Comparison of hematologic and biochemical values for blood samples obtained via jugular venipuncture and via vascular access ports in cats

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Objective—To determine whether hematologic and serum biochemical values for blood samples obtained from cats via vascular access ports (VAP) are comparable to those for samples obtained by direct venipuncture.

Design—Prospective study.

Animals—14 healthy cats.

Procedure—A VAP was surgically implanted in a jugular vein in each cat. Blood samples were obtained from the VAP and by direct venipuncture of the contralateral jugular vein 10 weeks after VAP placement. Results of hematologic and serum biochemical analyses were compared by use of a paired *t*-test. The *P* value to reject the null hypothesis was adjusted to account for multiple comparisons by using the Bonferroni procedure in which the nominal *P*-to-reject value is divided by the number of comparisons (0.05/24 = 0.002).

Results—Paired samples (VAP and venipuncture) obtained 10 weeks after VAP placement were evaluated for each cat. Of the 24 measured analytes, only potassium, total protein, and albumin concentrations differed significantly ($P < 0.001$ for all 3) between VAP and venipuncture samples.

Conclusions and Clinical Relevance—Results suggest that samples obtained from VAP are suitable for routine hematologic monitoring of feline cancer patients. Sample hemolysis may account for a slight increase in potassium, total protein, and albumin concentrations obtained from VAP samples. However, the values of variables most critical for monitoring of patients receiving chemotherapy (ie, mature neutrophil and platelet counts) are comparable. If proper techniques are used, VAP may be used for administration of chemotherapy as well as for blood collection in cats undergoing cancer treatment. (*J Am Vet Med Assoc* 2002;220:482–485)

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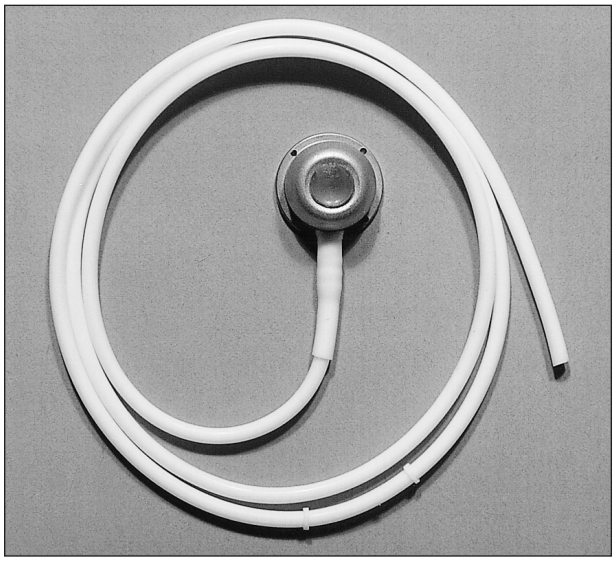
Vascular access systems were first developed for long-term administration of cytotoxic agents to human cancer patients.[1] Because cytotoxic agents and repeated venipuncture damage vascular integrity, placement of central venous catheters is warranted for patients receiving chemotherapy over an extended period of time. Unlike percutaneous catheters, closed and totally implantable systems do not necessitate frequent bandage changes and heparinization, and they have a reduced risk of infection and accidental dislodgement.[2] The basic design of **vascular access ports (VAP)** includes 2 parts: an indwelling catheter that is implanted into the vessel of choice (generally jugular or femoral vein) and an injection port that is implanted in the subcutaneous tissues near the vessel (**Fig 1**). These devices may be used for chemotherapy administration, blood sampling, and delivery of blood products and hyperalimentation solutions.[3]

The use of VAP is becoming more commonplace in companion animal oncology.[3,4] These totally implantable devices allow ready venous access with minimal restraint for blood collection and chemotherapy administration. This is particularly attractive for fractious patients, those likely to dislodge percutaneous catheters, and for animals receiving infusions of

Figure 1—Photograph of vascular access port implanted in 14 cats.



