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Hemodynamic and Biochemical Alterations in Dogs with Lymphoma after Induction of Chemotherapy

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Background: Doxorubicin is a common antineoplastic agent with dose-dependent cardiotoxic adverse effects, and pre-existing myocardial dysfunction is a contraindication to its use.

Objectives: To systematically define the hemodynamic and biochemical alterations in dogs undergoing chemotherapy for newly diagnosed lymphoma and assess the reversibility of these alterations with fluid administration.

Animals: Twenty-one client-owned dogs with newly diagnosed lymphoma were evaluated 1 week after induction of chemotherapy. Underlying degenerative valve disease was exclusionary. Eighteen healthy age- and weight-matched dogs were used as controls.

Methods: Physical examination, blood pressure by Doppler, echocardiography, and biochemical evaluation (routine serum biochemistry, plasma renin activity and aldosterone concentrations, plasma and urine osmolalities, and urine electrolyte concentrations) were measured in dogs with lymphoma and compared to controls. Dogs with lymphoma received crystalloids IV at 6 mL/kg/h for 24 hours. All variables were reassessed at 4 and 24 hours. Deuterium oxide dilution and bromide dilution were used to determine total body water and extracellular water space, respectively.

Results: Baseline echocardiograms showed significantly smaller chamber dimensions in dogs with lymphoma compared to controls. These changes were reversed by fluid administration. Systolic blood pressure and urine sodium concentration were significantly increased, and bromide dilution space, PCV, urine specific gravity, and urine potassium concentration were significantly decreased compared to controls.

Conclusion and Clinical Importance: Echocardiographic and biochemical abnormalities in dogs with lymphoma appear consistent with volume depletion, and may be the result of systemic hypertension and subsequent pressure natriuresis.

Key words: Doxorubicin; Extracellular volume depletion; Lymphoma; Prednisone; Systemic hypertension.

Doxorubicin, a widely used antineoplastic chemotherapeutic agent, has well-known, dose-dependent cardiotoxic effects.[1] Although the prevalence of underlying cardiac disease appears to be relatively low in patients with neoplasia, it still is commonly recommended to perform cardiac evaluation before administration of doxorubicin.[2,3] Patients with pre-existing cardiac arrhythmias or myocardial dysfunction often are treated with alternative agents such as mitoxantrone, cardioprotective agents, or by limiting the total number of doxorubicin treatments.[4] Similar to previously published reports,[2] pre-existing cardiac dysfunction in dogs with lymphoma is rare at our institution. Rather, we commonly observe these patients to have left ventricular (LV) chamber dimensions that are below the reference range for size-matched normal dogs. We hypothesized that these changes were the result of volume depletion. Therefore, this study was undertaken to (1) systematically define the hemodynamic and biochemical alterations in dogs undergoing chemotherapy induction for newly diagnosed lymphoma and (2) assess the reversibility of these alterations with fluid administration.

Abbreviations:

2D	two-dimensional
BP	blood pressure
D_20	deuterium oxide
FE NA+	fractional excretion of sodium
K+	potassium
LV	left ventricular
Na+	sodium
NaBr	sodium bromide
PRA	plasma renin activity
TP	total protein
UPC	urine protein-to-creatinine ratio
USG	urine specific gravity

Materials and Methods

Study Population

Twenty-one dogs with newly diagnosed lymphoma were recruited to participate in this study. Complete staging was defined as CBC, serum biochemistry profile, urinalysis, thoracic radiographs, abdominal radiographs with or without ultrasound examination, and bone marrow aspiration cytology. Ten dogs were completely staged and the other 11 had variable staging.[5] Dogs were staged ≥2a (n = 1), 3a (n = 1), ≥3a (n = 3), ≥3b (n = 1), 4a (n = 4), ≥4b (n = 1), 5a (n = 2), and 5b (n = 5). In 2 of the dogs, stage 5 was assigned on the basis of extranodal (advanced ocular) involvement or circulating lymphoblasts in 1 each without full staging. Adequate information to assign stage was unavailable in 3 dogs. The presence of degenerative

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atrioventricular valve disease at diagnosis was exclusionary. Eighteen healthy, weight- and age-matched normal dogs were recruited from among the staff and students at the Veterinary Medical Teaching Hospital, University of Missouri, to serve as a control group. Enrollment of eligible lymphoma patients was by convenience sampling of owners willing to participate, in the order that dogs were presented to the hospital. No attempt at randomization between the fluid administration study and body water analyses study was made. All animals participated in the study with signed owner consent, and the study was approved by the University of Missouri's Animal Care and Use Committee.

