Intensive monitoring of anesthetized patients allows for early detection of life-threatening changes in patient homeostasis. Currently, human and veterinary variables such as arterial blood pressure, cardiac rate and rhythm, end-tidal carbon dioxide concentration, arterial oxygen saturation, and body temperature are routinely monitored continuously in real time. A simple method to continuously measure blood glucose concentration has not been available until recently. Clinical trials in adult humans undergoing surgical procedures reveal that strict glycemic control results in a 35% to 53% reduction in mortality rate and even greater reduction in morbidity attributable to those procedures. These findings support the importance of accurate and diligent monitoring of blood glucose concentration in anesthetized patients.

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Evaluation of a real-time, continuous monitor of glucose concentration in healthy dogs during anesthesia

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Objective—To evaluate the accuracy of a real-time, continuous glucose monitoring system (CGMS) in healthy dogs undergoing anesthesia for elective ovariohysterectomy or orchiectomy.

Animals—10 healthy dogs undergoing routine elective surgery.

Procedures—A CGMS was placed and used to obtain calculated glucose measurements before, during, and after anesthesia in each dog. Periodically, CGMS measurements were compared with concurrent measurements of glucose concentration in peripheral venous blood obtained with a portable chemistry analyzer (PCA).

Results—CGMS-calculated glucose measurements were significantly different from PCA blood glucose measurements during most of the anesthetic period. The CGMS values differed from PCA values by > 20% in 54 of 126 (42.9%) paired measurements obtained during the anesthetic period. Hypoglycemia was evident in CGMS measurements 25 of 126 (19.8%) times during anesthesia. By comparison, only 1 incident of hypoglycemia was detected with the PCA during the same period.

Conclusions and Clinical Relevance—Use of the CGMS for routine monitoring of interstitial glucose concentration as an indicator of blood glucose concentration during anesthesia cannot be recommended. Additional investigation is necessary to elucidate the cause of discrepancy between CGMS results and PCA data during anesthesia. (Am J Vet Res 2010;71:11–16)

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Abstract

Recent advances in technology have provided real-time, continuous glucose monitoring systems (CGMS) that can be used in diabetic patients to maintain tight glycemic control. CGMS devices continuously monitor the interstitial fluid glucose concentration and may be used to assist in the regulation of diabetes mellitus. Some systems, however, have been validated in non-diabetic patients and are utilized for routine monitoring of glucose concentrations in anesthetized animals. Continuous monitoring of glucose concentration during anesthesia may increase detection of important changes in glucose concentration that might be missed with intermittent measurement.

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Abbreviations

CGMS = Continuous glucose monitoring system
PCA = Portable chemistry analyzer

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Materials and Methods

Animals—Ten clinically normal dogs scheduled for elective ovariohysterectomy or orchietomy were included in the study. Criteria for inclusion were a minimum body weight of 15 kg, a body condition score of 2 or 3 (on a 5-point scale), and a record of normoglycemia when admitted. All dogs were expected to undergo a surgical procedure lasting at least 60 minutes. The study protocol was approved by the Kansas State University Institutional Animal Care and Use Committee, and consent was obtained from owners of all participating dogs.

Physical examination of each dog was performed by a board-certified veterinary surgeon or surgical resident to confirm the dog was overtly healthy. Serum total protein concentration (determined by use of a refractometer) and Hct were measured prior to anesthesia. Normoglycemia was verified in all dogs at the time of CGMS calibration by measurement of whole blood glucose concentration with a PCA.

CGMS sensor and transmitter placement—The CGMS2 was placed and activated at least 18 hours prior to surgery. Sensor placement and CGMS set up were performed as described8; however, an upgraded CGMS was used. Briefly, hair was shaved from a 10-cm² patch of skin on the right lateral aspect of the thorax and the area was cleaned with alcohol. The sensor was introduced into the subcutaneous space by use of a needle stylet provided with the CGMS. The stylet was subsequently removed, and the sensor was adhered to the skin with adhesive tape. After a 5-minute so-called wetting period to establish sensor contact with the interstitial fluid, the wireless transmitter was connected to the sensor and the monitor was activated. Elastic adhesive tape was used to secure the sensor and transmitter to the skin once successful communication between the transmitter and the monitor was verified. Use of an Elizabethan collar prevented dogs from removing or damaging the sensor. The monitor was placed on the door of the dog's cage and remained within a 1.5-m radius of the dog at all times, including during anesthesia and surgery.

