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Infrared thermography to assess proliferation and involution of infantile hemangiomas: A prospective cohort study

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Original Investigation

Infrared Thermography to Assess Proliferation and Involution of Infantile Hemangiomas
A Prospective Cohort Study

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IMPORTANCE Infantile hemangiomas (IHs) are common benign tumors of infancy that have the potential to interfere with vital organ function and cause permanent disfigurement. Currently, few objective and validated measures exist to assess IHs.

OBJECTIVE To determine the utility of infrared thermography in assessing and monitoring the growth of IHs.

DESIGN, SETTING, AND PARTICIPANTS In a prospective cohort study conducted at an outpatient dermatology clinic of a tertiary care hospital between February 2011 and December 2012, a convenience sample of 42 infants aged 0 to 6 months with an IH were enrolled. The mean age of the study group was 3.7 months, with the majority of IHs being mixed type (57%) affecting the head and neck (81%). Of the infants, 36 (86%) were receiving active treatment during the study period, and patients were followed for a minimum of 3 clinical visits, at least 1 month apart.

MAIN OUTCOMES AND MEASURES Ability of infrared thermography to assess the proliferation and involution of IHs compared with a visual analog scale. Secondary outcomes were reliability, ease of use, and parental acceptance of the instrument.

RESULTS The mean temperature difference at baseline was 1.9°F (95% CI, 1.2°F to 2.7°F), which peaked at 3 months to 2.5°F (95% CI, 0.8°F to 4.2°F), and decreased progressively to 0.2°F (95% CI, −1.1°F to 1.4°F) at 18.5 months ($P < .001$). This change in temperature was inversely correlated with mean visual analog scale ($r = −0.25$). Mean temperature differences recorded at baseline and 30 minutes later were not significant (least squares mean baseline temperature, 87.9°F [95% CI, 87.4°F to 88.3°F], vs least squares mean temperature after 30 minutes, 88.1°F [95% CI, 87.7°F to 88.6°F] [$P = .14$]). Multivariate analysis demonstrated facial location ($F_{1,365} = 47.63$, $P < .001$), IH type ($F_{2,365} = 3.26$, $P = .04$), age ($F_{2,365} = 7.03$, $P = .001$), and surface area at baseline ($F_{2,365} = 8.18$, $P < .001$) as factors significantly affecting temperature difference over time. Only IH type (Wald $\chi^2_2 = 6.79$, $P = .03$) and treatment (Wald $\chi^2_1 = 4.29$, $P = .04$) significantly affected time to reach a zero-temperature difference. All caregivers (100%) reported IRT to be easy to implement, quick to perform, and comfortable for their child.

CONCLUSIONS AND RELEVANCE Infrared thermography is a reliable and valid measure of IH growth that is noninvasive, convenient, and well tolerated by infants, making it well suited to daily clinical practice. It has the potential to provide real-time objective results that can be used for routine monitoring and evaluating treatment efficacy.

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Infantile hemangiomas (IHs) are the most common benign tumors of infancy, affecting nearly 10% of children.[1,2] Their clinical presentation can vary significantly, from small superficial papules to large tumors that can interfere with vital organ function and/or cause permanent disfigurement. The natural history of IHs is characterized by proliferation and slow involution over several years.[2] Accurate assessments of where on the proliferation-involution curve a particular IH lies, at any given time, is important in both making appropriate treatment recommendations, as well as evaluating treatment efficacy. Despite its importance, routine assessment of IHs has largely remained unchanged for decades, often relying solely on the physician's subjective assessment of color, size, tenseness, and temperature.

Currently, few objective and validated measures exist to assess IHs. Visual analog scales (VAS) have been widely used in the literature to measure the change in the size and extent of IHs.[3-6] Several mathematical formulas using measured parameters have been proposed to be accurate estimates of IH volume, but none have proven ideal for all types.[7-9] Other modalities such as ultrasonography[10,11] and various imaging techniques are not always practical for routine clinical assessments.

