pISSN 1598-298X / eISSN 2384-0749
J Vet Clin 34(4) : 249-254 (2017)
http://dx.doi.org/10.17555/jvc.2017.08.34.4.249

Journal of
Veterinary Clinics
www.ksvc.or.kr

Evaluation of Skin Microcirculation by Laser Doppler Flowmeter in Healthy Beagle Dogs

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(Received: Jun 18, 2017 / Accepted: July 26, 2017)

Abstract : The cutaneous microcirculation plays a role in various physiological processes and pathological conditions. Two non-invasive methods were used in this study to obtain reference values for cutaneous microcirculation in intact male beagles. Twenty intact male beagles were used. The experimental environments were standardized. Laser Doppler flowmetry was used to measure cutaneous blood flow, and an infrared thermometer was used to measure cutaneous temperature. The blood flow and temperature were measured from the right side of the subjects at 20 cutaneous sites. Based on the laser Doppler flowmetry, the region with the highest blood flow was the periocular region that with the lowest was the forelimb foot pad. In addition, the standard deviation of the chest wall was the highest while that of the periocular region was the lowest. For skin temperature, the inguinal region had the highest mean skin temperature and the forelimb foot pad had the lowest. The correlation coefficient between the two methods was 0.72. Similar to a previous study, the values derived from repeated measurements at the 20 regions are reproducible and can contribute to research. Compared to the results of a previous study, the temperatures of the two smallest skin regions were the same; however, no specific trend was observed. The correlation coefficient between the two methods was significantly comparable, and this good correlation can reduce their limitations and variables complementarily. In addition to possible use in human studies, accumulated resources on measurements of skin blood flow in the future will potentiate its use in the veterinary medicine field.

***Key words* :** skin microcirculation, skin temperature, laser Doppler, dog.

Introduction

The skin is the largest organ in the body, covering the entire body surface. Many studies on blood flow in the skin have been performed over the past several decades; it has also been quantitatively studied *in vitro* as well as *in vivo* in humans (19). The cutaneous microcirculation reflects many physiologic processes and pathological conditions (2). In addition, cutaneous blood flow plays a role in epidermal nutrition, controlling heat loss, and regulating body temperature. Good perfusion enhances wound healing and reduces the risk of surgical wound infection (3,4,9-11). Perfusion can be affected by actinically damaged skin, chronologically aged skin, psoriasis, and inflammation (4).

Measuring this cutaneous blood flow can be done in variety of ways such as with 133 Xenon clearance (18), venous occlusion plethysmography (22), tissue pH measurement, capillary microscopy, fluorescein tracers, photoplethysmography, determination of skin temperature and transcutaneous pO_2, and laser Doppler flowmetry (5). Among these methods, laser Doppler flowmetry and skin temperature measurement are non-invasive methods that do not cause any discomfort to the subjects (15).

The laser Doppler technique is a sensitive, real-time, continuous and easy method for measuring cutaneous microcirculation in any region of the body. The principle of laser Doppler flowmetry is as follows. Laser light applied to tissues results in reflections, transmission, absorption, and scattering. Laser light backscattered from moving particles, for example, red blood cells, is shifted in frequency. However, laser light reflected off stationary matter has the same original frequency in compliance with the Doppler effect. Therefore, a mixture of these light frequencies is detected by a photodetector and converted into an electrical signal that is processed and digitalized linearly with blood flow at the point of measurement (3-12).

Measured skin temperature should exactly yield the temperatures of the corresponding skin regions. Infrared thermography can estimate the changes in temperature of the whole body surface quickly and easily, which makes it a reliable and useful method for measuring skin temperature (22).

There are many human studies on cutaneous blood flow. In particular, laser Doppler flowmetry is being frequently used to evaluate the response of the skin blood flow to physiologic and pharmacologic stimuli and assess the results of reconstructive surgery (14). Moreover, several studies have confirmed a good correlation between laser Doppler flowmetry and other blood flow measurement (7,15).

In this study, we have used a non-invasive method of skin blood flow measurement, laser Doppler flowmetry, to evalu-

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ate microcirculation based on the skin blood flow in various cutaneous sites in intact male beagles. Additionally, we have investigated the relationship between the laser Doppler values and skin temperature and suggested a complementary method for application to dermatologic studies.

