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Sedation with dexmedetomidine decreases skin perfusion in cats

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OBJECTIVE
To evaluate skin perfusion in cats receiving dexmedetomidine compared to a placebo.

ANIMALS
9 healthy adult research cats.

METHODS
A randomized, blinded, placebo-controlled study design was used. Two sites, the dorsal metatarsus (site: limb) and lateral flank (site: flank), were evaluated with laser speckle contrast imaging (LSCI) at baseline and following administration of dexmedetomidine (1, 3, or 5 mcg/kg, IV) or a placebo (0.9% saline, IV). Mean speckle contrast (MSC), a surrogate for perfusion, was obtained from LSCI and compared between treatments. Heart rate, sedation score, and body temperature were recorded. Skin perfusion to the flank and limb, reported as MSC, was assessed via LSCI at baseline and at 5, 10, and 15 minutes posttreatment.

RESULTS
There was a significant decrease in heart rate ($P < .001$) in cats receiving 1, 3, and 5 mcg/kg dexmedetomidine compared to placebo. There was a significant increase in median sedation score at all time points postsedation compared to baseline ($P < .018$). Changes in MSC for the metatarsus were not significantly different between treatments at any time point ($P = .12$). For the flank, MSC was significantly higher for cats treated with dexmedetomidine compared to baseline ($P \leq .01$). Skin perfusion to the flank decreased as early as 5 minutes posttreatment with dexmedetomidine and persisted for at least 15 minutes, regardless of dexmedetomidine dose.

CLINICAL RELEVANCE
Dexmedetomidine decreased skin perfusion in cats, even at low doses. Veterinarians may elect for an alternative sedative medication when decreased skin perfusion is a concern.

Keywords: perfusion, veterinary, sedation, reconstructive surgery, feline

Reconstructive surgery with local or subdermal plexus flaps, axial pattern flaps (APFs), or skin grafts is common in small animal patients. Gentle tissue handling and preservation of blood supply are key principles of reconstructive surgery. APFs in cats and dogs have a high overall complication rate of 89%.[1] However, overall flap survival, particularly for flaps with a direct cutaneous blood supply, remains high with reports up to 95%.[1–3] The most common complications are inadequate blood supply and infection.[2,4]

Veterinary patients undergoing reconstructive procedures may require sedation for evaluation of their surgical site in the days and weeks following surgery. Dexmedetomidine, a common sedative medication, is a highly selective α_2-adrenergic agonist.[5,6] Hemodynamic changes with dexmedetomidine are biphasic; first, there is peripheral vasoconstriction that results in transient hypertension and reflex bradycardia. This initial phase is followed by a period of hypotension.[5,6] Dexmedetomidine may impact

perfusion to the skin secondary to its dose-dependent effects on blood pressure, heart rate, cardiac output, and body temperature.[5–8] While it is known that blood vessel density and perfusion to the skin are critical elements of cutaneous wound healing,[9] the effect of dexmedetomidine on blood flow at the level of the skin remains poorly understood.

Over the last 30 years, various laser imaging techniques have emerged to measure blood flow patterns in tissues. These imaging modalities tend to be more consistent for assessing microcirculation and detecting regional differences in tissue perfusion.[10,11] Laser Doppler imaging and laser speckle contrast imaging (LSCI) are 2 methods that do not require direct contact with the subject.[12] However, data acquisition with LSCI is faster and evaluates a larger area than laser Doppler.[13,14] These characteristics make LSCI appealing for investigating changes in blood flow after an intervention, such as drug administration, intraoperatively for skin flaps, or for evaluating microcirculation during wound healing.[15]

LSCI has been widely used in experimental and human studies to assess the perfusion of various tissues. Data acquisition with LSCI technology is accomplished through reflections of light from the laser that are received at the detector. A camera captures images at the detector for analysis. Backscattered light creates a random interference pattern called a speckle pattern.[12,16,17] The primary source of scattering in biological tissues is the motion of red blood cells, which causes a blurring of the speckle pattern. The amount of blurring, or speckle contrast, is a unitless measurement that is indirectly related to blood flow.[17] LSCI can detect changes in blood flow, allowing for comparison of perfusion to a baseline or between treatment groups. However, since the speckle contrast pattern is affected by motion, care must be taken to limit movement during image acquisition, including motion from patient respiration. Data acquisition with the LSCI unit is rapid (milliseconds) and similar to taking a photograph. Advantages of LSCI for clinical use include that it is noninvasive, rapidly acquires data, and images a larger field of view than was previously possible with laser Doppler imaging. Although LSCI has been utilized in a variety of clinical applications in the human field,[18–21] its use in veterinary patients has not been evaluated.