Both physicians and parents report that surface temperature tends to correlate with IH growth; the proliferative phase is characterized by increased tactile local temperature with normalization during involution. Its major limiting factor has been the lack of a quantifiable and convenient tool that can measure these temperature changes in the clinical setting. Recently, infrared thermography (IRT) has been shown to be an objective measure of local temperature differences and a safe and useful method to evaluate several thermal-related pathologic states.[12] Infrared thermography has been used in the assessment of vascular malformations and burns, as well as digit reimplantation and prediction of diabetic foot ulcers.[12-14] However, its use in IHs has been limited to date, with only a few studies reporting its use.[12,15,16] The purpose of the present study was to examine the clinical utility, reliability, and validity of IRT in monitoring the growth pattern of IHs.

Methods

The study protocol was approved by the Hospital for Sick Children Research Ethics Board, Toronto, Ontario, Canada. Written informed consent was obtained from the infants' parents prior to inclusion in the study. This prospective cohort study was conducted between February 2011 and December 2012 at the Dermatology Department at the Hospital for Sick Children, Toronto, a tertiary academic referral center. Infants with an IH diagnosed between the ages of 0 and 6 months, with a minimum of 3 follow-up visits at least 1 month apart, were included. Exclusion criteria were mid-line lesions (due to inability to select a nonaffected contralateral side) and ulcerated, secondarily infected, or actively bleeding IH. Age and sex were recorded for each patient, as well as the clinical characteristics of the IH including type (superficial, deep, or mixed), location, and surface area. Photographic documentation was performed for all IHs at each visit. The procedure for acquiring photographs was standardized through written guidelines. Data on the ease of administration of IRT, perception of invasiveness, and time to measure the temperature were collected using a structured questionnaire administered to parents.

The local temperature of each IH was independently measured by a research assistant using the TempTouch digital IRT device (Diabetica Solutions Inc). Several studies demonstrated its utility in reducing the incidence of diabetic foot ulcers by monitoring skin temperature.[13,14] This thermographic device has a "gooseneck"-designed probe, allowing for easy access to nearly all anatomical locations. The probe is touched to the surface of the IH, and after a few seconds of contact it automatically displays the temperature on a digital screen. The device measures the temperature in Fahrenheit, and as a result these units were used for all subsequent analysis. For IHs with a width (measured across the lesion) of 3.99 cm or less, a single reading was taken from the center of the IH. For an IH with a width of 4 cm or greater, 2 readings were taken, one from the central region and one from the periphery of the IH. These values were chosen based on the IRT probe having a diameter of 1.5 cm. Infrared thermography was also used to measure the temperature from the contralateral nonaffected side to obtain a temperature difference, similarly to previous studies using this thermographic device.[13,14] In addition, a temperature reading was performed 30 minutes from the first measurement to test reliability. This method was used at the first baseline visit and at all subsequent visits, which were typically within 2 months of each other. Patients were included in the final data analysis if they had a baseline visit and at least 2 follow-up visits.

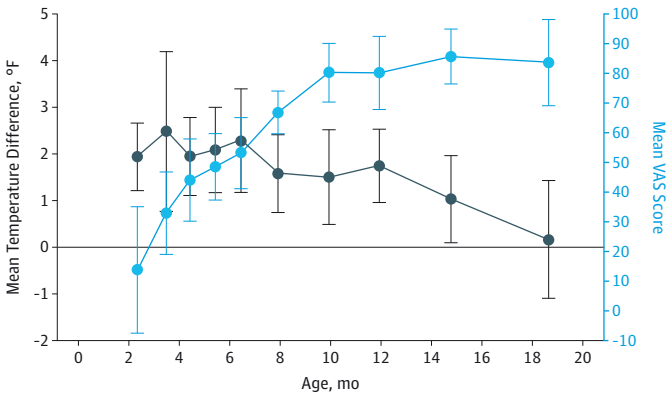
The primary outcome of the study was to examine the ability of IRT to assess the proliferation and involution of IHs as evaluated using a VAS. The VAS uses a 100-mm scale, where −100 represents a doubling in the size and extent of the IH; 0, no change, and +100, complete resolution (therefore, 5 mm reflects a 10% change). One assessor (J.A.M.), blinded to the temperature readings, reviewed all pictures at the end of the study and provided a VAS score at each visit by comparing each follow-up visit photograph with baseline in terms of size and extent. The temperature difference (temperature of the IH minus temperature of the contralateral side) for each patient was compared with the changes in the VAS over time.