Materials and Methods

Experimental design

Twenty healthy intact male beagles were used in this study. Their mean body weight was 10.2 kg (7.2-12.7 kg) and their mean age was 3 years. All dogs were healthy by physical examination, complete blood count (CBC), and blood chemistry testing. Dermatologic tests were performed with these dogs and no skin lesions were found.

All dogs were acclimated to the closed examination room for at least 1 hour before the experiment. Environmental conditions were standardized, with room temperature maintained at 23°C, relative humidity at 50 ± 10%, and air movement at ≤ 0.1 m/s. Other factors that could possibly affect the measured values, such as physical activity, food, and beverage intake were also controlled.

The measurement sites were shaved 24 hours prior to the experiment. Clipping was performed on the selected cutaneous anatomic sites with a standard clipper (Oyster®pro76, No40, Oyster Co., USA). No pharmacologic restraint was applied to the experimental dogs. During measurements, the assistants physically restrained the dogs to prevent movement, and the values were measured while they were standing. When measuring the foot pad and ventral region of the tail base, the parts were maneuvered gently and carefully so that the manipulation would not affect the results.

All the values were measured on the right side of the subjects. Measurements were performed at the same cutaneous sites five times sequentially. A software program calculated the mean values during the 10 seconds after applying the probes. Temperature measurements were also conducted on the same sites and repeated three times. This was performed by the same investigator, and the sensor measurement distance was 2 to 3 cm from the measuring point as instructed in the manual.

The measurement sites included the periocular region (lateral canthus), ventral region of the neck, concave surface of the ear, forelimb foot pad (the third digit), metacarpal region (not on a pad), elbow, humeroscapular junction, cranial angle of the scapula, chest wall (the fourth rib, costochondral junction), sternum (approximately xiphoid process), umbilicus, inguinal region, hind limb foot pad (the third digit), metatarsal region (not on a pad), calcaneus, patella, croup region (cranial dorsal iliac spine), hip region (ischiatic tuberosity), thoracolumbar junction, and ventral region of the tail base. The locations of the measurement sites are illustrated in Fig 2.

Laser Doppler flowmeter

To measure cutaneous blood flow, a needle probe (MNP110, length 25 mm, diameter 480 μm) for laser Doppler flowmetry (PowerLab ML192, AD Instruments, Australia) and PowerLab 2/20 (PowerLab ML820, AD Instruments, Australia) were used. All data were recorded with a laptop computer for further analysis by using Labchart 7 for Windows software (PowerLab, AD Instruments, Australia). The digital filter of the instrument sets the cut-off frequency to 50 Hz, and the transition width (filter sharpness) is auto-adjusted depending on the sampling rate. It records signal output as volts, which is automatically established by our equipment manufacturers.

Prior to use, the probe was calibrated by facing perpendicularly against a solid white-plastic port supplied by the manufacturer. This process allowed the instruments to adjust the offset to instrumental zero. The contact gel was a commercial product. (LUB-GEL, Firson Co., Ltd, Korea)

To control the contact pressure, instead of using an adhesive disk, self-designed equipment was used for convenient and consecutive measuring. It was made from the cannula portion of a 24 G catheter and installed as shown in Fig 1.

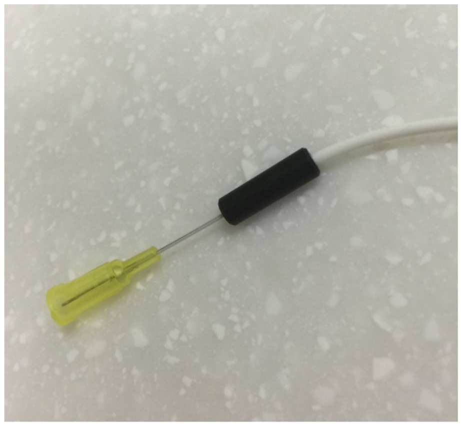

Fig 1. A needle probe (MNP11) was equipped with manufactured equipment made from the cannula portion of a 24 G catheter.