CGMS initialization and calibration—After a 2-hour system initialization period, 0.2 mL of blood was collected into a heparinized syringe via peripheral venipuncture for blood glucose concentration determination with a PCA validated for use in dogs.10 The measurement served to verify normoglycemia and was entered into the CGMS as the first value for system calibration. Additional calibration measurements were performed 8 hours after initialization, and then every 12 hours thereafter as indicated in the manufacturer's instructions. Instances of technical failure, defined as a period during which the sensor failed to report data or ceased to function with or without sounding an alarm, were recorded throughout the study.

Anesthesia—Anesthetic duration was defined as the period from induction (designated time 0) to extubation. Dogs were premedicated with acepromazine (0.04 mg/kg, SC) and morphine (0.5 mg/kg, SC). Anesthesia was induced with thiopental (10 mg/kg, IV). Dogs were endotracheally intubated, and anesthesia was maintained with isoflurane in oxygen (1.0% to 2.5% isoflurane). The isoflurane vaporizer was adjusted as necessary to maintain an appropriate anesthetic plane. All dogs received an IV infusion of lactated Ringer's solution (10 mL/kg/h) throughout the anesthetic period.

CGMS evaluation—The function and accuracy of the CGMS before anesthesia and 2 and 8 hours after anesthesia were evaluated by comparing glucose readings registered by the CGMS with those from the PCA. To do so, blood samples (0.2 mL) were collected via
Peripheral venipuncture into heparinized syringes for immediate analysis by the PCA. The results of these determinations were used to confirm the CGMS was providing accurate readings in the preanesthetic and postanesthetic periods. Verification samples were not used as calibration samples. The CGMS values were considered accurate when within 20% of PCA values. Because the working range of the CGMS is glucose concentrations between 40 and 400 mg/dL, all values less than or greater than this range were reported by the CGMS as 40 and 400 mg/dL, respectively.

Immediately after anesthetic induction, 0.2 mL of blood was collected from a peripheral vein into a heparinized syringe and analyzed immediately with the PCA. The PCA measurement and concurrent CGMS measurement were recorded as time 0. For each dog, pulse rate, respiratory rate, and systolic arterial blood pressure were recorded every 5 minutes and esophageal temperature was recorded every 15 minutes. The glucose value displayed by the CGMS was recorded every 15 minutes beginning at time 0, and a peripheral venous blood sample was obtained for evaluation with the PCA. The last PCA and CGMS measurements of the anesthetic period were acquired immediately after extubation. All surgical procedures were performed by senior veterinary students under the supervision of a veterinarian.

Statistical analysis—Statistical software was used for all analyses. Mean glucose concentrations measured with the CGMS and PCA were compared at each measurement point with a paired t test. Changes in glucose concentration over time determined by each measurement device were analyzed by use of repeated-measures ANOVA with a Newman-Keuls post hoc comparison. A correlation coefficient matrix was used to assess effects of age, body weight, surgery duration, anesthetic duration, esophageal temperature, and blood pressure on glucose concentrations measured with the CGMS and PCA. A value of P ≤ 0.05 was considered significant for all comparisons.