Study Design

Dogs diagnosed with lymphoma were enrolled in the study approximately 1 week postchemotherapy induction. The drugs used for induction were prednisone (2 mg/kg PO q24h), l-asparaginase (10,000 IU/m^2 IM), and vincristine (0.5 mg/m^2 IV). Food was withheld from all dogs for 12 hours before baseline measurements, but they were allowed free access to water. Evaluation of subjects included physical examination, echocardiogram, and biochemical evaluations. Systolic blood pressure (BP) was determined by Doppler methodology using previously described methods.[a,6] Dogs were positioned in right lateral recumbency, and a cuff measuring approximately 40% of the circumference of the distal left forelimb was used to occlude flow. A Doppler arterial flow signal was identified and readings were repeated until 3 measurements were consecutively recorded within 5 mmHg, and the mean of the 3 measurements was recorded. Heart rate was obtained by auscultation before obtaining BP. Body weight was measured using the same scale, after voluntary urination.

Thirteen lymphoma patients were enrolled in the fluid administration study and given Normosol R solution supplemented with 16 mEq potassium chloride per liter at 6 mL/kg/h IV for 24 hours by cephalic catheter. All variables were reevaluated at 4 and 24 hours.

Two subsets of dogs (lymphoma, n = 8) and (control, n = 6) were used to compare body fluid compartment volumes.

To assess the influence of corticosteroids on hemodynamic and biochemical parameters in the lymphoma subjects, a subset of healthy dogs (n = 9) was treated with prednisone (2 mg/kg PO q24h) for 7 days. All study parameters were measured at baseline and after treatment.

Biochemical Evaluation

Jugular venous blood was collected into lithium heparin tubes for measurement of glucose, urea nitrogen, creatinine, sodium, potassium and chloride concentrations, packed cell volume (PCV), and total protein (TP) concentration. Samples were assayed within 30 minutes of collection by the Veterinary Medical Diagnostic Laboratory, University of Missouri. A voided urine sample was obtained for measurement of urine specific gravity (USG), sodium and potassium concentrations, and osmolality. Urine and extracted plasma were frozen at −80°C and subsequently analyzed for osmolality using a vapor pressure osmometer.[b] Blood samples for plasma renin activity (PRA) and aldosterone concentration were drawn into prechilled 3 mL EDTA tubes, immediately placed into ice, centrifuged at 2°C, and extracted plasma was stored frozen at −80°C.[c,d] Assay of PRA was performed as previously described.[7] Aldosterone was assayed using a commercially available radioimmunoassay kit.[e]

Total body water and extracellular water space were determined after withholding food for 12 hours, using methods of deuterium oxide (D_2O) dilution[8] and sodium bromide (NaBr) dilution,[7,9,10] respectively. Dogs received a venous infusion over 2 min of 1 g/kg of a sterile filtered[f] solution of 30 g/kg NaBr,[g] 440 g/kg D_2O (99.8%),[h] and 590 g/kg sterile water.[i] Enrichments of D_2O and NaBr were determined from serum collected at 2 hours after solution infusion. Change in D_2O enrichment indicated body water mass (and volume). Change in serum bromide concentration with the NaBr infusion indicated the volume of the extracellular fluid space. Subjects were not allowed access to food or water during the 2 hours after initial infusion.

Echocardiography

Two-dimensional, M-mode, and Doppler echocardiographic examinations were performed utilizing standard views in unsedated dogs.[11–13] Left ventricular short-axis area was measured from a right parasternal view by tracing the endocardial borders, excluding the papillary muscles. Left ventricular volume was calculated from the right parasternal long axis view using the sum of disks method.[14] Cardiac index was calculated as (stroke volume × heart rate)/body surface area. Heart rate was derived from the same cycles as the stroke volume measurements. Three to 6 consecutive cycles were measured and averaged for each variable. All examinations and measurements were performed by a single examiner (DMF).