The purpose of this study was to investigate the effect of clinically relevant doses of dexmedetomidine, a commonly used sedative medication,[22] on skin perfusion in cats using LSCI. The hypothesis was that skin perfusion would decrease in a dose-dependent manner following IV administration of dexmedetomidine. This work represents the first step in determining whether a relationship exists between dexmedetomidine and skin perfusion in cats, which may impact the treatment of patients where skin perfusion may already be altered, including cats undergoing frequent sedation for evaluation and treatment following reconstructive surgery, wound management, and radiation therapy. There is a need for noninvasive, clinically applicable methods to evaluate skin perfusion in all species. This work will also help determine if LSCI is a feasible method for detecting alterations in skin perfusion in both awake and sedated cats.

Methods

This was a randomized, blinded, placebo-controlled study. Nine adult spayed female research cats were enrolled in this study, which was approved by our IACUC (protocol reference No. 125804). All cats had a complete physical exam by a veterinarian before enrollment to confirm they were healthy enough to receive sedation. The primary investigators acclimated the cats to the researchers and equipment before the start of the study. All standards for housing and care were in accordance with the Texas A&M University College of Veterinary Medicine and Biomedical Sciences IACUC. Cats remained in a research facility under controlled light (12/12-hour light/dark cycle), temperature (21 to 22 °C), and humidity (55% to 60%) conditions and housed in 5 rooms of 2.4 m X 2.4 m X 3.0 m (length X width X height). Environmental enrichment was achieved with the use of toys, scratch posts, condos, and bedding. One wall consisted of large windows that provided natural light and the ability to visualize their surroundings. Food and water were available ad libitum but removed immediately before and up to 4 hours following treatment administration.

Four treatments were administered once weekly to each cat for 4 consecutive weeks. Treatments included dexmedetomidine at 1, 3, and 5 mcg/kg (groups 2 to 4, respectively) and a placebo of 0.9% saline (group 1) in a volume equivalent to a 5 mcg/kg dose of dexmedetomidine. All treatments were administered IV via a 1-cc syringe and 25-gauge needle into a cephalic vein. Blood was aspirated into the syringe before injection to confirm accurate placement in the vessel. To ensure patient comfort during IV injection, Eutectic Mixture Local Anesthetics cream was applied over the site at least 20 minutes before treatment. The treatment order for each cat was randomly assigned using a random number generator (www.random.org).

Skin perfusion to the left flank (site: flank) and left dorsal metatarsus (site: limb) were evaluated with an LSCI unit (Dynamic Light, Inc). The day before data collection each week, a minimum of a 2 X 2-cm region of fur on the left flank and a 1 X 2-cm region on the left dorsal metatarsus on each cat were shaved with a No. 40 clipper blade. Cats were placed on a standard exam table, and the laser was centered about 20 cm from the shaved skin surface. Cats were minimally restrained with hands at the hips and offered food for enrichment during image acquisition. This, along with the short time for image acquisition (milliseconds), helped mitigate artifacts due to motion.

Laser speckle images of both sites and sedation score were recorded before treatment (Time 0/baseline) and 5, 10, and 15 minutes posttreatment (times 5, 10, and 15, respectively). Sedation scoring was based on a previously published feline sedation scoring scheme ranging from 0 (not sedate) to 9 (very sedate).[23] Heart rate and body temperature

were recorded at baseline and time 15. The LSCI camera acquired images at 100 frames per second with a 5-millisecond exposure time. The software automatically averaged the 100 frames into 10 separate speckle contrast images. Image acquisition was repeated 3 times in immediate succession for each site (flank and limb) at each time point (0, 5, 10, and 15 minutes), yielding 30 images each. In all cases, flank data were collected first and immediately followed by limb data. After completion of all measurements, blinded investigators left the room. Cats that received dexmedetomidine were reversed with the appropriate dose of atipamezole intramuscularly at the discretion of the unblinded veterinarian.