Results

Animals—The 10 dogs (9 females and 1 male) used in the study were deemed healthy on the basis of the preadmission physical examination and met the inclusion criteria. Specific breeds represented included mixed-breed dogs (n = 7) and 1 each of Boxer, German Shorthaired Pointer, and German Shepherd Dog. Mean age was 20 months (range, 6 to 49 months). Mean body weight was 22 kg (range, 15 to 38 kg). All 10 dogs underwent abdominal surgery. The 9 female dogs had an ovariohysterectomy, and the male dog had a bilateral orchiectomy but required abdominal exploration to locate a cryptorchid testis. The mean surgical duration was 110 minutes (range, 8 to 145 minutes), and the mean anesthetic duration was 171 minutes (range, 128 to 215 minutes). The median number of paired PCA and CGMS measurements obtained per dog during the anesthetic period was 12 (range, 8 to 15), yielding a total of 126 paired datum points for analysis.

CGMS evaluation—Blood glucose concentration was measured with the PCA for CGMS calibration at the time of initial CGMS set up. The mean blood glucose concentration (n = 10 dogs) as determined by the PCA at the time of initial calibration was 89 mg/dL (range, 74 to 109 mg/dL; reference range, 60 to 115 mg/dL). Preanesthetic verification samples were collected a mean of 136 minutes prior to anesthetic induction (range, 75 to 290 minutes). The mean glucose concentration as measured with the CGMS before anesthetic induction was 85.1 mg/dL (range, 68 to 106 mg/dL), and that as measured with the PCA was 86.4 mg/dL (range, 75 to 105 mg/dL).

Verification samples were also obtained 2 and 8 hours after extubation. The mean glucose concentration as measured with the CGMS 2 hours after extubation was 90.8 mg/dL (range, 70 to 118 mg/dL), and that as measured with the PCA was 93.3 mg/dL (range, 63 to 118 mg/dL). Respective values 8 hours after extubation were 92.4 mg/dL (range, 66 to 120 mg/dL) and 92.9 mg/dL (range, 61 to 114 mg/dL).

Analysis of all verification samples revealed no significant differences between glucose concentrations as measured by the 2 devices before anesthetic induction and 2 and 8 hours after extubation. Analysis of the 126 paired datum points from the anesthetic period revealed agreement (< 20% difference) in 72 paired samples (57.1% samples; mean ± SD difference, 5.54 ± 6.9 mg/dL). Disagreement (> 20% difference) between CGMS and PCA measurements was evident in 54 paired samples (42.9% of all samples; mean difference, 41.29 ± 17.81 mg/dL). Values from the CGMS were lower than those from the PCA in all discordant pairs. Hypoglycemic readings (< 60 mg/dL) were obtained with the CGMS in 25 of 126 paired samples, 4 of which were reported as 40 mg/dL (the lower limit of detection by
the CGMS). By contrast, only 1 hypoglycemic reading among these 25 paired samples was obtained with the PCA.

When paired CGMS and PCA data for individual dogs were examined over the anesthetic period, a distinct pattern was detected for most (n = 8) dogs. In those dogs, CGMS glucose values began to diverge from PCA values soon after anesthetic induction but became concordant near the end of the anesthetic period (Figure 1). Anesthetic periods among study dogs were not of equal duration, and it appeared from analysis of individual data that agreement between CGMS and PCA results improved near the end of the anesthetic period. To evaluate this potential agreement further, the last 5 paired datum points obtained from each dog were used to examine the relationship between CGMS and PCA values in the 60 minutes immediately prior to extubation (Figure 2). The glucose concentration determined by the CGMS was significantly lower than that determined by the PCA at 60 and 45 minutes prior to extubation, but no significant differences were detected beginning 30 minutes prior to and at the time of extubation.

No significant correlations existed between measurements made with the 2 devices with respect to dog age, body weight, surgery duration, anesthesia duration, esophageal temperature, or systolic arterial blood pressure.

**Discussion**

In the study reported here, the high percentage of discordant results between the CGMS and PCA (used as the reference criterion) suggested that the CGMS does not provide reliable data regarding blood glucose concentration in anesthetized dogs. The PCA used in this study was validated in a study that indicated 99% of all PCA readings were within 15% of values obtained by a reference laboratory. Although this is a high degree of accuracy, it is possible that even a 15% discrepancy from actual values influenced the results in our study. This factor could have been addressed by use of in-house laboratory values as reference data or by random selection of blood samples throughout the study for in-house laboratory analysis to verify the accuracy of the PCA used.