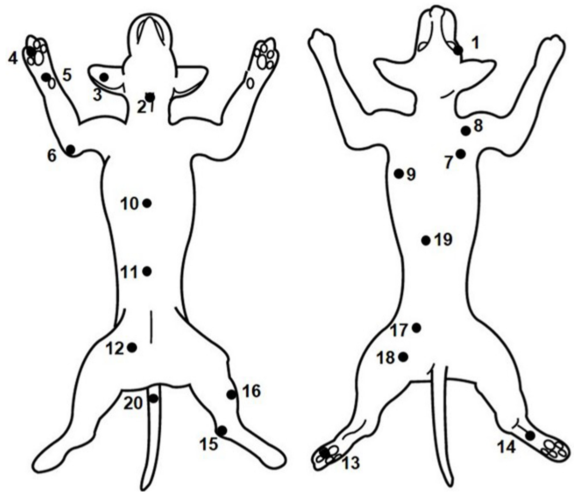

Fig 2. A schematic figure of the cutaneous sites. 1. Periocular region; 2. Ventral region of the neck; 3. Concave surface of the ear; 4. Forelimb foot pad; 5. Metacarpal region; 6. Elbow; 7. Humeroscapular junction; 8. Cranial angle of the scapula; 9. Chest wall; 10. Sternum; 11. Umbilicus; 12. Inguinal region; 13. Hind limb foot pad; 14. Metatarsal region; 15. Calcaneus; 16. Patella; 17. Croup region; 18. Hip region; 19. Thoracolumbar junction; 20. Ventral region of the tail base.

Infrared thermometer

To measure temperature, a Non-Contact Infrared Forehead Thermometer (FS-300, HuBDIC Co., LTD, Korea) was used.

Statistical analysis

The results of laser Doppler flowmetry were rounded off to the second decimal places. Statistical analysis was conducted using GraphPad Prism 7 for Windows (Version 7.02, GraphPad Software, Inc.). To determine the statistical difference across each region, Tukey's multiple comparisons test was conducted. The correlation between skin temperature and cutaneous blood flow by measuring laser Doppler flow-

Table 1. The skin blood flow values measured by laser Doppler flowmetry (n = 20)

	Mean ± SD (V)	Maximum (V)	Minimum (V)	Range width
Periocular region	4.51 ± 0.59	5.10	3.17	1.93
Ventral region of the neck	3.71 ± 0.82	5.09	2.07	3.01
Concave surface of the ear	2.97 ± 0.97	4.90	1.37	3.52
Forelimb foot pad	1.90 ± 0.87	4.30	0.44	3.87
Metacarpal region	4.00 ± 0.82	5.09	2.36	2.73
Elbow	3.99 ± 0.83	5.08	2.41	2.67
Humeroscapular junction	4.20 ± 0.83	5.10	1.81	3.29
Cranial angle of the scapula	3.52 ± 0.96	5.03	1.20	3.83
Chest wall	3.37 ± 1.04	4.96	1.47	3.49
Sternum	3.20 ± 0.75	4.95	1.96	3.00
Umbilicus	3.60 ± 0.79	4.92	1.88	3.04
Inguinal region	3.64 ± 0.99	5.02	2.02	3.01
Hind limb foot pad	2.32 ± 1.00	4.94	0.35	4.59
Metatarsal region	3.94 ± 0.76	5.09	1.99	3.10
Calcaneous	4.34 ± 0.82	5.08	1.53	3.56
Patella	3.79 ± 0.78	5.06	1.84	3.22
Croup region	3.29 ± 0.94	5.08	1.23	3.84
Hip region	4.26 ± 0.74	5.07	2.67	2.40
Thoracolumbar junction	2.96 ± 0.77	4.66	1.27	3.39
Ventral region of the tail base	4.07 ± 0.91	5.08	1.73	3.36

Table 2. The skin temperature values measured by infrared forehead thermometer (n = 20)

	Mean ± SD (ºC)	Maximum (ºC)	Minimum (ºC)	Range width
Periocular region	36.19 ± 0.26	36.9	35.5	1.4
Ventral region of the neck	37.07 ± 0.39	37.8	36.2	1.6
Concave surface of the ear	36.94 ± 0.68	38.2	35.7	2.5
Forelimb foot pad	26.02 ± 1.08	27.7	24.0	3.7
Metacarpal region	36.62 ± 0.56	37.8	35.5	2.3
Elbow	36.46 ± 0.46	37.5	35.5	2.0
Humeroscapular junction	37.11 ± 0.62	38.2	36.0	2.2
Cranial angle of the scapula	37.06 ± 0.47	37.9	36.3	1.6
Chest wall	36.91 ± 0.54	38.2	36.0	2.2
Sternum	37.10 ± 0.34	38.1	36.5	1.6
Umbilicus	37.18 ± 0.52	38.1	36.0	2.1
Inguinal region	37.93 ± 0.57	39.1	36.7	2.4
Hind limb foot pad	26.30 ± 1.38	28.5	22.6	5.9
Metatarsal region	36.72 ± 0.57	38.0	36.1	1.9
Calcaneous	36.00 ± 0.40	36.7	35.4	1.3
Patella	36.65 ± 0.45	37.7	36.1	1.6
Croup region	36.78 ± 0.49	37.7	35.7	2.0
Hip region	36.93 ± 0.43	37.7	36.4	1.3
Thoracolumbar junction	36.56 ± 0.52	37.8	35.8	2.0
Ventral region of the tail base	37.31 ± 0.66	38.5	36.1	2.4

