Evaluation of a point-of-care coagulation analyzer for measurement of prothrombin time, activated partial thromboplastin time, and activated clotting time in dogs

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Objective—To evaluate a point-of-care coagulation analyzer (PCCA) in dogs with coagulopathies and healthy dogs.

Animals—27 healthy and 32 diseased dogs with and without evidence of bleeding.

Procedure—Prothrombin time (PT), activated partial thromboplastin time (aPTT), and activated clotting time (ACT) were determined, using a PCCA and standard methods.

Results—Using the PCCA, mean (± SD) PT of citrated whole blood (CWB) from healthy dogs was 14.5 ± 1.2 seconds, whereas PT of nonanticoagulated whole blood (NAWB) was 10.4 ± 0.5 seconds. Activated partial thromboplastin time using CWB was 86.4 ± 6.9 seconds, whereas aPTT was 71.2 ± 6.7 seconds using NAWB. Reference ranges for PT and aPTT using CWB were 12.2 to 16.8 seconds and 72.5 to 100.3 seconds, respectively. Activated clotting time in NAWB was 71 ± 11.8 seconds. Agreement with standard PT and aPTT methods using citrated plasma was good (overall agreement was 93% for PT and 87.5% for aPTT in CWB). Comparing CWB by the PCCA and conventional coagulation methods using citrated plasma, sensitivity and specificity were 85.7 and 95.5% for PT and 100 and 82.9% for aPTT, respectively. Overall agreement between the PCCA using NAWB and the clinical laboratory was 73% for PT and 88% for aPTT. Using NAWB for the PCCA and citrated plasma for conventional methods, sensitivity and specificity was 85.7 and 68.4% for PT and 86.7 and 88.9% for aPTT, respectively.

Conclusions and Clinical Relevance—The PCCA detected intrinsic, extrinsic, and common pathway abnormalities in a similar fashion to clinical laboratory tests. (*Am J Vet Res* 2001;62:1455–1460)

Hemostasis is comprised of primary and secondary phases.[1] Primary hemostasis results in formation of an unstable platelet plug that is stabilized by fibrin produced during secondary hemostasis. Secondary hemostasis is a process of controlled and localized activation of plasma coagulation factors that greatly augments fibrin production. Hereditary coagulopathies as well as acquired abnormalities of secondary hemostasis, such as disseminated intravascular coagulation, rodenticide intoxication, and liver dysfunction, are commonly seen in dogs. Evaluation of coagulation status is important in dogs with hemorrhage and may also be useful in presurgical screening of animals at risk for coagulopathy.

Screening tests of coagulation involve in vitro activation of parts of the clotting cascade and measurement of the time until clot formation.[2-4] **Prothrombin time (PT)** is used to evaluate the extrinsic and common pathways,[2,3,5] whereas **activated partial thromboplastin time (aPTT)** and **activated clotting time (ACT)** are used to screen the intrinsic and common pathways.[2,3,6,7] Except for the ACT, the methods and equipment required for conventional coagulation assays have restricted the performance of these tests to larger veterinary laboratories and thereby hindered their immediate usefulness in veterinary practice. Furthermore, submitting blood samples to external laboratories requires careful handling and shipment of samples, and the delay in obtaining results may hinder appropriate treatment of critically ill animals. Simple standardized point-of-care tests of coagulation are therefore desirable and could greatly increase the timely use of coagulation testing in veterinary medicine.

The purpose of the study reported here was to assess the clinical usefulness of a **point-of-care analyzer**[a] **(PCCA)** and compare results of PT, aPTT, and ACT obtained with the PCCA with standard laboratory methods in dogs.

Materials and Methods

Dogs—Fifty-nine dogs, aged 4 months to 14 years, were studied at the **Veterinary Hospital of the University of Pennsylvania (VHUP)**. There were 27 healthy dogs and 32 diseased dogs, 22 of which had clinical evidence of bleeding. Dogs were deemed healthy if there was no history of bleeding or current medical problems and physical examination findings were normal. Diseased dogs were selected from patients examined at the Emergency Service of the VHUP during a 9-month period. Because of the potential for inadequate blood sample volume and difficulty in sampling, dogs weighing < 10 kg were excluded. This study was approved by the VHUP Client Owned Animal Committee.