vesicants. The cost of VAP purchase, placement, and maintenance is offset by the time savings associated with quick venous access and by eliminating the need to sedate fractious patients. In addition, the risk of bacterial infection associated with catheterization may be decreased by using totally implantable devices, rather than those with catheters and ports that exit the skin.[5] One study indicated a 32% occurrence of local bacterial infections around IV catheters in dogs, and this is the most common long-term catheter complication in humans.[5-8]

In addition to vessel preservation and reduced risk of infection for patients receiving long-term chemotherapy, use of VAP facilitates blood collection for regular monitoring of myelosuppression and biochemical abnormalities related to chemotherapy. However, to our knowledge, no companion animal studies have been performed that examined the effects of blood collection via VAP on hematologic and serum biochemistry results. Because treatment decisions are often determined on the basis of results of CBC (particularly segmented neutrophil and platelet count) and serum biochemistry analysis in cancer patients, the reliability of these values is crucial. Artifactual changes in laboratory values for blood samples obtained from VAP could potentially result from hemolysis, sample dilution with heparin, or sample contamination and disruption of cells and platelets secondary to fibrin or cellular debris within the port or catheter. In 1 study[9] in humans, 50% (n = 25) of venous access devices had clots present in the catheter as identified by evaluation of 5 ml "discard" samples withdrawn from the catheter into a syringe and analyzed immediately. Hemolysis during sample collection may lead to artifactual decreases in Hct, mean corpuscular volume, glucose, and sodium and increases in mean corpuscular hemoglobin, albumin, calcium, potassium, **alanine aminotransferase (ALT)**, and phosphorus concentrations.[10-15] Sample dilution with heparin may lead to erroneous laboratory values, including false decreases in total CO_2 concentrations.[13] Improper sampling technique from indwelling catheters may cause increases or decreases in sodium and potassium concentrations.[13] Because of the potential for these and other errors in laboratory evaluation of blood samples, we designed this study to evaluate for sample integrity from vascular access ports. The purpose of the study reported here was to determine whether hematologic and serum biochemical values for blood obtained from VAP are comparable to values obtained from venipuncture samples.

Materials and Methods

Cats—Fourteen healthy cats were enrolled in the study. A VAP[a] (Fig 1) was surgically implanted in the left external jugular vein of each cat. For port implantation, cats were anesthetized and positioned in right lateral recumbency. A 2-cm skin incision was made parallel to the external jugular vein. A second skin incision of similar size was made dorsally, perpendicular to the first skin incision. Subcutaneous tissues were bluntly dissected to create a pocket for port placement lateral to the second skin incision. The injection port was positioned within the subcutaneous tissue pocket and sutured to the underlying fascia. The catheter was tunneled through the subcutaneous tissue from the injection port site to the external jugular vein site. The vein was isolated by standard cut-down procedure and manipulated via stay sutures. The catheter was flushed with heparinized saline (0.9% NaCl) solution and transected at a 45° angle at the appropriate length. Catheter length was approximated such that the end of the catheter would be situated in the cranial vena cava near the junction with the right atrium. The external jugular vein was occluded cranially and then incised distal to this occlusion for introduction of the catheter. After threading of the catheter into the jugular vein, a ligature was placed around the vein to secure the catheter in place. A more cranial ligature was placed around the external jugular vein to prevent leakage at the venotomy site. Catheter patency was ensured by withdrawing blood and flushing the port with heparinized saline solution. Surgical incisions were closed in 2 layers. Blood samples were drawn from the VAP and from the contralateral jugular vein 10 weeks after VAP placement for comparison of hematologic and serum biochemical analysis results. In each instance, the VAP sample was collected first, followed immediately by direct venipuncture of the contralateral jugular vein. All samples were identified only by number codes, such that the laboratory personnel were blinded as to sample origin. Samples were maintained at room temperature (22 C) between collection time and analysis, which was within 90 minutes of collection. Complete blood count results were determined, using a hematology analyzer,[b] with differential WBC and platelet counts performed manually. Analytes included segmented neutrophils, band neutrophils, lymphocytes, monocytes, basophils, eosinophils, platelets, RBC, hemoglobin, and Hct. Hematocrits were determined by use of the automated hematology analyzer. Biochemical analyses were performed on serum samples, using an automated analyzer.[c] Biochemical results reported and analyzed in this study included calcium, chloride, phosphorus, potassium, sodium, creatinine, urea nitrogen, total CO_2, cholesterol, glucose, total protein, and albumin concentrations and **alkaline phosphatase (ALP)** and ALT activities.