Descriptive statistics were used to summarize the data. For the primary outcome, the correlation (r) between investigator VAS and temperature difference was calculated. Analysis of variance was used to compare initial and 30-minute temperature differences. To ascertain factors affecting temperature difference over time, a multivariate analysis using temperature as a continuous variable was used. Factors affecting time to zero-temperature difference were calculated using a multivariate log-logistic regression analysis. Statistical significance was set at $P < .05$. All analyses were performed using SAS 9.2 (SAS Institute Inc).

Results

Forty-two infants were enrolled, with the majority being female (n = 35 [83%]). The mean (SD) age at enrollment was 3.7

Figure. Change in Mean Temperature Difference as Measured by Infrared Thermography and Mean VAS Score With Age



VAS indicates visual analog scale. Error bars indicate 95% confidence interval.

Table. Multivariate Analysis of Factors Affecting Time to Reach a Zero-Temperature Difference Between Contralateral and Affected Sides

Characteristic	No. of IHs	Median Months to Zero-Temperature Difference	*P* Value
Treatment			
Yes	36	3.4	.04
No	6	9.4	
Facial location			
Yes	27	3.4	.18
No	15	7.3	
IH type			
Superficial	14	7.8	.03
Deep	4	0.7	
Mixed	24	3.4	
Age at baseline, mo			
1-2	7	7.4	.34
3-4	18	4.5	
≥5	17	7.6	
Surface area at baseline, cm^2			
≤1.75	11	7.1	.23
>1.75 and ≤7.0	11	3.3	
>7.0	12	4.1	

Abbreviation: IHs, infantile hemangiomas.

(1.36) months. The most common location was the head and neck area (n = 34 [81%]), followed by the trunk (n = 3 [7%]), extremities (n = 3 [7%]), and genital area (n = 2 [5%]). Mixed IHs (superficial and deep components) were the predominant type (n = 24 [57%]), with the least common being deep type (n = 4 [10%]). Most patients (n = 36 [86%]) were receiving treatment during the study, which included propranolol hydrochloride (n = 20 [56%]), nadolol (n = 6 [17%]), timolol maleate gel, 0.5% (n = 5 [14%]), and combination treatment (n = 5 [14%]).

The mean temperature difference at baseline was 1.9°F (95% CI, 1.2°F to 2.7°F), which peaked at 3 months to 2.5°F (95% CI, 0.8°F to 4.2°F). This was followed by a plateau between 8 to 12 months after which the temperature decreased progressively to 0.2°F (95% CI, −1.1°F to 1.4°F) at 18.5 months ($P < .001$) (**Figure**). The mean VAS score increased progressively over the same period and was inversely correlated with mean temperature difference ($r = −0.25$) (Figure). A multivariate analysis demonstrated facial location ($F_{1,365} = 47.63$, $P < .001$), IH type ($F_{2,365} = 3.26$, $P = .04$), age ($F_{2,365} = 7.03$, $P = .001$), and surface area at baseline ($F_{2,365} = 8.18$, $P < .001$) as factors affecting temperature difference over time. In an analysis of variables affecting time to reach a zero-temperature difference, between the affected and contralateral side, only IH type (Wald $\chi^2_2 = 6.79$, $P = .03$) and treatment (Wald $\chi^2_1 = 4.29$, $P = .04$) were significant (**Table**). Receiving active treatment was associated with less time to reach a zero-temperature difference. At 18 months, 32 of 36 treated IHs (89%) reached a zero-temperature difference vs 3 of 6 untreated IHs (50%). For IH types, deep IHs required the least amount of time to reach a zero-temperature difference, followed by mixed and superficial IH. All deep (4 of 4) and superficial (14 of 14) IHs had zero-temperature difference at 18 months vs 17 of 24 mixed IHs (72%)

To assess reliability of the IRT, IH temperature assessments were repeated 30 minutes after the initial reading. The mean temperature difference between these 2 time points was not significant (least squares mean baseline temperature, 87.9°F (95% CI, 87.4°F to 88.3°F) vs least squares mean temperature after 30 minutes, 88.1°F (95% CI, 87.7°F to 88.6°F) (P = .14).