Procedure—An 8-ml blood sample was obtained by atraumatic cephalic or jugular venipuncture, using a 10-ml syringe and 20-gauge needle. Any samples obtained with difficulty from the jugular or cephalic veins were discarded. Samples were immediately processed as follows: 50 µl of **nonanticoagulated whole blood (NAWB)** was used for measurement of PT, aPTT, and ACT on 3 PCCA instruments; 2 ml was placed into a warmed ACT tube containing 6 to 10 mg

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siliceous earth[b] for determination of ACT, using a heating block at 37 C; and 1.8 ml was added to each of 2 tubes containing 0.2 ml of buffered 3.8% sodium citrate.[c] **Citrated whole blood (CWB)** from 1 tube was used to determine PT and aPTT on 3 PCCA instruments within 10 minutes of sample collection, and results were reported as the mean of the 3 values. The other tube was immediately centrifuged, and the separated plasma was stored in plastic tubes at –70 C for determination of PT and aPTT within 24 hours in the laboratory by use of conventional reagents[d,e] and a fibrometer.[f] Determination of PT and aPTT in citrated plasma was performed in the clinical laboratory in duplicate and reported as the mean of the 2 results. Samples were not batched for analysis.

Specific cuvettes were used on the PCCA for NAWB for measurement of PT, aPTT, and ACT (termed ACT+) and for CWB to determine PT and aPTT. The contents of each cuvette type were as follows: the aPTT cuvette contained kaolin, phospholipid, stabilizers, and buffers; the citrate aPTT cuvette contained kaolin, phospholipid, stabilizers, buffers, and calcium salts; the PT cuvette contained rabbit brain thromboplastin, stabilizers, and buffers; the citrate PT cuvette contained rabbit brain thromboplastin, stabilizers, buffers, and calcium salts; and the ACT+ cuvette contained silica, kaolin, phospholipid, stabilizers, and buffers.[g] Following insertion into the PCCA and warming of the cuvette to 37 C, a 50=μl drop of fresh NAWB or CWB kept at room temperature (20 C) was placed into the sample well, and 15 μl was then aspirated by the instrument. Blood is mixed with reagents in the cuvette and is then moved backwards and forwards through a test channel. The time until clot formation is measured by light-emitting diode optical detectors at each end of the channel that recognizes slower movement of the sample as clotting develops. Samples testing greater than the upper time limit of the standard method or PCCA were assigned arbitrary values. These were 100 seconds for the clinical laboratory PT, aPTT, and both PCCA PT tests, 300 seconds for the tube ACT, 300 seconds for the PCCA aPTT, and 1,005 seconds for the PCCA ACT+.

The mean between instrument variation for samples that were run in triplicate on separate instruments by use of CWB was 1 second (range, 0 to 3 seconds) for PT and 5.5 seconds (range, 1 to 20 seconds) for aPTT. Overfilling and underfilling the sample well and air bubbles in the cuvette well yielded error messages in 8 of 507 tests (1.6%); repeating the test once always provided measurable results.

Statistical analyses—Descriptive statistics and frequency distribution analyses were performed on all data. Normality was assessed by use of the Kolmogorov Smirnoff test. Reference ranges were calculated as mean ± 2 SD. Correlation of results from the PCCA and agreement with clinical laboratory results was examined by use of the Bland-Altman method[8] for PT and the κ test for agreement[9] for PT and aPTT. Sensitivity and specificity were calculated by defining abnormal and normal clinical laboratory results as true positives and true negatives, respectively. Predictive values of positive and negative test results were determined for 2 hypothetical disease prevalences (50% and 1%). Differences between groups were examined, using a Mann-Whitney Rank Sum test for non-normal data. Differences were considered significant when $P < 0.05$.