The protocol for maintenance of catheter patency was dictated by the fact that these cats were enrolled in a concurrent study investigating the use of **recombinant human granulocyte colony stimulating factor (rhG-CSF)** in cats receiving chemotherapy. As part of the concurrent study, all cats received mitoxantrone[d] (10 mg/m^2, IV) every 21 days for 4 treatments. Samples for this study were collected before the fourth treatment. Beginning 5 days after mitoxantrone treatment, a 5-day course of rhG-CSF was administered subcutaneously once daily. The VAP were used for chemotherapy administration and blood collection prior to each chemotherapy and before each rhG-CSF injection. As such, catheter flushing was done on a regular basis with each sample collection. For each sample collection, 1.5 ml of blood was withdrawn into a 3-ml syringe containing heparinized saline solution and placed aside. Five milliliters of blood was then withdrawn for hematologic analysis and divided between an EDTA tube and serum clot tube for CBC and serum biochemical analysis. The initial removed aliquot of 1.5 ml of blood was subsequently reinfused. The VAP were flushed with 1.5 additional milliliters of heparinized saline solution after each blood collection.

Statistical analyses—Measured dependent variables included counts of segmented neutrophils, band neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets and erythrocytes, Hct, blood hemoglobin concentration, serum concentrations of urea nitrogen, creatinine, glucose, cholesterol, total protein, albumin, calcium, phosphorous, sodium, chloride, potassium, total CO_2, and serum activities of ALT and ALP.

Table 1—Results of analysis of hematologic and serum biochemical values for direct venipuncture samples, compared with values for samples obtained via a vascular access port (VAP) in 14 cats

Analyte	Venipuncture sample mean (SD)	VAP sample mean (SD)	Difference mean (SD)
Total CO_2 (mmol/L)	18.9 (2.4)	18.2 (2.2)	0.7 (1.3)
Calcium (mg/dl)	8.9 (2.0)	9.2 (1.9)	–0.3 (0.5)
Chloride (mmol/L)	122.9 (2.1)	123.0 (2.4)	–0.1 (0.5)
Phosphorus (mg/dl)	6.1 (1.0)	6.1 (1.0)	–0.0 (0.1)
Potassium* (mmol/L)	4.2 (0.5)	4.6 (0.4)	–0.33 (0.18)
Sodium (mmol/L)	157 (2.2)	157 (2.2)	0 (1.0)
Creatinine† (mg/dl)	1.25 (0.3)	1.26 (0.3)	–0.01 (0.06)
Urea nitrogen (mg/dl)	27.4 (4.6)	27.6 (5.2)	–0.2 (2.0)
ALP (U/L)	29.7 (14.7)	31.8 (16.2)	–2.1 (2.24)
ALT (U/L)	67.0 (30.2)	69.7 (31.9)	–2.7 (3.5)
Cholesterol (mg/dl)	82.9 (28.0)	86.0 (28.5)	–3.1 (3.5)
Glucose (mg/dl)	123 (35.0)	107 (29.0)	15 (21.0)
Total protein* g/dl	6.1 (0.4)	6.3 (0.3)	–0.2 (0.2)
Albumin* (g/dl)	2.99 (0.21)	3.17 (0.23)	–0.18 (0.16)
Hct (%)	30.6 (4.0)	31.4 (4.0)	–0.8 (2.2)
Hemoglobin (g/dl)	9.4 (1.3)	9.9 (1.3)	–0.4 (0.8)
RBC ($\times 10^6/\mu l$)	6.74 (0.81)	6.97 (0.88)	–0.23 (0.42)
Platelets ($\times 10^3/\mu l$)	231,071 (76,995)	222,614 (70,978)	8,457 (32980)
Mature neutrophils ($\times 10^3/\mu l$)	6,096 (3,292)	6,408 (4,287)	–311 (749)
Band neutrophils ($\times 10^3/\mu l$)	8.1 (30.5)	0.0 (0.0)	8.1 (30.5)
Lymphocytes ($\times 10^3/\mu l$)	2,087 (1,205)	2,187 (1,187)	–100 (739)
Monocytes ($\times 10^3/\mu l$)	433 (298)	378 (340)	55 (225)
Basophils† ($\times 10^3/\mu l$)	73.1 (107.7)	94.7 (124.9)	–21.6 (124.7)
Eosinophils ($\times 10^3/\mu l$)	590 (498)	882 (917)	–292 (513)