LSCI data analysis

ImageJ[24] software was used for data analysis of the averaged speckle contrast images. A region of interest in the center of each image was manually selected, and mean speckle contrast (MSC) was recorded. The average MSC of all 30 images was calculated and used for statistical analysis for each site, time point, and treatment group. The mathematical model used 1/MSC and the speckle contrast was defined as the ratio of the SD to the mean intensity. A 7 X 7-pixel sliding window was used to calculate the speckle contrast. MSC is inversely related to perfusion and is a unitless measurement.[25] A higher MSC indicates a decrease in perfusion. The primary investigators remained blinded until all data were recorded.

Statistical analysis

Normality of the errors was assessed with a histogram and a normal probability plot. MSC was normally distributed and evaluated with a mixed ANOVA, and the mean was reported. Multiple comparisons were evaluated with a Bonferroni post hoc test. $P < .05$ was considered significant. Analyses were performed using the Number Cruncher Statistical Systems 19.0.7.

Results

There were 9 spayed female domestic shorthair cats included in the study. Median age was 6.22 years (range, 6.19 to 6.24 years). Median body weight was 4.0 kg (range, 3.6 to 5.1 kg). All cats completed the study without complication. Baseline sedation scores were normal (0) for all treatment groups and for group 1 at all time points **(Figure 1)**. Raw data for treatment group, sedation score, heart rate, and body temperature are provided in the supplementary materials **(Supplementary Table S1)**. There was a significant difference between baseline sedation scores and scores at times 5, 10, and 15 for groups 2 to 4 ($P < .02$ at all time points for group 2; $P < .01$ at all time points for groups 3 and 4).

There was no significant difference in heart rate between baseline and time 15 in group 1 ($P = 1$) (Figure 1). For groups 2 to 4, heart rate was significantly lower at time 15 compared to baseline ($P < .01$). There was no significant difference in body temperature across treatments ($P = .86$) or time points within each study week ($P = .33$).

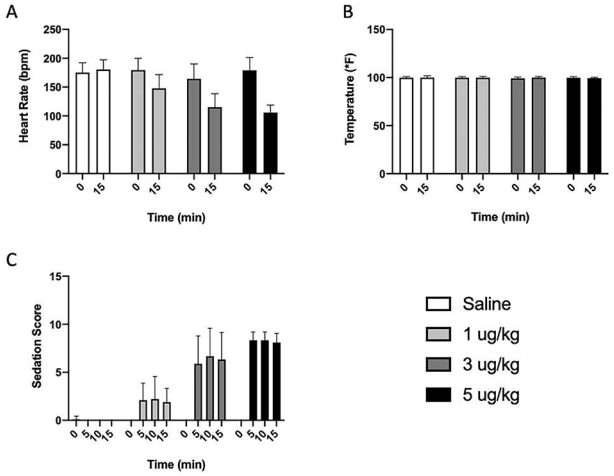

Figure 1—A through C—Heart rate (A), body temperature (B), and sedation scores (C) of 9 cats following administration of saline or 1, 3, or 5 µg/kg dexmedetomidine. Heart rate (A) remained stable over time for the saline group while decreasing over time following all doses of dexmedetomidine. Body temperature (B) did not change over time for any treatment group. Sedation scores (C) increased after 5 minutes following all doses of dexmedetomidine but not for saline. bpm = Beats per minute.

Perfusion data for the limb and flank are reported **(Figures 2 and 3)**. There was no significant difference in perfusion to the limb between treatment groups at any time point. For the flank, there was no significant difference in baseline perfusion between treatment groups or in perfusion between time points for group 1. MSC was significantly higher for group 2 at time 5 ($P = .01$) and time 15 ($P = .002$) compared to baseline but not at time 10 ($P = .08$). For groups 3 and 4, the MSC was significantly higher ($P \leq .001$) for all time points posttreatment compared to baseline. There was no significant difference between MSC for treatment groups 2 to 4 at any time point posttreatment.