Results

Reference ranges for PT and aPTT were generated from 27 healthy dogs (**Table 1**); however, a shortage of NAWB cuvettes limited the number of dogs in which tests using NAWB were performed. In healthy dogs, PT measured on the PCCA using CWB was slightly but significantly longer than the plasma PT determined in the clinical laboratory, whereas PT of NAWB on the PCCA was significantly shorter than results obtained in the clinical laboratory. The aPTT measured on the PCCA

Table 1—Prothrombin (PT), activated partial thromboplastin time (aPTT) and activated clotting time (ACT) in healthy dogs, as measured by use of a point-of-care coagulation analyzer (PCCA) or in a clinical laboratory. Data for PT and aPTT are mean values of samples run in triplicate on 3 separate PCCA

Coagulation test	n	Mean ± SD (sec)	Median (sec)	Reference range (sec)
PT				
Laboratory (CP)	26	12.7 ± 1.1	12.4	10.5–14.9
PCCA (CWB)	27	14.5 ± 1.2	14.7	12.2–16.8
PCCA (NAWB)	6	10.4 ± 0.5	10.2	9.3–11.5
APTT				
Laboratory (CP)	25	13.9 ± 1.5	13.9	10.9–16.9
PCCA (CWB)	26	86.4 ± 6.9	87.5	72.5–0.3
PCCA (NAWB)	12	71.2 ± 6.7	73.5	57.9–84.5
ACT				
Tube ACT (NAWB)	27	103 ± 20.3	100	63–144
PCCA (NAWB)	15	71 ± 11.8	67	47–95

CP = Citrated plasma. CWB = Citrated whole blood. NAWB = Nonanticoagulated whole blood. Tube ACT = Conventional method of measuring ACT.

Table 2—Contingency tables for determination of sensitivity and specificity for PT and aPTT for citrated whole blood and nonanticoagulated whole blood with the PCCA, compared with conventional measurements of PT and aPTT on citrated plasma (CP) as measured in a clinical laboratory

	Citrated whole blood					
	PT (PCCA)			PTT (PCCA)		
Laboratory result (CP)	Normal	Abnormal	Total	Normal	Abnormal	Total
Normal	42	2	44	34	7	41
Abnormal	2	12	14	0	15	15
Total	44	14	58	34	22	56
	Nonanticoagulated whole blood					
	PT (PCCA)			PTT (PCCA)		
Laboratory result (CP)	Normal	Abnormal	Total	Normal	Abnormal	Total
Normal	13	6	19	16	2	18
Abnormal	1	6	7	2	12	15
Total	14	12	26	18	15	33

Normal = Within reference range. Abnormal = Outside of reference range.

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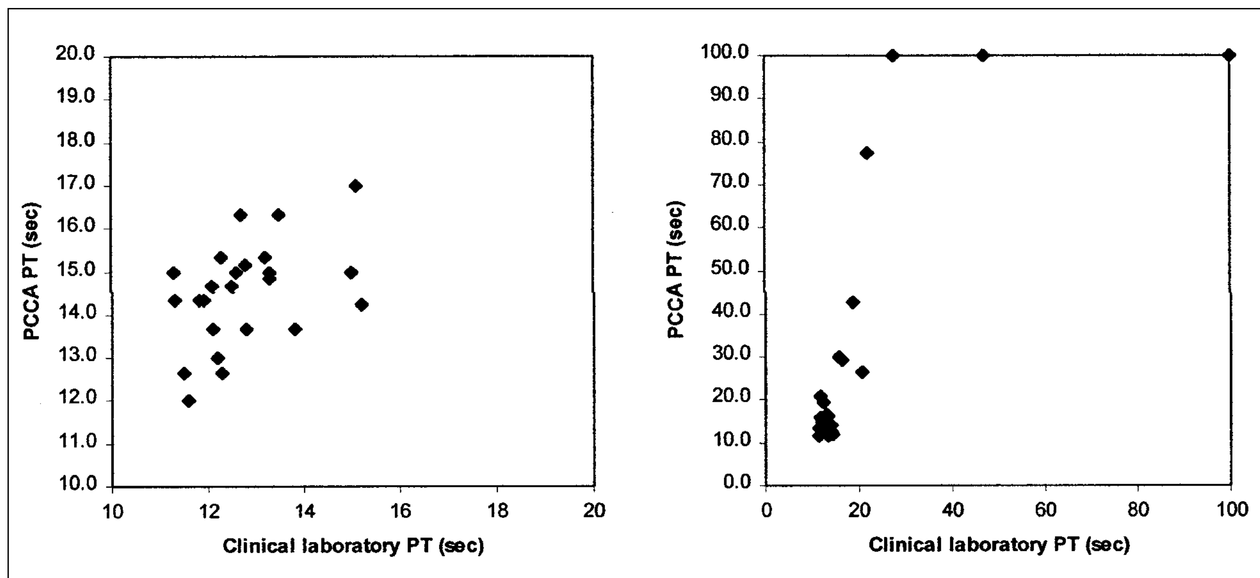

