaemia was caused by the neoplasm.

In several dogs with SP due to renal cell carcinoma or chronic pyelonephritis, the disease was associated with PUPD (Scott and Patnaik 1972, Peterson and Zanjani 1981, Waters and Prueter 1988). Although PUPD may be a clinical feature in renal adenocarcinoma not associated with polycythaemia (Goldschmidt 1984), it also has been reported as a consequence of PV in the dog (Meyer et al. 1993) and the cat (Swinney et al. 1992). Therefore, it is likely that polycythaemia per se causes PUPD.

In the water deprivation test performed in dog 1, the inability to produce concentrated urine provided indirect evidence for impaired osmoregulation of VP release and/or resistance at the level of the kidney. During hypertonic saline infusion, the osmotic threshold of VP release was markedly increased in both dogs, resulting in a delayed VP response to increasing Posm. The sensitivity of the VP response was just above the lower limit of the reference range in both dogs.

The hallmarks of polycythaemia are blood volume expansion and hyperviscosity (Conley 1987). Increased blood volume may lead to atrial stretch and increased release of atrial natriuretic peptide (ANP) (Stokhof et al. 1994), which has been observed in two dogs with PV in our Department (unpublished data). This may result in PUPD, because ANP inhibits the water permeability response to VP in the renal collecting ducts (Dillingham and Anderson 1986). Furthermore, ANP inhibits basal as well as KCl-stimulated VP release (Obana et al. 1985, Iitake et al. 1986, Lee et al. 1987), which may explain the impaired VP release during hypertonic saline infusion in our dogs.

Vasopressin release is controlled mainly by hypothalamic osmoreceptors and atrial and carotid bifurcation baroreceptors in order to maintain osmotic and fluid balance (Reeves and Andreoli 1992). The PUPD in the two dogs described here was very likely a consequence of delayed VP release, resulting in a decrease in permeability of the renal collecting ducts to water. Hyperviscosity and increased blood volume may have stimulated baroreceptors which consequently caused the delay in VP release. In humans (Robertson and Athar 1976) as well as in dogs (Quillen and Cowley 1983), hypervolaemia impairs the VP response to hypertonic saline infusion. In dogs with experimentally induced hypervolaemia the threshold
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of VP release is increased and the sensitivity of the response is decreased (Quillen and Cowley 1983), similar to what was observed in the two dogs with SP described here. In conclusion, our observations in two dogs with SP indicate that the associated polyuria was at least partially the result of impaired VP release.

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References


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