The results of the parent questionnaire revealed that of the 38 of 42 parents who completed the survey, 38 (100%) believed that IRT was an easy method to implement, with no parents disclosing any inconveniences of the tool. Similarly they reported that it took less than 30 seconds to measure the temperature and no parent expressed concerns about the child's discomfort during the testing.

Discussion

In this prospective study, IRT was demonstrated to be an objective and reliable method for assessing the proliferation and involution of IHs. It was also found to be a convenient and noninvasive technique that is well tolerated by patients and easily implemented into routine clinical practice.

Infantile hemangiomas are clinically heterogeneous, making it difficult to adequately quantify the size of one particular lesion and to monitor progression over time. At present, a standardized method for assessing the growth of IHs is lacking. Few modalities exist that are objective, reliable, and validated for every day clinical practice. Visual analog scale has been widely used as an objective measure,[3-6] but its validity is dependent on the quality of the picture and it is subject to intrapersonal and interpersonal variability. Several reports have proposed estimating the volume of IHs using mathematical formulas based on measured parameters. Both Tsang et al[7] and Dixon et al[8] described formulas for estimating the volume of IHs through assuming their shapes as perfect or half spheres. A third more versatile method has been developed that accurately measures the volume of ellipsoid IHs, not accounted for by the aforementioned formulas, and is as accurate in measuring spherical IHs.[9] Although these methods can be performed at the bedside, no one formula is universally applicable to all IH shapes, and none measure the volume of IHs below the skin.[7-9] Furthermore, they all require taking precise measurements from an active infant and at times from difficult to access anatomical areas. Most recently, grading scales that attempt to standardize the severity of IHs and its complications have been developed for longitudinal use.[17] These have been shown to have good reliability, but they were not designed to provide information with regard to IH volume and extent.[17] Imaging such as ultrasonography and magnetic resonance imaging have also been used to objectively measure IH growth and involution. Several studies have used ultrasonography to measure IH thickness, as well as resistivity index, as a measure of blood flow to follow IH regression.[11,18,19] However, the objectivity and reliability of the resistivity index has been questioned by some authors owing to high variability and dependency on the activity of the patient.[11] Its everyday clinical use is further limited by interoperator variability[11,20,21] and the need for an experienced ultrasonographer. In addition, painful ulcerated IHs and certain anatomical locations are not amenable to acquiring a sufficient ultrasound study, particularly in young, active children.[11,19] In a study by Schiestl et al[11] examining the efficacy of propranolol to treat IHs, only 11 of the 25 patients studied had technically sufficient ultrasound studies.[11] Magnetic resonance imaging may provide an assessment of the volume and extent of IH,[22,23] but its cost, need for sedation in young children, and limited availability precludes its routine use for monitoring of the progression of IHs. Magnetic resonance imaging use is largely limited to the diagnosis, evaluation, and progression of extracutaneous IHs.[24]