The cause of the discrepancies between results of the CGMS and PCA obtained during the anesthetic period was not clear. Erroneous data caused by CGMS malfunction (defective sensor or electrode, transmitter error, unit calibration error, or incorrect sensor placement) are not a likely explanation because excellent agreement between devices was evident in results for samples obtained before and after that anesthetic period. Discordance between CGMS data and directly measured blood glucose values was revealed in a study of nocturnal hypoglycemia in humans with tightly controlled type 1 diabetes. In that study, the lowest glucose concentration of the evening recorded by the CGMS underestimated blood glucose by a mean of 38% when concurrent results from a glucose analyzer were available. Although a true difference in the gradient between interstitial and plasma glucose concentrations during sleep could not be ruled out, a calibration problem was believed the most likely cause of the low glucose readings recorded overnight. In the present study, calibration error was an unlikely source of the discrepancy between glucose values determined by the CGMS and PCA. First, the CGMS made use of the latest software version provided by the manufacturer, including updated calibration algorithms, and great care was taken when obtaining and processing blood samples for calibration and when entering the results into the CGMS monitor. Second, a calibration error would not sufficiently explain why inaccurate readings were only obtained when dogs were anesthetized or why agreement between CGMS and PCA results improved near the end of the anesthetic period.

Validation and use of a CGMS have been extensively addressed in human medicine. Only a few studies, however, involved evaluation of a CGMS in anesthetized patients, and there are no reports of use of a CGMS in the routine glycemic management of anesthetized veterinary patients. In a study of adult humans undergoing various abdominal procedures, the CGMS used had a high rate of technical failure during the anesthetic period (66% of all measurement points during the anesthetic period were deemed invalid, compared with only 18% of data obtained in the postoperative period). Interestingly, the accuracy was just 74% in anesthetized humans even when valid CGMS data were obtained. Reading interference when electrocautery was used was a suspected cause for technical failure in that and another study. In the present study, electrocautery was not used and no incidents of technical failure were detected; all sensors used continued to register data throughout the anesthetic period. However, patient-monitoring equipment was used and included an ECG monitor and battery-operated devices such as a pulse oximeter, Doppler systolic blood press...
sure monitor, and esophageal temperature probe. It is possible that one or more of these devices interfered with the function of the CGMS, but to our knowledge, there are no reports of use of patient-monitoring devices contributing to CGMS failure. Furthermore, CGMS and PCA measurements began to converge before the monitoring equipment was disconnected and removed from the dogs’ surroundings.

Because glucose concentrations measured with the CGMS and the PCA make use of interstitial fluid and blood, respectively, a true physiologic gradient between the 2 compartments might have caused the disagreement between device values. For example, changes in body temperature, peripheral blood flow, or size of the interstitial fluid compartment might have contributed to a discrepancy between interstitial glucose concentration and blood glucose concentration. However, because the influence of changes in these variables on device readings has not been evaluated to our knowledge, it is not known whether the discrepancies we detected represent inaccuracy of the CGMS or a real difference in these 2 fluid compartments. The effect of body temperature on CGMS function has not been extensively evaluated; however, hypothermia reportedly had little effect on CGMS results in pediatric humans undergoing surgery. In the present study, esophageal temperature did not correlate with results from the CGMS or the PCA. Esophageal temperature of the study dogs remained fairly constant near the end of the anesthetic period, when agreement between CGMS and PCA measurements improved, suggesting the improvement was independent of temperature. However, temperature fluctuations may have been more pronounced in the skin and subcutaneous interstitial space.