metry was analyzed with a Pearson correlation test. A value of $p < 0.001$ was defined as statistically significant.

Results

Laser Doppler flowmetry

The cutaneous blood flow values are shown in Table 1. From the measured values, the maximum, minimum, standard deviation, mean, and range width were calculated for each region. The highest value for blood flow was obtained from the periocular region, followed by the calcaneus, hip, humeroscapular junction, and tail base. The lowest value for blood flow was obtained from the forelimb foot pad, followed by the hind limb foot pad. The largest value was 5.10 at the humeroscapular junction and the smallest was 0.35 at the hind foot pad. The widest range of values (0.35-4.94, the difference of values = 4.59) was for the hind foot pad, and the smallest one was for the periocular region (3.17-5.10, the difference of values = 1.93). The chest wall had the largest standard deviation at 1.04, and the periocular region had the smallest standard deviation at 0.59. The significance of the difference between each region is shown in Table 3.

Skin temperature

Table 2 shows the skin temperature results. The inguinal region had the highest mean skin temperature at 37.93°C and the forelimb foot pad had the lowest mean skin temperature of 26.02°C. Among all the values determined, the highest was 39.1°C in the inguinal region and the lowest was 22.6°C for the hind foot pad. The hind foot pad region also had the widest temperature range of 5.9 (22.6-28.5). The regions representing the smallest range were the hip and calcaneus; the difference between these values was 1.3. The hind limb foot pad temperature displayed the highest standard deviation value of 1.38, while the periocular region had the lowest at standard deviation of 0.26, followed by the sternum, neck, and calcaneus. The areas displaying the most variable values for standard deviation were the extremities, fore- and hindlimbs, and the foot pads, each with an standard deviation less than 1; these were followed by the ear, tail base, and hum-

Table 3. Tukey's multiple comparisons test on the skin blood flow values measured by laser Doppler flowmetry

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1		Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
2			Y	Y	N	N	Y	N	N	Y	N	N	Y	N	Y	N	Y	Y	Y	N
3				Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y
4					Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
5						N	N	Y	Y	Y	Y	N	Y	N	N	N	Y	N	Y	N
6							N	Y	Y	Y	Y	N	Y	N	N	N	Y	N	Y	N
7								Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	N
8									N	N	N	N	Y	Y	Y	N	N	Y	Y	Y
9										N	N	N	Y	Y	Y	Y	N	Y	N	Y
10											Y	Y	Y	Y	Y	Y	N	Y	N	Y
11												N	Y	N	Y	N	N	Y	Y	Y
12													Y	N	Y	N	N	Y	Y	N
13														Y	Y	Y	Y	Y	Y	Y
14															Y	N	Y	N	Y	N
15																Y	Y	N	Y	N
16																	Y	Y	Y	N
17																		Y	N	Y
18																			Y	N
19																				Y
20																				

1. Periocular region; 2. Ventral region of the neck; 3. Concave surface of the ear; 4. Forelimb foot pad; 5. Metacarpal region; 6. Elbow; 7. Humeroscapular junction; 8. Cranial angle of the scapula; 9. Chest wall; 10. Sternum; 11. Umbilicus; 12. Inguinal region; 13. Hind limb foot pad; 14. Metatarsal region; 15. Calcaneus; 16. Patella; 17. Croup region; 18. Hip region; 19. Thoracolumbar junction; 20. Ventral region of the tail base. Adjusted p-value < 0.0001.