Statistical Analysis

Calculations were performed using a commercial statistical software package.[j] Normality of data was assessed by the Shapiro–Wilk test. Normally distributed values were reported as mean ± standard deviation. Non-normally distributed data were reported as median and range. The baseline values of the lymphoma and control groups were compared using unpaired *t*-tests for normally distributed data and the Mann–Whitney rank sum test for non-normally distributed data. The effects of fluid administration in the lymphoma group were analyzed using repeated measures ANOVA. When indicated, posthoc analysis was performed using the Tukey Kramer multiple comparison test. Nonparametric repeated measures data were tested for significance using the Friedman test. If any time point within a repeated measures group was not normally distributed, then the entire group was analyzed as non-normally distributed data. Results obtained at 4 and 8 hours were compared to time 0. Baseline and postprednisone results were analyzed using paired *t*-tests. A P value <.05 was accepted as significant.

Results

The time from the initial diagnosis of lymphoma to enrollment in the study was 8.5 ± 0.3 days. There were small but significant decreases in TP and USG, and an increase in serum glucose concentration between initial presentation and study enrollment. There were no significant differences between the lymphoma and control groups in age (7.4 ± 1.2 versus 5.7 ± 0.7 years, P = .13), or weight (23.6 ± 12.2 versus 26.5 ± 7.9 kg, P = .41). At study enrollment, the lymphoma group had significantly higher systolic BP, plasma glucose, urine sodium concentration, and fractional excretion of sodium compared to controls. The lymphoma group also had significantly lower PCV, USG, plasma creatinine concentration, and urine potassium concentration compared to control (Table 1).

Table 1. Physical and biochemical comparisons of the lymphoma (n = 13) and control group (n = 12). Column 1 shows the lymphoma results at initial diagnosis. Column 2 shows the lymphoma results at the time of study enrollment (1 week later).

	Lymphoma: Pretreatment	Lymphoma: Study Enrollment	Control
Weight	23.6 ± 11.8	23.6 ± 12.2	26.5 ± 7.9
SBP (mmHg)	145 ± 18	147 ± 19	120 ± 14[a]
Heart rate (bpm)	115 ± 35	118 ± 29	109 ± 20
Glucose (mg/dL)	97 ± 7[b]	112 ± 12	99 ± 8[a]
Urea nitrogen (mg/dL)	15.5 ± 4.5	16.2 ± 6.5	13.8 ± 2.6
Creatinine (mg/dL)	0.95 ± 0.4	0.71 ± 0.2	0.96 ± 0.1[a]
Sodium (mEq/L)	147.8 ± 3.9	146.8 ± 2.9	146.5 ± 1.6
Potassium (mEq/L)	3.8 ± 0.4	3.97 ± 0.3	4.1 ± 0.2
Chloride (mEq/L)	111.6 ± 4.1	110.2 ± 4.1	112.8 ± 1.5
PCV (%)	43.2 ± 6.6	39.4 ± 6.2	49.8 ± 4.5[a]
Total protein (g/dL)	6.3 ± 0.6[b]	7.1 ± 0.8	6.9 ± 0.6
Urine specific gravity	1.031 ± 0.001[b]	1.021 ± 0.008	1.032 ± 0.01[a]
Urine protein : creatinine		0.15 (0.09–1.71)	0.09 (0.06–0.78)
Urine [Na^+] (mEq/L)		133.5 ± 59.4	56.3 ± 41.1[a]
Urine [K^+] (mEq/L)		60.2 ± 36.4	107.9 ± 64.9[a]
FE Na^+ (%)		0.57 (0.19–2.2)	0.11 (0.02–1.1)[a]
Posm (mOsm/kg)		319.4 ± 8.0	317.2 ± 3.4
Uosm (mOsm/kg)		814.7 ± 464.6	1,117.3 ± 536
PRA (ng A1/mL/h)		2.3 ± 0.9	1.6 ± 1.1
Aldosterone (nmol/L)		22 (0–368)	53 (0–332)

[a]Significant difference between pretherapy lymphoma and study enrollment lymphoma results.

[b]Significant difference between lymphoma at study enrollment and control group.

Values reported as mean ± standard deviation, or median (range) as appropriate. FE Na^+, fractional excretion of sodium; [K^+], potassium concentration; [Na^+], sodium concentration; SBP, systolic blood pressure; PCV, packed cell volume; Posm, plasma osmolality; PRA, plasma renin activity; Uosm, urine osmolality.