Alteration in the dynamics between glucose concentrations in blood and interstitial fluid attributable to anesthesia is another possible cause of discordance between CGMS and PCA results. An increase in blood glucose concentration from the time 0 value was present throughout most of the anesthetic period. This increase may have resulted from catecholamine release stimulated by surgery or from anesthesia. In rats, anesthesia with isoflurane, which was used to maintain anesthesia in the study dogs, can increase blood glucose concentration through a mechanism that may involve inhibition of insulin release. It is unlikely that a similar mechanism explains the detected discrepancy between the CGMS and PCA data because blood and interstitial glucose concentrations can remain in equilibrium despite changes in insulin concentration.

Another factor to explain the disparity between CGMS and PCA glucose measurements is a delay in equilibration of glucose concentration between the blood and interstitial compartments. The time needed for glucose concentrations to equilibrate ranges between 5 and 12 minutes, with changes in CGMS readings lagging behind changes in plasma glucose concentrations. Accuracy of the CGMS should not be considerably influenced by the lag because the device makes use of internal calibration and a digital filter to correct for equilibration delay. Rapid fluctuations in blood glucose concentration were not detected in the present study, suggesting that large concentration differences did not develop between the blood and interstitial compartments at any time during the anesthetic period.

Prolonged immobility and IV administration of fluids during the anesthetic period may alter fluid dynamics in interstitial compartments. Dogs in the present study received fluids administered IV at a predetermined, standard rate. It is conceivable that the fluid volume administered during anesthesia expanded the interstitial compartment in some dogs. Anesthetized children undergoing cardiopulmonary bypass can develop pronounced edema caused by inflammatory and capillary-leak mechanisms. However, CGMS results were reportedly unaffected by development of subcutaneous edema in a study involving similar subjects, and no clinically detectable edema developed in any dog in the present study. Consequently, subcutaneous edema and expansion of the interstitial compartment are unlikely explanations for the discrepancies between CGMS and PCA readings in our study.

A limitation to the present study was the working range of the CGMS. Glucose readings lower or higher than the range of 40 to 400 mg/dL are indicated as simply 40 and 400 mg/dL, respectively. Although in our study there were no CGMS readings of 400 mg/dL, there were 4 readings of 40 mg/dL, and it is possible that one or more of these readings represented actual glucose concentrations < 40 mg/dL. The PCA glucose concentrations that corresponded to these 4 CGMS readings were between 100 and 108 mg/dL. Thus, although the CGMS readings may not have been precise at low glucose concentrations, this limitation was unlikely to have influenced overall study findings regarding CGMS accuracy.

The CGMS used in the present study reports data in real time and, to our knowledge, has not been used in other veterinary studies. An earlier model of the CGMS collected data similarly to the system used here but only reported data once those data were uploaded to a computer and therefore did not report data in real time. The algorithm that was used to calibrate the older system made use of a retrospective rolling mean of calibration measurements to report glucose readings, whereas the system in our study made use of an updated algorithm to provide real-time readings. Despite the difference in calibration algorithm, one would expect all readings to be affected equally, regardless of the point at which they were acquired, so differences in the CGMS system used in our study were unlikely to have contributed to differences in our results.

All dogs in this study were maintained with isoflurane in oxygen during the anesthetic period. High inspired oxygen concentrations are expected to increase the partial pressure of oxygen in blood and tissues, although blood gas analysis was not performed during these routine procedures. The specific effects of increases in oxygen tension on the accuracy of the CGMS have not been investigated; therefore, it is not known whether this is a potential source of inaccuracy.

In the study reported here, the CGMS was well tolerated and functioned well for > 36 hours in awake dogs. Although results of other studies have suggested good agreement between interstitial fluid glucose measurements detected via CGMS and blood glucose
concentrations in veterinary species, the 2 values diverged significantly when the dogs in our study were anesthetized. Only approximately 30% of CGMS results agreed with the corresponding PCA results. The CGMS values were consistently lower than those measured with the PCA. Unexpectedly, agreement between the devices improved near the end of the anesthetic period and values were not significantly different once the dogs were awake. Although a specific cause for the discrepancy between CGMS- and PCA-measured glucose concentrations during anesthesia was not identified, use of the CGMS during anesthesia in dogs cannot be recommended at this time.

References