The use of IRT in the assessment of IH growth has been scarcely reported since it was first described in 1975 in a heterogeneous population of IHs and vascular malformations.[15] Subsequently, Desmons et al,[16] in a study of 25 IHs and IRT, reported a temperature difference of greater than 0.5°C between the IH center and the surrounding or contralateral skin in 92% of the IHs studied. Most recently, IRT was used to follow the clinical progression of 32 cutaneous IHs.[12] Consistent with our findings, both studies reported a decrease in the temperature difference over the course of the studies, although the specific data, including patient ages and follow-up times, were not provided.[12,16] In addition, the temperature change observed over time in the present study was closely correlated with previous studies describing IH growth characteristics.[25] The peak temperature difference was achieved at 3 to 4 months of age, the period during which the most rapid proliferation of IHs is known to occur, while a steady decrease in temperature was noted starting at 12 months of age, when most IHs begin to involute.[25] The changing temperature in IHs is thought to reflect changes in blood flow with ongoing proliferation characterized by increasing blood flow and involution characterized by a reduced blood flow secondary to endothelial cell apoptosis. The changes in blood flow lead to varying degrees of transmitted infrared radiation, which is detected by the IRT device.[12,15,16] Interestingly, as some IHs neared almost complete involution, a negative temperature difference was detected (data not shown). These results suggest that the fibrofatty tissue that replaces tumoral tissue may be less well perfused than normal skin. Alternatively, this finding may reflect the fact that residual fibrofatty tissue, particularly from those resulting from mixed IH, may be farther from the body, leading to a reduced surface temperature.

Several factors were demonstrated to influence temperature change over time including facial location, IH type, age, and surface area at baseline. It has been well described that superficial IHs have a shorter growth phase than deep IHs,[25] while clinically smaller IHs are often observed to involute more rapidly, potentially owing to their smaller volume. The influence of age at baseline may relate to its impact on the timing of the presentation before or after the peak temperature difference and as a result the overall temperature difference. We also examined variables affecting time to reach a zero-temperature difference because this was believed to be the best outcome measure correlating with significant clinical IH involution. In this analysis, only IH type and treatment were found to be significant. As expected, receiving active treatment was associated with a reduced time to zero-temperature difference. Of the IH types, deep IHs required the least amount of time to

reach this outcome. This may have been secondary to the small sample size and thus needs to be interpreted with caution. Interestingly, the median time required to reach a zero-temperature difference for mixed IHs was less than for superficial IHs. However, a higher percentage of patients with superficial IHs (100%) vs mixed IHs (72%) achieved this end point at 18 months of age, reflecting the quicker overall involution of superficial IHs often observed in clinical practice.

As a tool to evaluate IH growth, IRT has several advantages. It is time efficient, safe, painless, and practical for monitoring IHs at virtually any cutaneous location. Most importantly, it was well accepted by parents as a noninvasive assessment tool and was well tolerated by infants. Saxena and Willital[12] reported similar findings in a 10-year review of IRT in various pediatric conditions including IHs, vascular malformations, burns, wound infections, and digit amputations. These characteristics make IRT an ideal tool for making treatment related decisions at the bedside, in addition to providing an objective measure of IH involution in treatment intervention studies, an area currently lacking a readily available and noninvasive objective outcome tool. Infrared thermography in conjunction with clinical assessments may be able to better reassure parents that a particular IH is involuting, possibly avoiding unnecessary β-blocker treatment and parental anxiety. Likewise, IRT provides a temperature trend over time that has the potential to detect treatment failures, identify rebound growth earlier, and improve treatment related end points such as timing of β-blocker weaning and cessation. This is supported by a recent pilot study from our center that demonstrated IRT to be a useful tool to measure therapeutic response to a systemic β-blocker.[26] Most promisingly, IRT has the advantage of potentially detecting all such changes before they are appreciated clinically; however, this requires further study. Its application to other vascular tumors such as congenital hemangiomas and hemangioendotheliomas also requires further investigation.

Several limitations of the study need to be considered. Imaging studies would have provided a more objective independent measure of IH growth; however, this was not feasible given the time needed and frequent follow-up required. For this reason, VAS was used because it is noninvasive, can be applied to all IH types, and is a well-accepted measure of growth in IH treatment trials. Although it was demonstrated that IRT can be used for monitoring all IH types at various locations, midline IHs were excluded because they do not have a corresponding contralateral area of normal skin from which to measure the temperature difference. Several studies have shown that the surrounding skin can be used, but this was not evaluated in the present study.[15,16] Ulcerated, bleeding, and infected IHs were also excluded because these may have caused false temperature elevations that were not truly reflective of increased IH growth. In theory, these IHs could be followed with IRT, which may have the additional advantage of detecting ulcerations before they occur clinically and monitoring their resolution. This is supported by evidence from adult studies in which IRT has been proven to reduce diabetic ulcerations through detection of asymptomatic inflammation. The application to ulcerated IHs requires further evaluation.