When expressed as a percentage of body weight, body fat and lean mass were not significantly different between the groups. However, the bromide dilution space, a measure of extracellular water volume, was significantly lower in the lymphoma group as compared to control dogs (25.6 ± 4.4% versus 30.9 ± 4.3%, respectively; $P = .04$). In contrast, there was no significant difference in the D_2O dilution space, a measure of total body water volume, between the groups (46.5 ± 4.1% versus 50.0 ± 10.6%, respectively; $P = .8$).

Twenty-four hours of IV fluid administration resulted in significant decreases in heart rate, urea nitrogen, PCV, TP, USG, urine potassium concentration, urine osmolality, PRA, and aldosterone. There was a small, but significant increase in the serum potassium concentration compared to baseline (Table 2).

The following echocardiographic measurements were significantly smaller in the lymphoma group compared to control: 2D and M-mode left atrium, M-mode LV internal diameter in systole and diastole, 2D LV short-axis area in systole and diastole, and 2D LV end-diastolic volume. There were no significant differences in stroke volume, percent fractional shortening, heart rate, septal or free wall thickness, transmitral filling velocities, aortic outflow velocity, or cardiac index (Table 3).

Twenty-four hours of IV fluid administration resulted in significant increases in the 2D left atrial and LV end-diastolic volume, 2D LV short-axis area in systole and diastole, and the M-mode LV diastolic dimension. There were no significant changes in cardiac index, wall thickness, or any Doppler-derived parameter. Fluid administration for 24 hours abolished all of the significant echocardiographic differences between the lymphoma group's baseline measurements and those of the control group (Table 3).

Seven days of prednisone treatment in healthy dogs had minimal effects. There were small but significant decreases in plasma creatinine concentration, PCV, USG, and a small increase in TP (Table 4). The only significant echocardiographic change was an increase in the end-diastolic volume (pretherapy, 57.2 ± 23 mL versus posttherapy, 61.2 ± 26 mL; $P = .04$).

Discussion

The genesis of this study was our clinical observation that dogs with lymphoma often have decreased chamber dimensions on echocardiogram compared to size-matched reference ranges. Echocardiography is the most common modality used to assess cardiac function before initiation of doxorubicin and to monitor for signs of cardiotoxicity.[2,3,15,16] To our knowledge, no other study has compared the echocardiographic findings in dogs with lymphoma after induction of chemotherpy to a control group. Our study demonstrated that dogs with lymphoma have decreased chamber dimensions compared to size-matched normal dogs.

Table 2. Biochemical and physical examination findings in lymphoma subjects (n = 13) undergoing IV fluid administration (6 mL/kg/h).

	Baseline	4 Hours	24 Hours
Weight (kg)	23.6 ± 12.2	23.3 ± 12.4	23.1 ± 12.6
SBP (mmHg)	147 ± 19	137 ± 24	137 ± 19
Heart rate (BPM)	118 ± 29	117 ± 28	105 ± 28[a]
Glucose (mg/dL)	112 ± 12	111 ± 6	108 ± 15
BUN (mg/dL)	16.2 ± 6.5	14.6 ± 4.3	9.75 ± 2.6[a]
Creatinine (mg/dL)	0.6 (0.5–1.2)	0.6 (0.4–1.2)	0.7 (0.5–1.2)
Sodium (mEq/L)	146.8 ± 2.9	148.2 ± 2.6	147.2 ± 1.5
Potassium (mEq/L)	3.97 ± 0.3	4.3 ± 0.3[a]	4.3 ± 0.4[a]
Chloride (mEq/L)	110.2 ± 4.1	111.7 ± 4.1	111.4 ± 3.4
PCV (%)	39.4 ± 6.2	35.9 ± 4.8[a]	35.8 ± 5.0[a]
Total protein (g/dL)	7.1 ± 0.8	6.8 ± 0.7[a]	6.5 ± 0.7[a]
Urine specific gravity	1.021 ± 0.008	1.015 ± 0.005	1.010 ± 0.002[a]
Urine protein : creatinine	0.15 (0.05–1.71)	0.14 (0.08–0.95)	0.19 (0.1–0.79)
Urine [Na^+] (mEq/L)	102.4 (41–371)	99.3 (48–162)	134.7 (105–193)
Urine [K^+] (mEq/L)	45.8 (20.7–151)	37.7 (11.6–79.3)	34.2 (17.4–51.8)
FE Na^+ (%)	0.57 (0.19–2.2)	0.73 (0.41–3.2)	2.38 (1.3–3.6)[a]
Posm (mOsm/kg)	319.4 ± 8.0	313.4 ± 6.6	312.8 ± 5.1
Uosm (mOsm/kg)	814.7 ± 464.6	584.9 ± 193[a]	405.8 ± 72[a]
PRA (ng A1/mL/h)	2.4 (1.3–3.7)	1.4 (0.54–5.1)	0.6 (0.04–1.2)[a]
Aldosterone (nmol/L)	22 (0–368)	0 (0–83)[a]	0 (0–17)[a]

[a]Significant difference between indicated time point and baseline.
See Table 1 for abbreviations.