Table 4. Tukey's multiple comparisons test on the skin temperature values measured by infrared forehead thermometer

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2			N	Y	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y
3				Y	Y	Y	N	N	N	N	N	Y	Y	N	Y	Y	N	N	N	Y
4					Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
5						N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	Y
6							Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	Y
7								N	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N
8									N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y
9										N	N	Y	Y	N	Y	Y	N	N	Y	Y
10											N	Y	Y	Y	Y	Y	Y	N	Y	N
11												Y	Y	Y	Y	Y	Y	N	Y	N
12													Y	Y	Y	Y	Y	Y	Y	Y
13														Y	Y	Y	Y	Y	Y	Y
14															Y	N	N	N	N	Y
15																Y	Y	Y	Y	Y
16																	N	Y	N	Y
17																		Y	N	Y
18																			Y	
19																				
20																				

1. Periocular region; 2. Ventral region of the neck; 3. Concave surface of the ear; 4. Forelimb foot pad; 5. Metacarpal region; 6. Elbow; 7. Humeroscapular junction; 8. Cranial angle of the scapula; 9. Chest wall; 10. Sternum; 11. Umbilicus; 12. Inguinal region; 13. Hind limb foot pad; 14. Metatarsal region; 15. Calcaneus; 16. Patella; 17. Croup region; 18. Hip region; 19. Thoracolumbar junction; 20. Ventral region of the tail base. Adjusted p-value < 0.0001.

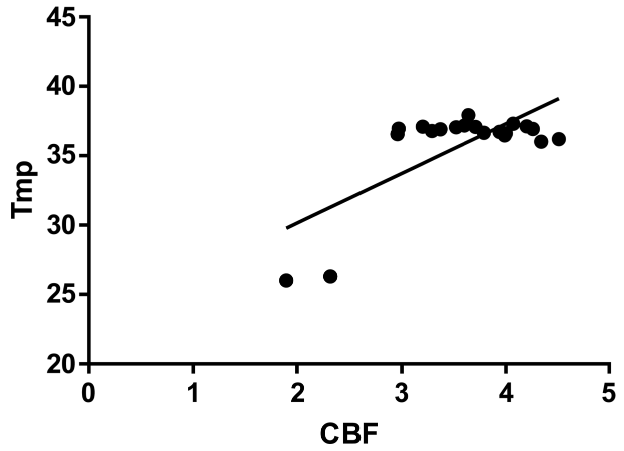

Fig 3. Pearson correlation between skin temperature and skin blood flow values measured by laser Doppler flowmetry (n = 20, coefficient = 0.72, p-value = 0.0003); Tmp = skin temperature; CBF = cutaneous blood flow by laser Doppler flowmetry.

eroscapular junction. Statistics indicating the significance of the differences between values in each region are shown in Table 4.

Correlation

A comparison between the two non-invasive cutaneous blood flow measurement methods is shown in Fig 3. The Pearson correlation coefficient between the two methods was 0.72 (p-value = 0.0003).

Excluded values

For each region, the measurements were obtained five times for statistical analysis. However, when an obtained value was over the maximum limit, it was considered an error and excluded from the results. The periocular region had the most errors followed by the humeroscapular junction and calcaneus. The region with one or fewer errors were the forelimb foot pad and the thoracolumbar junction.

Discussion

The aims and results of this study can be discussed in two different points. First, the measured skin blood flow values using laser Doppler flowmetry can be used as reference values. Second, by comparing them with the other non-invasive methods, such as the skin temperature, the relationship between the two methods can be assessed.

A previous study performed with several animal species using laser Doppler flowmetry (14) did not maintain uniform conditions for canine subjects, and included dogs of different sexes and age. This study is therefore the first to measure skin blood flow using laser Doppler flowmetry that was carried out under controlled conditions with intact male beagles. The values derived from five repeated measurements at more than 20 regions, were reproducible and hence can be used as a reference for additional research. Therefore, this can be used as an essential baseline for the study of dermatology, cutaneous pharmacology, and reconstructive surgery, which are frequently studied in dogs.

The value with the highest standard deviation of laser Doppler output is the chest wall; it is believed that the inter-individual cutaneous vascular distribution is most diverse in this region. Additionally, the authors of a previous study concluded that the thick stratum corneum and epidermis in this region is not appropriate for laser Doppler flowmetry (14). When skin experiments that can be affected by cutaneous blood flow are conducted, it is possible that the use of some previously described regions can be disadvantageous. The periocular region has the smallest standard deviation, so it can provide the most valuable site for measuring various skin indexes that can be affected by cutaneous blood flow. Through the selection of the advantageous regions, future researchers can obtain accurate and reproducible outcomes of cutaneous microcirculation related experiments with high accuracy and reproducibility.