Figure 1—Scatter plot of prothrombin time (PT) in healthy dogs, using citrated whole blood, as measured by use of a point-of-care coagulation analyzer (PCCA) versus PT using citrated plasma, as measured in a laboratory (left). Scatter plot of PT in dogs with bleeding disorders, using citrated whole blood, as measured by use of a PCCA versus PT measured in a laboratory using citrated plasma (right).

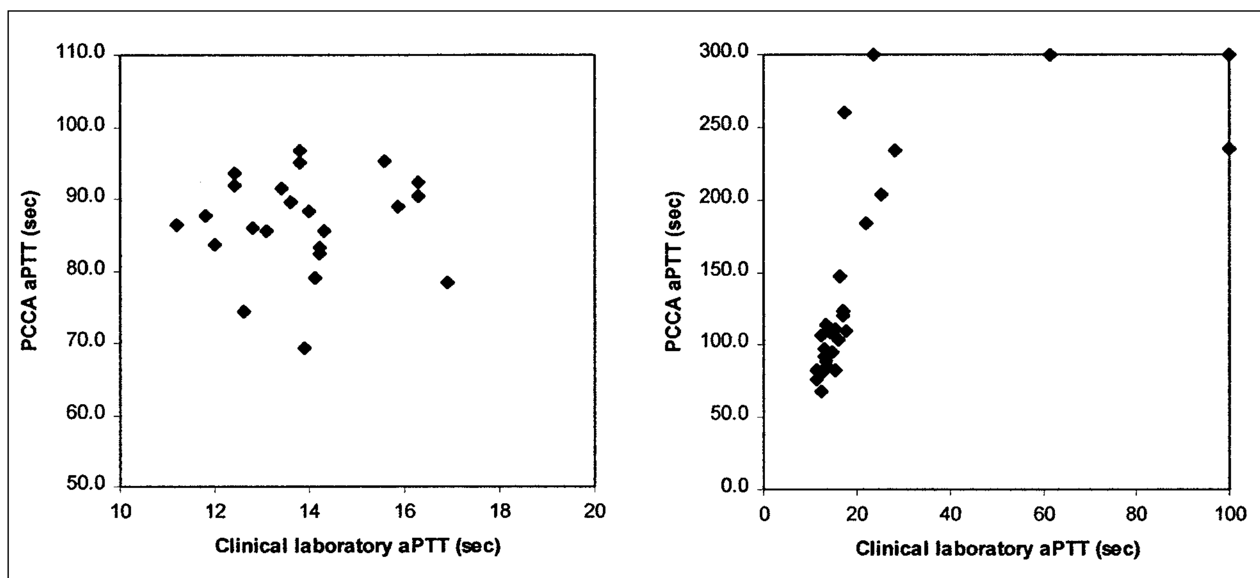

Figure 2—Scatter plot of activated partial thromboplastin time (aPTT) in healthy dogs, using citrated whole blood, as measured by use of a PCCA versus aPTT using citrated plasma, as measured in a laboratory (left). Scatter plot of aPTT in dogs with bleeding disorders, using citrated whole blood, as measured by use of a PCCA versus aPTT measured in a laboratory using citrated plasma (right).

using CWB or NAWB was significantly longer than aPTT determined on citrated plasma in the clinical laboratory. The ACT values determined using the PCCA were significantly shorter than ACT tube test results.