Table 3. Echocardiographic comparisons of lymphoma group (n = 13) and control group (n = 12), and the effect of 24 hours of fluid therapy on lymphoma measurements.

	Control	Lymphoma Baseline	4 Hours	24 Hours
2D LA (cm)	3.7 ± 0.4[a]	3.1 ± 0.9	3.4 ± 0.9[b]	3.5 ± 0.8[b]
LV EDV (mL)	60.3 ± 12.3[a]	43.2 ± 15.8	46.5 ± 25.4	50.4 ± 25.9[b]
LV ESV (mL)	22.1 ± 9.8	15.2 ± 7.9	15.1 ± 9.1	17.2 ± 10.0
Stroke volume (mL)	38.2 ± 10.5	30.7 ± 16.3	31.4 ± 17.4	33.2 ± 17.0
MM LA (cm)	2.8 ± 0.4[a]	2.4 ± 0.5	2.6 ± 0.6	2.6 ± 0.5
MM LA/Ao	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	1.3 ± 0.2
MM LVIDd (cm)	3.9 ± 0.6[a]	3.4 ± 0.7	3.5 ± 0.8	3.6 ± 0.8[b]
MM LVIDs (cm)	2.7 ± 0.5[a]	2.2 ± 0.7	2.3 ± 0.7	2.4 ± 0.7
MM IVSd (cm)	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.2
MM LVPWd (cm)	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.2
FS (%)	33 ± 5	36 ± 9	35 ± 6	35 ± 8
MFV E wave (m/s)	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
MFV A wave (m/s)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
MFV slope (m/s^2)	6.6 ± 2.8	6.1 ± 1.9	6.4 ± 1.5	7.0 ± 2.8
LV SAAd (cm^2)	13.6 ± 3.2[a]	10.0 ± 3.7	10.4 ± 3.5	11.6 ± 4.2[b]
LV SAAs (cm^2)	6.2 ± 2.2[a]	4.1 ± 2.3	4.4 ± 2.1	5.1 ± 2.6[b]
Ao velocity (m/s)	1.3 ± 0.3	1.4 ± 0.9	1.6 ± 0.8	1.3 ± 0.6
CI ($L/min/M^2$)	3.7 ± 1.1	3.2 ± 1.2	3.6 ± 0.9	3.6 ± 0.9

[a]Significant difference between control group and lymphoma baseline.
[b]Significant difference between indicated time point and lymphoma baseline.
2D, two-dimensional; Ao, aorta; CI, cardiac index; FS, fractional shortening, LA, left atrium; LA/Ao, left atrial to aortic root ratio; LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; MFV, transmitral filling velocity; MM, M-mode; PG, pressure gradient; SAAd, short-axis area in diastole; SAAs, short-axis area in systole.

Body water analyses in dogs with lymphoma showed a significant diminution in bromide dilution space compared to controls. Bromide dilution space is a measure of extracellular fluid volume, of which approximately 25% is intravascular and 75% is interstitial. Body composition analyses in children with newly diagnosed lymphoma yielded results similar to our own. Children with lymphoma had lower lean body mass (primarily water) and increased fat mass when compared to children with solid tumors or

Table 4. Physical and biochemical comparisons of the normal dogs (n = 9) before and after 7 days of prednisone (2.0 ± 0.1 mg/kg q24h).

