Improvement Achieved in the Optical Quality of Thermography by Using a Contrast Medium to Early Diagnosis Non-invasive of Breast Pathologies

Angel Luis Rodríguez Morales¹, Angel Ramón Hernández-Martínez¹, Martha Cruz Soto², Julián García Espinoza³, María Guadalupe Ferreira García¹, Liliana Amada Argüello Labandera¹ and Miriam Rocío Estévez González²

¹. Center for Applied Physics and Advanced Technology, UNAM, Juriquilla 3000, Querétaro, México
². University of Mexico Valley, Juriquilla 3000, Querétaro, México
³. Medical Specialties Unit of Breast Cancer Detection and Diagnosis, Querétaro, México

Corresponding author: Miriam Rocío Estévez González (miries@fata.unam.mx)

Abstract: Breast cancer is one of the most commonly diagnosed cancers in women. In most of cases, it can be treated in an early detection. There are many breast cancer diagnosis techniques including thermography. However, reliance on the definition of the thermal image is one of the determining factors for successful diagnosis. This paper aims to demonstrate an improvement of high contrast definition in thermographic maps by using a cellulose-based hydrogel as thermal contrast. This hydrogel was topic used in high risk areas of the mammary gland, making possible to obtain high definition thermograph images. In cases of irregular temperature patterns in control subjects, a decrease of general temperature in thermal maps by the use of this hydrogel was shown, allowing to identify blood vessels in more regular patterns. This performance was due to the increase of thermal tissue homogeneity facilitating the interpretation of the results, which were analyzed by traditional image processing using FLIR TOOLS + software. A statistical analysis on 350 subjects sample showed up to a 400% improvement in contrast and definition of thermograph image results. Blood vessels were clearly seen compared to non-hydrogel treated areas, and a thermal homogeneity of the affected areas was also observed.

Keywords: Thermography, breast cancer, hydrogel, early diagnosis noninvasive.

1. Introduction

In 1982, the FDA (Food and Drug Administration) accepted the Infrared imaging of the breast, or breast thermography, as an auxiliary method for the detection of breast cancer. Different findings confirm that thermography is the only early initial signal in 10% of breast cancers with an average sensitivity and specificity of 90%. Some reports assure that its complementary use with clinical examination and mammography would increase significantly the probability of early cancers detection [1-13]. Therefore, breast thermography may have prognostic significance of great importance due to it can be correlated with a variety of pathological prognostic features such as tumor size, tumor grade, lymph node status and markers of tumor growth [14, 15]. For this reason, at Center for Applied Physics and Advanced Technology of UNAM, we are developing a Statistical and Referential Model of Mammary Gland Thermal Distribution. For this purpose; as a first stage a database of 1385 patients and voluntaries has been used to analyze several malignant and non-malignant pathologies of the breast with the main purpose to describe specific thermal patterns in early breast cancer stages.
During this stage of our research, two healthy patients had abnormal thermographs that caught our attention; a thermal mottling on arms, chest, abdomen, and breasts had been observed. These patterns represent a difficulty in the generation of a thermal map because they mask the information from pathology. Different parameters were varied aiming to reduce interference from these patterns, none attempt was successful. Then the use of a contrast medium was tested as is done in the contrast-enhanced ultrasound imaging (sonography), subsequent to this finding all thermography were taken with and without contrast medium for future comparison.

The aim of this short release is to communicate the improvement obtained in the definition of thermograph image using a contrast medium (contrast thermography) versus a thermal image without contrast medium (normal thermography).

The paper is organized as follows: Section 2 is a brief review of the technique for thermographic detection of pathologies in the mammary glands and description of the experimental methodology in volunteers; Section 3 shows the results of analysis of volunteers with and without pathological conditions and evaluation of hydrogel as contrast media; Section 4 concludes the paper.

2. Techniques, Methods, Materials, and Volunteers

2.1 Thermal Contrast

Four hydrogel formulations (HF1, HF2, HF3, and HF4) were used as thermal contrast. In all cases the hydrogel preparation required: CMSC (carboxyl methyl sodium cellulose) (Sigma-Aldrich), Gly 99% (glycerol) (J.T. Baker), PGly (propylene glycol) (J.T. Baker), ceramic nanoparticles (NPs), and distilled water. On 50 mL distilled water at 80 °C carefully, these materials were added in different proportions of Gly; 20%, 25%, 30% and 35% for HF1, HF2, HF3, and HF4 respectively. The thermal performance of all formulations was studied by TGA (thermogravimetric analysis) and DSC (differential scanning calorimetry); TGA was performed in an argon atmosphere using a TGA Model Mettler Toledo TGA/SDTA 851e and the DSC was performed using a Model Mettler Toledo DSC822e.