*Analytes for which significant ($P > 0.001$) differences were detected between venipuncture and VAP samples. †Analytes for which values failed normality tests and differences were examined, with a rank sum procedure.
ALP = Alkaline phosphatase. ALT = Alanine aminotransferase.

Table 2—Results of linear regression models predicting concentration of an analyte (from a sample obtained by jugular venipuncture) as a function of concentration of the same analyte (from a sample obtained from a VAP)

Analyte	Intercept	Regression coefficient	r^2	*P* value
Total CO_2	2.0	0.93	0.71	< 0.001
Calcium	–0.42	1.014	0.94	< 0.001
Chloride	18.8	0.85	0.97	< 0.001
Phosphorus	–0.10	1.01	0.98	< 0.001
Potassium	–0.17	0.97	0.85	< 0.001
Sodium	11.8	0.93	0.89	< 0.001
Creatinine	–0.03	1.02	0.95	< 0.001
Urea nitrogen	4.8	0.82	0.86	< 0.001
ALP	1.04	0.90	0.99	< 0.001
ALT	1.24	0.94	0.99	< 0.001
Cholesterol	–0.83	0.97	0.99	< 0.001
Glucose	17.8	0.98	0.62	< 0.001
Total protein	–0.63	1.07	0.80	< 0.001
Albumin	0.86	0.67	0.56	0.002
Hct	4.0	0.85	0.73	< 0.001
Hemoglobin	1.57	0.80	0.64	< 0.001
RBC	1.13	0.81	0.77	< 0.001
Platelets	12817	0.98	0.82	< 0.001
Mature neutrophils	309	0.90	0.98	< 0.001
Band neutrophils*	NA	NA	NA	NA
Lymphocytes	292	0.82	0.66	< 0.001
Monocytes	181	0.66	0.58	0.002
Basophils	37	0.4	0.19	0.121
Eosinophils	157	0.49	0.82	< 0.001

*Regression model could not be developed for band neutrophils because none were observed in VAP samples, and only 1 cat had band neutrophils in the venipuncture sample.
NA = Not applicable.
See Table 1 for key.

For each analyte, sample A (jugular venipuncture sample) concentrations were compared with sample B (VAP) concentrations by use of a paired *t*-test. In those instances in which the observed difference was not normally distributed, a Wilcoxon signed-rank test was performed. The *P* value to reject the null hypothesis was adjusted to account for multiple comparisons by use of the Bonferroni procedure, in which the nominal *P*-to-reject is divided by the number of comparisons (0.05/24 = 0.002). Additionally, for each analyte, linear regression models were developed predicting sample A concentration as a function of sample B concentration.

Results

Vascular access port placement was successfully performed in all 14 cats. Port patency was maintained throughout the study period in all cats, and no catheter-related complications were noticed. Blood samples were evaluated from each cat 10 weeks after VAP placement. Serum potassium, total protein, and albumin concentrations were significantly ($P < 0.001$) higher in VAP samples than direct venipuncture samples. None of the other measured analytes differed significantly between VAP and venipuncture samples (**Tables 1** and **2**).