	Baseline	Post
Weight	27.8 ± 11.5	27.1 ± 11.6
SBP (mmHg)	128 (95–134)	128 (98–152)
Heart rate (bpm)	96.8 ± 21.3	77.9 ± 12.9[a]
Glucose (mg/dL)	96.9 ± 8.3	100.1 ± 6.5
Urea nitrogen (mg/dL)	14.7 ± 3.9	17.4 ± 3.0
Creatinine (mg/dL)	1.1 ± 0.2	0.9 ± 0.1[a]
Sodium (mEq/L)	145.6 ± 1.6	144.7 ± 1.9
Potassium (mEq/L)	4.0 ± 0.3	4.0 ± 0.2
Chloride (mEq/L)	113.7 ± 1.0	106.8 ± 3.3
PCV (%)	44.2 ± 3.2	42.7 ± 3.7[a]
Total protein (g/dL)	6.1 ± 0.5	6.7 ± 0.5[a]
Urine specific gravity	1.038 ± 0.02	1.022 ± 0.01[a]
Urine protein : creatinine	0.07 (0.05–0.3)	0.12 (0.08–0.2)
Urine [Na^+] (mEq/L)	90 (37–187)	41 (16–183)
Urine [K^+] (mEq/L)	117 (55–253)	64.2 (20–152)
FE Na^+ (%)	0.24 (0.1–0.7)	0.26 (0.1–0.8)
Posm (mOsm/kg)	312.4 ± 11.7	313.3 ± 11.6
Uosm (mOsm/kg)	1,377 ± 620	821 ± 445
PRA (ng A1/mL/h)	1.84 ± 0.6	2.06 ± 1.1
Aldosterone (nmol/L)	16 (0–194)	55 (6–307)
NaBr dilution (%)	22.8 ± 1.8	21.5 ± 2.7
D_2O dilution (%)	16.7 ± 6.9	15.4 ± 6.0

[a]Significant difference between pre- and postprednisone results.

Values reported as mean ± standard deviation, or median (range) as appropriate. NaBr, sodium bromide; D_20, deuterium; see Table 1 for other abbreviations.

normal controls.[17,18] Fluid deficits in human patients with advanced cancer are considered common and have a multifactorial pathogenesis that includes anorexia, gastrointestinal disturbances, and altered metabolism.[19] Authors of 1 study suggested that the pathological mechanism of intravascular volume depletion may be a fluid shift from the intravascular space to the interstitial compartment.[20]

Fluid administration for 24 hours eliminated the baseline echocardiographic differences between the lymphoma and control groups. Taken with the lower bromide dilution space, these findings support the hypothesis that the changes in the lymphoma group were a result of volume depletion. However, the lymphoma group did not gain weight after fluid administration, indicating that baseline echocardiographic differences could not be attributed to a simple imbalance of water intake and excretion.

Potentially, the most important difference between the groups was the increase in systolic BP in the lymphoma group. There were no differences in heart rate, stroke volume, or cardiac index between groups, and therefore the alteration was most likely mediated by increased systemic vascular resistance. Although the mean of the systolic BP was only 147 mmHg, over half of the subjects had systolic blood pressures ≥150 mmHg and 2 dogs were >170 mmHg. This is considered mild to moderate hypertension in dogs,[6] and presents a potentially compelling explanation for the echocardiographic and biochemical abnormalities seen in the lymphoma dogs. That is, the changes observed may be a consequence of pressure natriuresis. Pressure natriuresis is considered to be a primary feedback mechanism for long-term regulation of systemic arterial pressure.[21–23] In normal subjects, a small increase in BP results in relatively large increases in sodium and water excretion.[24,25] Although intrarenal prostaglandins and nitric oxide may influence pressure natriuresis, it does not require neural or hormonal influences to function.[21,24]

Hypertension has not been described previously in dogs with lymphoma, most likely because of the low incidence of routine BP screening in veterinary medicine and an apparent lack of severe manifestations of end-organ damage in this population. However, a similar degree of mild-to-moderate hypertension appears to be common in children presenting with newly diagnosed lymphoma and leukemia.[26,27] The cause of hypertension in the children was uncertain, but renal leukemic infiltration was hypothesized to contribute to its development.[28] Furthermore, humans with essential hypertension also have been shown to have decreased plasma volume compared to normotensive controls.[29]

Azotemia was not present in the lymphoma group, nor did any of the dogs that underwent abdominal ultrasound examination (n = 10) show changes consistent with renal involvement. However, an interesting finding in our study was an increase in the UPC ratio in the lymphoma group. Although the difference was not significant, it may still represent a biologically relevant change. Furthermore, another study showed a similar increase in the UPC ratio in dogs with lymphoma compared to normal dogs that was significant.[30]