2.2 Thermographic Technique

The volunteers were appropriately positioned with the arms at one side and up of the head, in an exploration room with controlled temperature at 25 °C and relative humidity of 75%. Then by normal thermographs; 125 thermal images without contrast medium were taken from each volunteer. Subsequently by contrast thermographs; on the same skin area, a thin layer of hydrogel was placed and another 125 thermal images were taken for each volunteer; this was repeated with each of the different hydrogel formulations. All images were taken using an infrared camera FLIR E40 series with a 160 × 120 pixels resolution and thermal sensibility of 0.07 °C obtained in JPG format were downloaded into a computer and were processed with the FLIR TOOLS + software (FLIR Systems, Inc. Wilsonville, OR) to obtain the final thermographs. Temperature differences in patients’ breasts were determined using this software and data obtained were treated statistically using a spreadsheet.

2.3 Volunteers Population

The universe was 350 women (153 with breast pathology and 197 healthy volunteers) between 18 to 78 years old of different socioeconomic status and academic achievement. Some were identified through the Registry of Medical Specialties Unit of Breast Cancer Detection and Diagnosis at Queretaro, Mexico, and also some volunteers were invited through the Center for Applied Physics and Advanced Technology of the UNAM.

The studied population was eligible by two conditions; been Queretaro’s resident, and have a benign pathology diagnosis as cysts or adenosis (VBP)
confirmed with mammography, biopsy or ultrasound between Sept. 1, 2013 and Aug. 31, 2014 and ectomorph somatic with breast volume of 150 to 300 cubic centimeters.

Thermograph images: A group of 24 women was formed for testing each hydrogel formulation; 12 healthy volunteers and 12 volunteers with some pathology, evaluating the contrast between hydrogel and non-hydrogel applied zone.

A third group was formed from the best contrast results of the 24 volunteers. This twelve group of images were compared to a referential statistics model of pre-diagnosis giving more precision to the probabilistic pathology result.

2.4 Biocompatibility Evaluation of Thermal Contrast

Three Wistar rats were used. Hair was cut with scissors to one Wistar rat used as control, hair was shaved with a blade to a second one, a third one was shaved and a thermal lesion was performed (modified from Dugan et al.); to evaluate the effects of the contrast medium on irritated and dehydrated skin injury, respectively. The back of each rat was divided into four areas and four different gel formulations were applied. All the animals were monitored for 30 min after the application of the gels and also after 6, 12 and 24 h. Animals were handled according to NOM-062-ZOO-1999 Lab animal handle, care, use and production.

3. Results and Discussion

3.1 Quality of Information Obtained on Healthy Volunteers

Fig. 1 shows the general view of a processed breast thermography with the FLIR TOOLS + software; there is a circle representing the area selected by the operator for being analyzed by the software and within it several temperatures are pointed, the highest and lowest temperature are highlighted with a red triangle and a blue triangle respectively; also here is a table of the temperature values at each marked point, and the maximum, minimum and average temperatures. Here it is easy to see that 8.1 °C is the arithmetic difference between the highest and lowest temperature.

Fig. 2 shows the thermograph of the right breast in the same patient as in Fig. 1; in this case the arithmetic difference between the highest and the lowest temperature is 9.1 °C, which is very similar to the one obtained in the thermograph acquired without contrast medium in the left breast of the same volunteer. However, thermograph obtained using contrast medium has greater detail and higher contrast; a higher resolution thermograph was obtained and this improvement in image quality can facilitate detection of any abnormalities linked to pathology.

The four formulations were tested on the same volunteer and Fig. 2 shows the best thermographs obtained in which HF2 was used.

Once hydrogel is applied, local perfusion is increased as a result of contraction of the muscular walls of the vessels (Vasoconstriction) seen in Fig. 3. In this figure, the eye can see the difference of getting a thermograph using contrast medium or acquire it regardless of it; the improvement in quality is clear, notice the blood vessel patterns on the images with higher definition on the right breast which has contrast medium.