Thirty-two diseased dogs were tested, 22 (69%) of which had clinical signs of bleeding. Comparing the PCCA results using CWB for the 22 dogs with bleeding, 11 of 22 (50%) had abnormal PT results on the PCCA as well as the clinical laboratory; 2 dogs had abnormal PT results on the PCCA, whereas the laboratory reported values within reference range; and 9 dogs had a PT within reference range on the PCCA and in the clinical laboratory. There were no dogs with bleeding disorders for which PT results using CWB were within reference range on the PCCA, and results from the clinical laboratory were abnormal, although 2 clinically normal dogs had mildly prolonged PT by the clinical laboratory test (0.1 to 0.3 sec) that were within reference range on the PCCA.

For the citrated aPTT, abnormal results were documented in 14 of 22 (64%) dogs with the PCCA as well as in the clinical laboratory; 5 dogs had prolonged values on the PCCA, with clinical laboratory results within reference range; and 3 dogs had aPTT within reference range on the PCCA and in the clinical laboratory. There were no instances where aPTT results on the PCCA (using CWB) were within reference range and clinical laboratory results were abnormal. The PCCA

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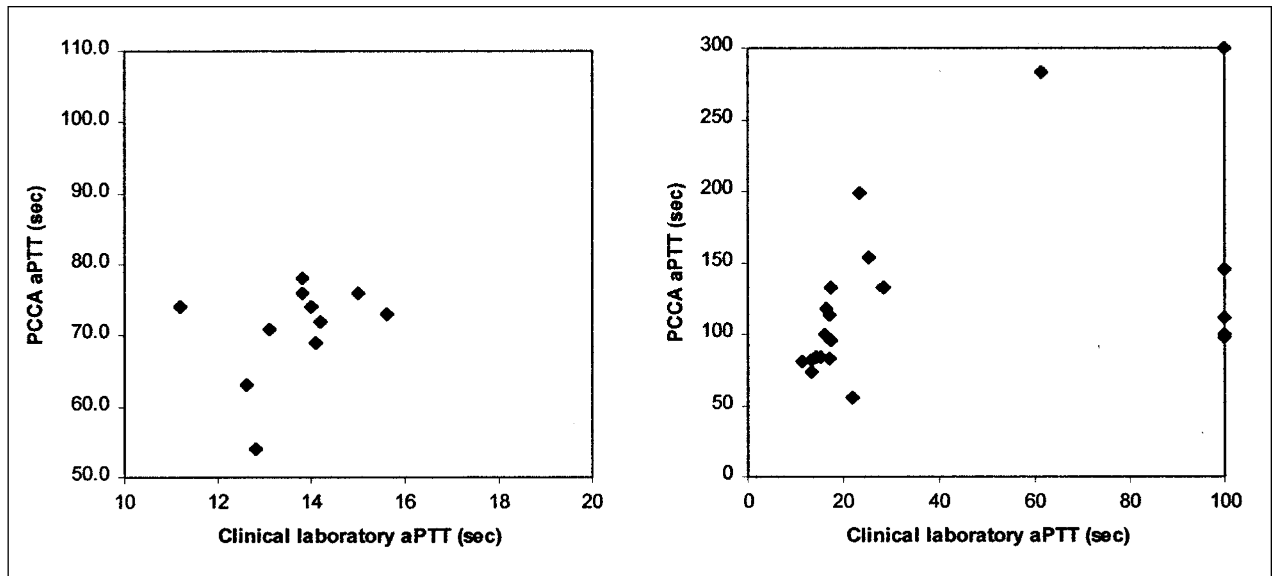

Figure 3—Scatter plot of aPTT in healthy dogs, using nonanticoagulated whole blood, as measured by use of a PCCA versus aPTT using citrated plasma, as measured in a laboratory (left). Scatter plot of aPTT in dogs with bleeding disorders, using nonanticoagulated whole blood, as measured by use of a PCCA versus aPTT using citrated plasma, as measured in a laboratory (right).

detected the expected prolongation of PT and aPTT values in 4 dogs that had anticoagulant rodenticide intoxication and detected a PT within reference range and prolonged aPTT in a dog with Factor IX deficiency.