Physical examination and biochemical findings after fluid administration support our hypothesis of pressure natriuresis-mediated loss of intravascular volume. Although heart rate decreased significantly, there was no significant diminution in systolic BP after 24 hours of hospitalization, indicating that the hypertension could not simply be ascribed to alterations in sympathetic tone. The urine sodium alterations were important. Had the baseline echocardiographic findings in the lymphoma group been because of simple volume depletion, there should have been compensatory renal sodium retention. However, the opposite was present: the lymphoma group had a significantly higher urine sodium concentration and fractional excretion of sodium compared to the control group. Furthermore, fluid administration resulted in an additional increase in the fractional excretion of sodium. If volume depletion alone been present, sodium retention would have continued until the volume deficit was corrected.[31] However, because the hypertension persisted, it was necessary to continue excreting sodium and water to prevent further increases in arterial pressure.

Several limitations of this study exist. The decision to evaluate dogs after induction chemotherapy, rather than at initial presentation was made because this time point was deemed to be more clinically relevant. Most lymphoma patients are evaluated by echocardiography

after the initiation of chemotherapy and before administration of doxorubicin. However, evaluating the subjects after chemotherapy was initiated precludes attributing the changes observed solely to the presence of lymphoma. Furthermore, it is likely that some of the differences between the lymphoma group and controls can be ascribed to prednisone. Specifically, glucose and TP were increased, and serum creatinine concentration, PCV, and USG were decreased in the lymphoma group. The differences were modest and similar to those seen in other studies,[32–34] and in our healthy dogs receiving prednisone. However, other differences in the lymphoma group are less likely secondary to prednisone treatment. In particular, urine sodium concentration and fractional excretion of sodium were increased, and urine potassium concentration and bromide dilution space were decreased in the lymphoma group. Prednisone had no significant effect on urinary electrolyte excretion or either measure of body water in the healthy dogs, but a small increase in LV end-diastolic volume was observed on echocardiogram. This finding is opposite the echocardiographic changes we observed in the lymphoma group. Nonetheless, dogs with lymphoma may not respond to prednisone the same as healthy dogs. Another important consideration is that bromide dilution estimates total extracellular water not plasma volume; therefore, we cannot definitively determine how much of the diminution we detected was secondary to decreased plasma volume versus decreased interstitial volume. Surprisingly, we did not detect significant changes in any of the Doppler measurements on echocardiogram, which was unexpected given that ventricular filling is very preload dependent. However, other factors such as myocardial compliance and relaxation, which are difficult, to measure also affect filling. Other more sensitive modalities such as strain or strain rate (which were not available) might have detected more subtle abnormalities. Additionally, the nature of the studies precluded blinding of the sonographer to the time points at which the echocardiographic measurements were obtained. Another potential confounder was the slight decrease in heart rate from baseline to 24 hours in the lymphoma group treated with IV fluids. Because heart rate is a contributor to diastolic filling, the decrease in heart rate may have contributed to the increase cardiac dimensions measured echocardiographically. Finally, additional work is necessary to confirm the hypothesis that the underlying changes are mediated by hypertension-induced pressure natriuresis. Theoretically, antihypertensive treatment may eliminate the changes identified in this study. However, additional diagnostic tests such as assay of natriuretic peptides, endogenous ouabain, and urodilatin would be appropriate to further elucidate this potential mechanism.

Conclusion

Results of this study support the hypothesis that the echocardiographic changes in dogs with lymphoma are related to intravascular volume depletion. In particular, bromide dilution space, a measure of extracellular water, was decreased, and fluid administration reversed baseline echocardiographic changes. We speculate that the changes may be the result of hypertension-induced pressure natriuresis. Systemic BP measurement should be part of baseline diagnostic tests in dogs with lymphoma, and those with pressures >160 mmHg should be evaluated for underlying diseases that cause hypertension.

Footnotes

[a] Parks Medical Electronics, Inc, model 811B, Aloha, OR
[b] Wescor, Inc, Logan, UT
[c] John D. Dingell VA Medical Center, Detroit, MI
[d] Radioimmunoassay Laboratory, University of Mississippi Medical Center, Jackson, MS
[e] Diagnostic Center for Population and Animal Health, Michigan State University, East Lansing, MI
[f] 0.2 μm filter disk, B. Braun Medical, Bethlehem, PA
[g] Mallinckrodt, St. Louis, MO
[h] Organics, Geel, Belgium
[i] Hospira, Lake Forest, IL
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