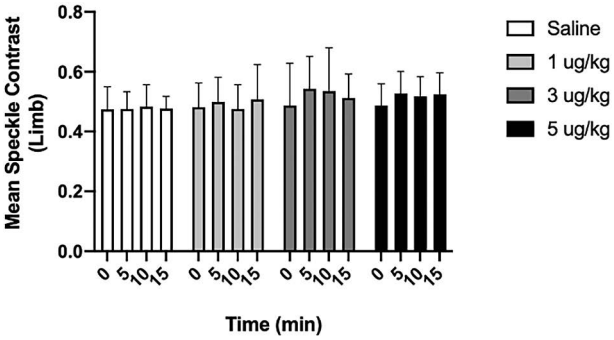

Figure 2—Mean speckle contrast (MSC) for the limb (dorsal metatarsus) (y-axis) over time (0 to 15 minutes) on x-axis for 9 cats receiving saline placebo or dexmedetomidine at 1, 3, or 5 µg/kg, IV. Higher MSC indicates a decrease in perfusion. While perfusion was slightly lower at 3 and 5 µg/kg dexmedetomidine, there were no statistically significant differences compared to baseline for any treatment group.

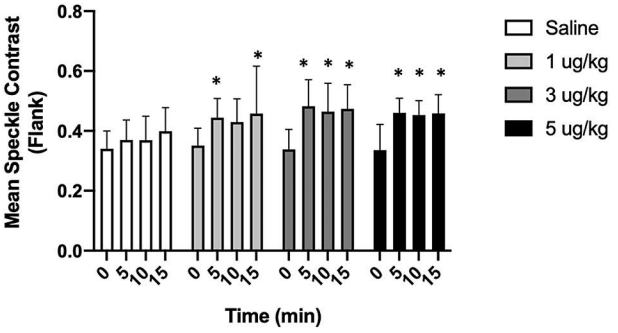

Figure 3—MSC for the flank (y-axis) over time (0 to 15 minutes) on x-axis for 9 cats receiving saline placebo or dexmedetomidine at 1, 3, or 5 µg/kg, IV. A higher MSC indicates a decrease in perfusion. *Significant difference from baseline. MSC was significantly higher at times 5 and 15 for 1 µg/kg dexmedetomidine and at all times postbaseline for 3 and 5 µg/kg dexmedetomidine.

Discussion

The objective of this study was to investigate the effect of dexmedetomidine, a commonly used sedative medication, on skin perfusion in cats via LSCI. The decrease in heart rate and increase in sedation scores for cats receiving dexmedetomidine support that the IV injection was effective. Body temperature was not different between treatment groups or over time. Although rectal temperature is a more accurate measure of body temperature, a previous study[26] showed no significant difference between median rectal and axillary temperature in cats. Peripheral perfusion and body temperature appear to be associated with a lower peripheral perfusion found in human patients experiencing intraoperative hypothermia.[27] Future studies are needed to better understand the relationship of body temperature and perfusions to regions of interest in our veterinary patients.

The LSCI means for the flank were significantly higher in cats receiving dexmedetomidine (groups 2 to 4) compared to baseline, indicating a decrease in perfusion posttreatment. Sedative medications may impact perfusion to the skin secondary to their effects on blood pressure, cardiac output (eg, heart rate and stroke volume), or vascular resistance, in either a direct or indirect (eg, body temperature) manner.[5–8] Hemodynamic changes with dexmedetomidine are biphasic; first, there is peripheral vasoconstriction that results in transient hypertension and reflex bradycardia. A secondary phase of continued bradycardia and reduced vascular resistance is often seen due to dexmedetomidine's sympatholytic effects and a lessening of the peripheral actions of the α_2-agonists (eg, vasoconstriction).[5,6] The most commonly reported adverse event with dexmedetomidine in the cat is vomiting.[7] Further research is required to understand how this impacts blood flow at the level of the skin and tissue healing.

Dexmedetomidine increased MSC in the flank, regardless of the dose used. This suggests that there is a decrease in skin perfusion even with a conservative dose (1 mcg/kg) of dexmedetomidine, which could have implications for wound healing and survival of skin flaps. In an early study[28] investigating dose-dependent cardiovascular effects of α_2-agonists in dogs, medetomidine was demonstrated to have mild effects at lower doses (1 to 2 mcg/kg), while there was a plateau at doses of 5 mcg/kg or higher. The true clinical significance of these findings at the level of the skin requires further research to fully elucidate.