3.2 Hiding of Information by Thermography Mottled

In Fig. 4, a grayscale thermograph is shown with mottled patterns; in the total sample (n = 350) occurred 2 cases of healthy volunteers whose thorax images showed heat spots associated with fat distribution, blood flow and sweating; we have named these variety such as the “Leopard pattern” because of its uncanny resemblance to a leopard skin.

Leopard pattern represents a difficulty in the generation of a thermal map because it masks the information from pathology and impedes a pre-diagnosis. The “Leopard pattern” particular thermal map does not adjust with the thermal model of routine, therefore, it is difficult to detect any breast
Improvement Achieved in the Optical Quality of Thermography by Using a Contrast Medium to Early Diagnosis Non-invasive of Breast Pathologies

Fig. 1  Healthy left breast thermography taken without contrast medium.

Fig. 2  Healthy right breast thermography taken with contrast medium.

Fig. 3  Thermographs from the same healthy volunteer; right breast with contrast medium and left breast without contrast medium.
Improvement Achieved in the Optical Quality of Thermography by Using a Contrast Medium to Early Diagnosis Non-invasive of Breast Pathologies

3.3 Quality of Information Obtained on Breasts with Pathology

Thermal images allowed discriminating between normal form and abnormal breast tissue with differential vascularization patterns as seen in Fig. 6. It was determined that using the contrast medium FH2 contrast of image increased up to 400% and it has more definition to visualize detailed vascularization patterns. FH2 applied on the skin decreases local surface temperature and allow the observation of pathology-related thermal patterns, by reducing thermal radiation emission of the tissue. In this case, on the right side of image with contrast medium shows clearly that the breast lobules are enlarged typical characteristic of a breast with adenosis which is not a cancer; the volunteer had a diagnosis confirmed when the thermal images were obtained.

3.4 Evaluation of Contrast Medium

Further evidence of the improvement obtained by using a medium contrast is shown in Fig. 7; for the
breast thermography, one breast with medium contrast (right breast) is compared to the other without it (left breast) the thermographs were taken after that thermal equilibrium was reached. Here the performance of HF1, HF2, HF3, and HF4 are shown in Figs. 7a-7d respectively. Fig. 7 shows the obtained resolution effect in correlation with Gly concentrations; image 7a has highest quality and definition in which are seen more clearly veins breast.

The contrast medium forms a thin film on the skin, altering the thermal energy than infrared camera captures. Without contrast medium the breast is the energy source emitting infrared radiation from their surface. According to Stefan-Boltzmann Law the relation between radiated energy and temperature by stating that the total radiation emitted by an object is directly proportional to area and emissivity of object and the fourth power of its absolute temperature; the emissivity of human skin is extremely high, hence measurements of infrared radiation emitted by the skin can be converted directly into accurate temperature values that can be processed to create a thermal map of a certain object, nowadays, infrared cameras are able to detect temperature changes about 0.025 °C [16-18]. When contrast medium is used the heat emitted by the breast must traverse to it by thermal conduction as illustrated in Scheme 1: According to Fourier Law, the heat transfer through a material is function of temperature is of first-order, area and conductivity of the contrast medium which in the case of anisotropic materials, the thermal conductivity ($k$) typically varies with orientation; in this case $k$ is represented by a second-order tensor.

![Scheme 1](image)

**Scheme 1** Simplified representation of the heat transfer mechanism from the breast; without contrast medium (left) versus with it.

![Fig. 7](image)

**Fig. 7** HF1, HF2, HF3, and HF4 thermographs in (a)-(d) respectively; right breast with medium contrast and left breast without it.
Improvement Achieved in the Optical Quality of Thermography by Using a Contrast Medium to Early Diagnosis Non-invasive of Breast Pathologies

Understanding the thermal performance of contrast medium is important and therefore TGAs were obtained from the 3 better contrast medium HF1, HF2, and HF3 to understand that the image enhancement. Fig. 8 shows the TGA (thermo-gravimetric) and SDTA (differential thermal analysis simultaneously): Figs. 8a and 8b respectively. HF4 gave does not good results, so it was decided not to get their TGA, SDTA and DSC thermals.