Ten diseased dogs without bleeding were evaluated: 3 had seizures, 2 had traumatic injuries, and individual dogs had pancreatitis, noncardiogenic pulmonary edema, immune-mediated arthropathy, hepatic/renal disease, and vomiting. All had a PT within reference range on the PCCA (using CWB) as well as in the clinical laboratory. Two dogs without clinical bleeding had mildly prolonged aPTT (11 sec) on the PCCA, yet results were within reference range in the clinical laboratory, and 1 dog had prolonged aPTT on the PCCA (9 sec) as well as in the laboratory (0.6 sec).

Data from all healthy and diseased dogs were combined for each test to determine agreement, sensitivity, and specificity between the PCCA and clinical laboratory methods over the clinically relevant range of possible values (**Table 2**; **Fig 1–3**). Sensitivity and specificity were not determined for ACT, because large variability in the conventional ACT tube method meant it could not be considered a gold standard for statistical analysis.

There was good agreement between data obtained from the clinical laboratory and that from the PCCA. Overall agreement between the PCCA and the clinical laboratory was 54 of 58 (93%) for PT and 49 of 56 (87.5%) for aPTT measured from CWB. The κ test for agreement yielded kappa statistics of 0.81 for PT and 0.72 for aPPT measured from CWB. Analysis of agreement and bias by the Bland-Altman method yielded a bias of 5.5 seconds and 95% limits of agreement of –21 to +32 seconds for PT measured from CWB and revealed that the variability in data points increased as the numbers increased. Comparing results obtained from the PCCA using CWB versus conventional coagulation methods using citrated plasma, the sensitivity and specificity were 85.7 and 95.5% for PT and 100 and 82.9% for aPTT, respectively. Overall agreement between results obtained from the PCCA using NAWB and the clinical laboratory was 19 of 26 (73%) for PT and 29 of 33 (88%) for aPTT. The κ test for agreement yielded kappa statistics of 0.44 for PT and 0.76 for aPPT using NAWB. Analysis of agreement and bias by the Bland-Altman method yielded a bias of 0.81 seconds and 95% limits of agreement of –9 to + 11 seconds for PT (using NAWB) and revealed that variability increased as the values increased. Using NAWB for the PCCA and citrated plasma for conventional methods, sensitivity and specificity were 85.7 and 68.4% for PT and 86.7 and 88.9% for aPTT, respectively.

Discussion

As may be expected from the different methods and reagents used,[10,11] reference ranges for PT and aPTT measured with the PCCA differed significantly from the clinical laboratory values. Differences in PT results were relatively small, whereas aPTT values measured with the PCCA were typically 5 to 6 times longer than conventional aPTT measured in plasma. These differences may be attributable to differences in thromboplastin, method of endpoint determination, and the fact that whole blood rather than plasma is used as the substrate for the PCCA. Although the absolute times generated for PT and aPTT differed between the clinical laboratory and the PCCA, the PCCA was accurate in predicting coagulation status. Overall agreement, sensitivity, and specificity were better for CWB than for NAWB. Furthermore, use of CWB is more convenient, because samples may be analyzed up to an hour following venipuncture rather than immediately as with NAWB. The PT and aPTT values obtained from CWB did not change in blood that was kept at room temperature (data not shown). Thus, CWB appears to be the sample of choice when using the PCCA. The PCCA appeared to correctly predict coagulation abnormalities such as factor IX deficiency, anticoagulant rodenticide

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intoxication, and presumed disseminated intravascular coagulation associated with other diseases (Table 2).