Discussion

The reliability of laboratory data is essential for cancer patients undergoing chemotherapy, as treatment decisions are based on these values. The use of totally implantable VAP for drug administration and hematologic monitoring is appealing for veterinary cancer patients, provided catheter-related complications are rare, specimen collection is easy, and laboratory values obtained from blood samples are reliable. In this study, VAP were placed in 14 cats and used for chemotherapy administration and blood collection for more than 3.5 months. The devices provided easy venous access, and no catheter-related infections or other complications were observed. Complete blood count results from VAP samples were comparable to those of direct venipuncture samples, indicating that this is a suitable method for routine hematologic monitoring of feline cancer patients.

The only analytes for which values varied significantly ($P < 0.001$) were potassium, albumin, and total protein. For these analytes, values from VAP samples were higher than those of direct venipuncture, suggesting some degree of hemolysis induced by withdrawing blood from the VAP. However, values for other analytes that may be decreased (Hct, glucose, sodium) or increased (calcium, ALT, phosphorus) by hemolysis were comparable in VAP and direct venipuncture samples. No visible difference in degree of hemolysis between VAP and direct venipuncture samples was evident. Heparin solutions containing chlorbutol may falsely increase potassium values. However, the heparin solution used for flushing the VAP did not contain chlorbutol. Although the difference in potassium values was small, results of linear regression analysis suggest that adjusting VAP-obtained potassium concentrations down by 0.2 to 0.3 mEq/L would approximate the values obtained by direct venipuncture. Because degree of hemolysis and

methodology used to measure potassium may affect values, this adjustment may not be applicable to all situations.

If values for the blood samples derived from VAP were perfect predictors of analyte concentrations in venipuncture-derived samples, our regression models (Table 2) would have a coefficient of 1, an intercept of 0, and an r^2 of 1. Coefficients either greater than or less than 1 suggest a less than perfect dose response relationship between the 2 samples. Seventeen of the 24 regression formulae had $r^2 > 0.70$, indicative of strong associations between VAP and venipuncture-derived samples. Positive intercepts were present when sample A analyte concentrations were greater than sample B concentrations.

The routine reinfusion of the initial 1.5 ml of blood withdrawn at each sampling time may be ill advised as a standard procedure because of the possibility of clot introduction into the bloodstream. Evaluation of this practice in human patients indicates that the initial blood sample is likely to contain clots, and reinfusion may present a risk to patient outcome.[9] The decision to reinfuse blood in this study was based on the frequency of sampling necessitated by a concurrent study and concerns relating to development of iatrogenic anemia. When less frequent monitoring is sufficient, reinfusion of discarded blood from VAP is not advised.

The accuracy of blood coagulation values obtained from VAP was not evaluated in the present study and may represent an exception to the routine use of VAP samples for patient monitoring. There is some evidence to suggest that prothrombin and partial thromboplastin times may be accurately determined on blood samples from IV access ports in humans.[16] However, until this is assessed in companion animals with VAP, the reliability of such values is unknown.

Our results suggest that samples obtained from VAP are suitable for routine patient monitoring in feline oncology. Although some hemolysis was suggested by the higher values of potassium, albumin, and total protein in the VAP samples, the slight differences are unlikely to be of clinical significance. When evaluating these values in terms of patient care, it would be advisable to consider that actual values may be slightly lower and to adjust plans for therapeutic intervention (such as potassium supplementation) accordingly. Long-term (> 3 months) use of venous access devices did not result in any catheter-related complications and facilitated both drug delivery and blood sampling in these cats. The ease of sample collection, maintenance of vascular integrity, and reduction of patient discomfort afforded by VAP warrant the routine use of these devices in cats undergoing long-term chemotherapy.

[a]CompanionPort, Norfolk Vet Products, a division of Norfolk Medical Products Inc, Skokie, Ill.
[b]Baker 9010, ABX Diagnostics, Irvine, Calif.
[c]Roche-Cobas-Mira Plus, Roche Diagnostics Corp, Indianapolis, Ind.
[d]Novantrone, Immunex Corp, Seattle, Wash.

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