Conclusions

With the emergence of newer and safer treatments for IHs, it has become increasingly important to have a standardized objective measure of growth. The present study demonstrates that IRT is a reliable and valid measure of IH growth that is well adapted to the clinical setting. It has the potential to provide the clinician with real-time results from which management decisions can be made and treatment efficacy evaluated. Future studies are required to evaluate IRT in relation to other objective measures of IH growth, as well as to assess its applicability in complicated IHs.

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Study concept and design: Balma-Mena, Chakkittakandiyil, Pope.
Acquisition, analysis, or interpretation of data: Mohammed, Matea, Pope.
Drafting of the manuscript: Mohammed, Balma-Mena, Matea.
Critical revision of the manuscript for important intellectual content: Mohammed, Chakkittakandiyil, Pope.
Statistical analysis: Mohammed.
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Administrative, technical, or material support: Balma-Mena, Chakkittakandiyil.
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NOTABLE NOTES

Carlo Forlanini, the Dermatologist Who Invented the Cure for Pulmonary Tuberculosis

Filippo Pesapane, MD; Antonella Coggi, MD; Raffaele Gianotti, MD

Carlo Forlanini was born in 1847 in Milan, Italy, and was the son of Federico Forlanini, the primary doctor from Milan's Fatebenefratelli Hospital. Carlo was the elder brother of Enrico Forlanini, an inventor and aeronautical pioneer well known for his works on helicopters, aircraft, hydrofoils, and dirigibles. Forlanini joined the faculty of medicine at the University of Pavia. In 1866, he volunteered to serve under Giuseppe Garibaldi, and in 1870 he graduated with a thesis focused on cutaneous inflammation entitled "Contribuzione alla Teoria della Piogenesi."[1] A close friend in his student days was Camillo Golgi, a man who would later achieve eminence as a histologist and receive the Nobel Prize in 1906.[2]

Milan's main hospital, "Ospedale Maggiore Policlinico" (now "Fondazione Ca' Granda"), attracted Forlanini, and he was accepted in 1871. He spent the next 13 years working in the departments of chronic diseases, eye diseases, and, particularly, skin diseases. In January 1876, he was appointed the head of the skin department, a post he would retain for the next 6 years in order to continue his interest in studying tuberculosis.[1]

In the 1882, the same year that Robert Koch discovered of the tubercle bacillus, Forlanini introduced a new treatment of pulmonary tuberculosis: the artificial pneumothorax. He based this treatment on the intuition that to heal from lung tuberculosis it was necessary suppress its function, or rather to collapse it to eliminate the respiratory trauma. The method is based on the technique of "collassoterapia," which Forlanini also invented. The technique consists of introducing inert gas into the pleural cavity corresponding to the injured lung so that it is placed in a state of functional rest to facilitate healing.[3] For some 40 years before the introduction of antituberculous drugs, artificial pneumothorax offered hope and, in many cases, healing to patients with tuberculosis around the world.

In 1884, he was appointed chair of Clinica Propedeutica at Turin, Italy, and, finally, in 1900 he obtained the chair of clinical medicine at the University of Pavia, an institution that boasted a glorious tradition. This was where Giulio Bizzozero had made discoveries on the physiologic characteristics of blood, where Paolo Mantegazza had signaled the importance of the glands of internal secretion, and where Edoardo Bassini had developed his method of treating inguinal hernia.[2] By all accounts, Forlanini was a popular teacher. Among his pupils was Scipione Riva-Rocca, who introduced the first practical sphygmomanometer in 1896.[1]

In 1913, Forlanini became a senator of the Italian Republic, and at the time of his death in 1918 he had been proposed for the Nobel Prize in Medicine. After his death, a research fund for the study of tuberculosis was created in his name. In 1934, the "Carlo Forlanini Institute" was founded in Rome, comprising a complex of sanatorium, university clinic, laboratories museum, and research center.[1]

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