The main source of discrepancy between the PCCA and the clinical laboratory was a small number of false positives with the PCCA for CWB aPTT and NAWB PT. For determination of aPTT using CWB, there were 7 dogs with prolonged results on the PCCA, but results were within reference range in the clinical laboratory. Five of these 7 dogs had prolonged aPTT, with the PCCA of 4 to 11 seconds above reference range. Six dogs had mildly prolonged PT on the PCCA using NAWB (1.5 to 4.5 seconds). Changing reagents and methods can greatly alter the sensitivity of clotting tests to factor deficiencies.[12,13] Many test reagent systems are insensitive to coagulation factor deficiency and do not detect prolongations until factor concentrations have decreased to < 20 to 40% of normal.[3] The reference range generated for PT with the PCCA (using NAWB) was likely too narrow, because only 6 healthy dogs were tested, and results were similar. Further studies will be necessary to confirm the true nature of the few discrepancies between the result obtained using the PCCA versus conventional methods.

It is important to appreciate the effect of prevalence on the interpretation of diagnostic tests. In this population of diseased dogs, the prevalence of abnormal coagulation tests was high because of the deliberate selection of animals with a bleeding disorder to provide positive results to test the PCCA over all possible values. Caution should be exercised in applying these results to clinical situations, depending on the expected prevalence of coagulopathy. By way of explanation, consider coagulation testing in 2 different populations of dogs prior to surgery: dogs with ruptured splenic hemangiosarcoma and clinically normal dogs undergoing ovariohysterectomy. The **predictive value of a positive test (PVP)** is the proportion of dogs that have the disease or abnormality being tested in which the test yielded positive results, whereas the **predictive value of a negative test (PVN)** is the proportion of dogs that do not have the disease or abnormality in which the test yielded negative results. In dogs with hemangiosarcomak, coagulopathy is likely, whereas in dogs undergoing ovariohysterectomy, it is unlikely. Assigning arbitrary prevalences of an increased PT of 50% in the first group and 1% in the second, respectively, will result in the following predictive values when measuring PT using the PCCA: with a prevalence of 50%, the PVP is 0.95 and the PVN is 0.87, whereas with a prevalence of 1%, the PVP is 0.16 and the PVN is 0.998.

Until recently, the ACT tube test was the only simple and widely available point-of-care coagulation test.[7,14] The ACT is presently used in people to monitor acute changes when using heparin during surgery because of the rapid turn-around time of this test.[15,16] In our study, results of the ACT, as measured by the PCCA, were less variable than the ACT tube test. Because both ACT and aPTT are used to assess intrinsic and common coagulation pathways, measuring the ACT offers no additional information regarding secondary hemostasis than measuring the aPTT. Because the ACT data from the PCCA were more variable than the aPTT data from the PCCA, there appears to be no reason to perform an ACT in addition to an aPTT. Performing an aPTT with the PCCA alone should detect all coagulopathies, with the exception of an isolated factor VII deficiency such as may be seen in early anticoagulant rodenticide intoxication.

Coagulation tests results may vary for several reasons, including venipuncture technique, sample handling, type and lot number of thromboplastin used, and the test method, including the method of endpoint determination.[11,17,18] Consequently, results from the same sample may be different between laboratories. The variability in results obtained from healthy dogs, as measured by the coefficient of variation, was better with the PCCA than with conventional methods for all coagulation tests. In addition, the error rate using the PCCA (8/507 tests [1.6%]) was much lower than that reported for another point-of-care assay for determination of PT in dogs (45/224 tests [20%]).[19] The availability of a simple PCCA from which results can be obtained immediately should greatly increase the appropriate use of coagulation testing in veterinary medicine. Widespread use of similar instruments (and therefore reagents and methods) may allow meaningful comparison of coagulation test results between clinics and facilitate multicenter coagulation studies.

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[a]SCA 2000 Veterinary Coagulation Analyzer, Synbiotics, San Diego, Calif.

[b]Vacutainer Brand Tube for Activated Coagulation time of whole blood, Becton Dickinson Vacutainer Systems, Becton Dickinson and Co, Franklin Lakes, NJ.