A limitation of the laser Doppler values is that they can only be used as relative figures. Although they are not absolute values, relative figures may be utilized in many ways to help with assessment of skin disease, such as tumors, inflammatory reactions, ulcers, burns, skin flaps, and grafts (18). The comparison cannot be depicted in absolute terms because the resulting values are not calculated from biological zero, but from instrumental zero. Because of direction insensitivity and diffusive light scattering, the problem of biological zero occurs in laser Doppler flowmetry. When the cutaneous arteriolar flow is thoroughly occluded, the biological zero can be calculated (10,21). Additionally, when the skin blood flow is completely blocked, laser Doppler flowmetry output decreases by 20 to 50% (19). There was a mathematical attempt to calculate biological zero; yet it is only possible in theories with many assumptions (3). The fact that the numbers differ by different equipment manufacturers and the wavelength also differs supports the concept that the output is semiquantitative.

The results of this experiment were compared with the results from a previous paper that measured blood flow in nine species at six different sites per animal (14). The environmental conditions were similar to our study, but the instrument used for measurement and regions measured were different. Furthermore, in the previous study, the dogs' breed, age, and sex were not presented. Although a strict comparison is impossible, the values of the six measured regions were compared to the same or similar regions in our study. The compared regions were the hip, ear, humeroscapular junction, metacarpal region, thoracolumbar junction, umbilicus (the previous study stated the site as the skin of the ventral portion of the abdomen midway between the umbilicus and the xiphoid, while this study stated it was the umbilicus). Compared to our study, the same result was found where the lowest reading was from the forelimb foot pad, and next in line was the thoracolumbar junction. It was difficult to find a certain trend with other values. Such a comparison would be more accurate with more data in the future.

It is known that there are considerable variations in cutaneous blood flow in different parts of the body (8). Due to the small measuring area of the probe and the complex anatomical architecture of the cutaneous vasculature (3), considerable variation in blood flow can be encountered, especially in certain regions, such as the canine foot pad; external ear; and mucocutaneous junctions of the nostril, eyelid, lip, nipple, vulva, prepuce, and anus, that do not have the general vascular arrangement of normal skin (16). The measured regions were selected based on a previous study that measured cutaneous blood flow in several species (including dogs) (3), and the reproducibility was maximized when the measurement was performed on the exact location with careful consideration of the superficial arteries of the canine body (16). To measure these points accurately, although there were differences in the body shapes of the subjects, the selected points were mainly characteristic bumpy regions.

In regards to skin blood flow research in humans (7,15), the Pearson correlation in this study between skin temperature and cutaneous blood flow measured by laser Doppler flowmetry ($r = 0.72$, p-value $= 0.0003$) is statistically significant. A good correlation between both reliable methods can reduce their limitations.

As shown in Table 1 and 2, the results from laser Doppler flowmetry have a relatively larger standard deviation than that of skin temperature. Although the number of dogs used in this study and five repetitive measurements were not small, the accumulation of results is needed for more reliable baseline data. Another limitation is that a laser Doppler flowmeter is a very sensitive instrument and can be affected by diverse variables. The factors that are considered to affect the experiments in humans are topical and systemic drugs, ambient temperature, air humidity, food and liquid intake, sex, age, anatomical location, skin temperature, laboratory hematologic abnormality, time of day, physical activity, mental activity, subject position, ethnic background, and the use of nicotine (3). These factors cannot be fully evaluated in the current study of dogs. Through further study of the effects of these many variables, we hope to reduce variability in measurements.

There are many comparisons and studies on skin blood flow in humans, and it has already been applied in various fields of study. For example, it has been proven that the skin blood flow is affected by oral intake of water, and that laser Doppler flowmetry is sensitive enough to detect this effect (22). Transepidermal water loss, used as one of the skin indexes, is affected by the barrier component and a driving force component. Blood flow, one of components in the force, can be determined by laser Doppler flowmetry (21). Then, any decrease in TEWL may be explained in part by the decrease in blood flow caused by blood vessel constriction after corticosteroid treatment (13). Considering these components, the accumulated resources on skin blood flow in the future will allow its measurement to be used as a possible indicator of skin blood flow and a method for assessment of the health of the skin barrier, improvement of the cutaneous microcirculation, and a clinical indicator of dehydration in the field of veterinary medicine.

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