In Figs. 8a and 8b, it is observed that HF1, HF2, and HF3 are stable for the use temperature range of 36 ± 3 °C. Around 40 °C begins covalent bonds breaking between hydrogel and water. HF1 (red line) has a higher resistance to this break, its thermal behavior indicates that is stronger in Van der Waals forces or have more covalent bonds; thus, this formulation (contrast mediums) has more stability of water molecules at temperatures below 40 °C. DSC results are shown in Fig. 9. In all thermographs two endothermic peaks appeared. The minimum of first peak is observed between 80 °C to 92.04 °C due to heat capacity (Cp) changes of hydrogel water system trapped in the amorphous hydrogel network. In this

![Fig. 8](image_url)  
(a) TGA and (b) SDTA curves of formulations HF1, HF2, and HF3.

![Fig. 9](image_url)  
DSC curves of formulations HF1, HF2, and HF3.
Improvement Achieved in the Optical Quality of Thermography by Using a Contrast Medium to Early Diagnosis Non-invasive of Breast Pathologies

endothermic event, weaker van der Waals interactions are broken and the amorphous hydrogel network begins to lose water trapped. The second minimum endothermic peak is observed about to 148.2 °C for HF2 and about to 155 °C for HF3; this is due to water free evaporation process. In HF1 the second minimum endothermic peak is observed on 225 °C due to the combination of water’s evaporation and decomposition processes.

The principal differences between the four formulations were in their ability to form hydrogen bonds, its viscosity and the ratio between free water and water bound to hydrophilic groups; that affected his local ability to retain water inside the polymeric network. Gels are polymeric materials which form a tridimensional hydrophilic network. Hydration increases polymer size resulting in soft and elastic materials with altered physicochemical properties. A -OH, -COOH group interaction occurs with water molecules and polymer chains. Gel texture is derived from the liquid/solid proportion; addition of water molecules depends on polymer chain intercross favored by covalent bonds, Van der Waals forces and hydrogen bonds.

No cases of hypersensitivity occurred during the study and before using the contrast medium in any volunteer tests were performed to evaluate the effects of the contrast medium of biocompatibility on irritated and dehydrated skin injury. Fig. 10 shows a specimen with thermal injury and body divided into four areas in each of the areas a different gel formulation was placed directly on its back. In this biocompatibility Test, signs of irritation in lessoned skin suggesting its safe use in patients were not observed.

4. Conclusions

In all tests conducted it was found that the arithmetic difference between the maximum and the minimum temperatures is higher in the thermograph of the breast with contrast medium. Also, the images of breast with contrast medium have higher resolution compared to the images without it.

Identifying abnormal patterns is quite difficult; mammary glands have an irregular fat or muscle distribution and differences in dermis thickness; by increasing contrast and definition of blood vessels in the thermal images more accurate clinical data can be obtained.

Contrast medium application markedly increased thermal image contrast and decreased “Leopard pattern” visualization and its application in breast with adenosis showed up to a 400% increase in thermal image contrast and definition; therefore contrast-thermography is a non-invasive method used in our staff research, to acquire infrared images showing differential temperature patterns from the mammary gland, resulting from neovascularization processes. This approach makes possible visualization of neovascularization processes in breast cancer early stages. Biocompatibility testing showed no signs of irritation in lessoned skin suggesting its safe use in patients.

Considering that the human body temperature is close to 36 °C with possible variations of ±5 °C and based in the thermal behavior here analyzed; in all cases the hydrogel formulations are suitable for achieve preclinical breast cancer detection, decrease treatment length and expenses, as well as improve prognosis by preventing metastasis.

Until today we have not found similar reports to this, at least in the search we did, therefore this is the first short-report where an improvement in the quality of thermography is achieved using a contrast medium.

![Fig. 10 Visual assessment of biocompatibility on Wistar rats it.](image)
Acknowledgments

The authors are grateful to: CONCYTEQ for support through Talented Youth Program; UNEME DEDICAM Querétaro for the medical support; M.C. Guillermo Vazquez for the computational support; D. Rangel Miranda for instrumentation support, and B. Rodriguez Morales for his technical support; and all participants and volunteers.

Ethical Approval

All volunteers were informed about the methods and techniques, objectives and scope of the study. And they all signed Informed Consent for Clinical Studies.

References