[c]Vacutainer Brand Tube for Coagulation Procedures, Becton Dickinson Vacutainer Systems, Becton Dickinson Co, Franklin Lakes, NJ.

[d]Thromboplastin Liquid, Pacific Hemostasis, Huntersville, NC.

[e]Kontact, Pacific Hemostasis, Huntersville, NC.

[f]BBL Fibrosystem Precision Coagulation Timer, Becton Dickinson Microbiology Systems, Cockeysville, Md.

[g]SCA 2000 Veterinary Coagulation Analyzer cuvette package insert, Synbiotics, San Diego, Calif.

References

1. Troy GC. An overview of hemostasis. *Vet Clin North Am Small Anim Pract* 1998;28:483–513.
2. Brooks M. Coagulation and thrombosis. In: Ettinger SJ, Feldman EC, eds. *Textbook of veterinary internal medicine*. 5th ed. Philadelphia: WB Saunders Co, 2000;1829–1841.
3. Furie B, Furie BC. Molecular basis of blood coagulation. In: Hoffman R, et al, eds. *Hematology: basic principles and practice*. New York: Churchill Livingstone Inc, 2000;1783–1803.
4. Santoro SA, Eby CS. Laboratory evaluation of hemostatic disorders. In: Hoffman R, et al, eds. *Hematology: basic principles and practice*. New York: Churchill Livingstone Inc, 2000;1841–1850.
5. Quick AJ. Determination of prothrombin. *Am J Med Sci* 1935;190:501.
6. Proctor RR, Rapaport SI. The partial thromboplastin time with kaolin. *Am J Clin Pathol* 1961;36:212–219.
7. Byars TD, Ling GV, Ferris NA, et al. Activated coagulation time (ACT) of whole blood in normal dogs. *Am J Vet Res* 1976;37:1359–1361.
8. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1:307–309, 1986–1989.
9. Altman DG. *Practical statistics for medical research*. London: Chapman & Hall, 1991;403–405.
10. Davis KD, Danielson CF, May LS, et al. Use of different thromboplastin reagents causes greater variability in international normalized ratio results than prolonged room temperature storage of specimens. *Arch Pathol Lab Med* 1998;122:972–977.
11. Naghibi F, Han Y, Dodds WJ, et al. Effects of reagent and

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instrument on prothrombin times and activated partial thromboplastin times and patient/control ratios. *Thromb Haemost* 1988;59:455–463.

12. Brandt JT, Arkin CF, Bovill EG, et al. Evaluation of APTT reagent sensitivity to factor IX and factor IX assay performance. Results from the College of American Pathologists Survey Program. *Arch Pathol Lab Med* 1990;114:135–141.

13. Hall DE. Sensitivity of different thromboplastin reagents to factor VII deficiency in the blood of beagle dogs. *Lab Anim* 1970;4:55–59.

14. Middleton DJ, Watson ADJ. Activated coagulation times of whole blood in normal dogs and dogs with coagulopathies. *J Small Anim Pract* 1978;19:417–418.

15. Helft G, Choktron S, Beygui F, et al. Comparison of activated clotting times to heparin management test for adequacy of heparin anticoagulation in percutaneous transluminal coronary angioplasty. *Cathet Cardiovasc Diagn* 1998;45:329–333.

16. Thomason T, Riegel B, Jessen D, et al. Clinical safety and cost of heparin titration using bedside activated clotting time. *Am J Crit Care* 1993;2:81–83.

17. O'Neill AI, McAllister C, Corke CF, et al. A comparison of five devices for the bedside monitoring of heparin therapy. *Anaesth Intensive Care* 1991;19:592–595.

18. Hassouna HI. Laboratory evaluation of hemostatic disorders. *Hematol Oncol Clin North Am* 1993;7:1161–1222.

19. Monce KA, Atkings CE, Loughman CM. Evaluation of a commercially available prothrombin time assay kit for use in dogs and cats. *J Am Vet Med Assoc* 1995;207:581–584.

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