Changes in perfusion in the metatarsus were not significant between groups (P = .12). However, perfusion did decrease after dexmedetomidine injection when compared to baseline. Baseline MSC for all cats was lower for the metatarsus compared to the flank. The most likely reason was the metatarsus was more difficult to shave in unsedated cats; thus, fur could have created a barrier to the laser and dampened backscattered light that was detected, creating more subtle perfusion changes than those seen in the flank. A future study evaluating perfusion in this area after shaving with a razor to remove the fur would help clarify if this finding was the result of fur confounding our results. The other alternative is that perfusion in the distal limb is truly decreased compared to the flank. Cats have fewer and more widely distributed SC vessels compared to dogs.[29,30] Normal feline skin also has lower levels of perfusion compared to dogs when evaluated by laser Doppler. After 1 week, sutured wounds are half as strong in cats compared to dogs and that healing by the second intention is overall slower in cats.[29] Blood vessel density and hypoperfusion may play a role in these species differences in healing between cats and dogs. It is also possible that blood vessel density in the cat metatarsus is decreased compared to other body regions, such as the flank. This could explain why no significant differences in MSC were seen in the metatarsus in the current study.

The flank and metatarsus were chosen to replicate areas of possible skin flaps and donor and recipient sites, respectively, for reconstruction while minimizing artifacts from respiration. The skin of the flank is also similar in composition to other donor sites for free skin grafts and is adjacent to locations for possible APFs. Necrosis and dehiscence are the most common complications in APFs. This is usually secondary to inadequate blood supply or infection.[2,4] In a study[31] evaluating caudal superficial epigastric axial pattern flaps in dogs (n = 51) and cats (19), complications were reported in 67% of dogs and 53% of cats with dehiscence and necrosis being the most common. When comparing flaps with a direct cutaneous blood supply, such as an APF, to those without, success rates were around 95% and 50%, respectively.[3] Adequate skin perfusion and preservation of blood supply are key aspects of reconstructive surgery.

A recent study[14] evaluated blood perfusion in random pattern flaps performed in pigs using LSCI. Skin perfusion was significantly lower further from the flap base and when tension was applied to stretch the flap. However, rotation of the flap to 45° and 90° only mildly decreased skin perfusion.[14] Combined with the work of Zotterman et al[32] looking at APFs in a porcine model, LSCI shows promise for a noninvasive

method of measuring changes in skin perfusion in veterinary species. Sedative medications may impact perfusion to the skin secondary to their effects on blood pressure, heart rate, cardiac output, and body temperature.[5–8] Hemodynamic changes with dexmedetomidine are biphasic; first, there is peripheral vasoconstriction that results in transient hypertension and reflex bradycardia. This initial phase is followed by a period of hypotension.[5,6] Further research is required to understand how this impacts blood flow at the level of the skin and tissue healing.

There were several limitations to this study. The first was the small sample size. Although adequate for a pilot study, a larger sample size and greater interpatient variation would be needed before applying these results to clinical patients. Similarly, a mixed model could have been performed for statistical analysis. However, given this was a pilot study with a small number of cats, analyzing data in an isolated manner was deemed more appropriate. The fur was also clipped with a No. 40 clipper blade the day before image acquisition. It is unknown whether or not shaving with a razor to remove all fur on the day of the procedure would make a significant difference in perfusion measures. Another limitation was that measurements were only taken for 15 minutes postsedation with dexmedetomidine and no measurements were taken after reversal with atipamezole. Without this information, we do not know how long cats had decreased skin perfusion or how quickly perfusion returned to normal after reversal. Future studies evaluating the impact of additional factors such as patient temperature, blood pressure, heart rate, changes in cardiac output, and changes in peripheral vascular resistance are warranted. Additionally, the magnitude of decreased skin perfusion required to yield undesirable clinical outcomes and the exact mechanism of changes in perfusion are unknown and worth investigating.

This work supports the use of LSCI as a feasible method for detecting alterations in skin perfusion in both awake and sedated cats. In the current study, dexmedetomidine decreased skin perfusion to the flank in cats, as measured by LSCI. This decrease in perfusion to the flank occurred rapidly, within 5 minutes of IV injection, and the effect was seen regardless of dexmedetomidine dose. Further research is needed to evaluate the clinical relevance of the changes in MSC seen in the current study and discordance between sites (flank vs metatarsus). This information can then be used to aid in recommendations for clinical cases, particularly skin flaps.

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Disclosures

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Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org