Chirurgia (2024) 119: 417-426
No. 4, July - August

http://dx.doi.org/10.21614/chirurgia.3008

# Experimenting with Pig-based Skin Model for Burns. Testing of Mean Literature Findings

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Received: 16.06.2024
Accepted: 12.08.2024

**Rezumat**

***Experiment cu un model animal porcin pentru arsuri. Validarea rezultatelor literaturii***

*Introducere:* Modelele de animale care imită îndeaproape procesele de vindecare a rănilor arse umane sunt esențiale pentru dezvoltarea unor tratamente eficiente. Porcii sunt modele animale utile pentru studiul vindecării rănilor arse. Din analiza lor extinsă a literaturii, Andrews and Cuttle (2017) raportează valorile medii ale temperaturii şi timpului de expunere. Acest studiu a fost făcut pentru a evalua adâncimea inițială de arsură pentru un alt experiment care compară două tratamente pentru arsuri. Obiectivul secundar a fost validarea unei revizuiri sistematice a standardizării modelului de ardere a modelelor animale.
*Materiale şi Metode:* Şase suine de patru săptămâni Large White x Landrace au fost adăpostite într-o structură închisă timp de 10 zile pentru a se aclimatiza. Procedurile au fost efectuate sub anestezie generală. O placă de cupru rotundă de 2,5 cm sudată la o bară de aluminiu cu un mâner de lemn a provocat rănile. Dispozitivul de ardere a fost încălzit pentru a atinge o temperatură de contact de 110ºC pe pielea porcului. Obiectivul a fost de a crea o arsură de adâncime parțială superficială (SPT) la o expunere de 10 secunde (Grupul 10s) şi o arsură parțială profundă (DPT) pentru 20 secunde expunere (Group 20s) folosind o placă încălzită la 110ºC. Nu a fost utilizat niciun stabilizator sau controlor de presiune. Rănile au fost

excizate şi recoltate 24 de ore mai târziu. Protocolul obişnuit de hematoxilină-eozină a fost utilizat pentru tăierea şi colorarea secțiunilor de 4 microni.
*Rezultate:* A fost observată o diferență semnificativă (p<0,01) în ceea ce priveşte implicarea dermului, cu o medie de 85,61 % (IC 95 % = 80,62 până la 90,61) pentru grupul 10s şi de 123,71% (CI 95 %= 114,91 până la 132,50) pentru grupul 20s. Un timp de expunere de 20 de secunde a crescut denaturarea totală a colagenului legată de adâncimea dermului cu aproape 50% comparativ cu grupul 10 secunde.
*Concluzii:* În concluzie, experimentul nostru a produs arsuri DPT în 10 secunde şi arsuri FT în 20 de secunde fără un dispozitiv de aplicare a presiunii.

Cuvinte cheie: model, animal, arsuri, porcin

**Abstract**
*Introduction:* Animal models that closely mimic human burn wound healing processes are essential for developing effective burn wound treatments. Pigs are useful animal models for studying burn wound healing. From their extensive literature review, Andrews and Cuttle (2017) reported mean temperature and exposure time values. This study was done to provide initial burn depth for another experiment comparing two burn wound treatments. The secondary goal was to validate a systematic review on porcine burn model standardization.
*Materials and Methods:* Six four-week-old Large White x Landrace gilts were housed in a closed structure for 10 days to acclimatize. The procedures were performed under general anesthesia. A round 2.5 cm copper plate welded to an aluminum rod with a wooden handle caused the injuries. The burning device was used to reach a contact temperature of 110ºC on the pig's skin. The objective was to create a superficial partial thickness (SPT) burn for 10 seconds (Group 10s) and a deep partial thickness (DPT) burn for 20 seconds (Group 20s) using a plate heated at 110ºC. No stabilizer or pressure controller was used. Wounds were conclusively dressed and harvested 24 hours later. The usual hematoxylin-eosin protocol was used to cut and stain 4-micron sections.
*Results:* A significant difference (p<0.01) was observed in dermis involvement, with a mean of 85.61 % (95% CI= 80.62 to 90.61) for group 10s and 123.71% (95% CI= 114.91 to 132.50) for group 20s. An exposure time of 20 seconds increased dermis depth-related total collagen denaturation by almost 50% compared to 10 seconds.
*Conclusions:* In conclusion, our experiment produced DPT burns in 10 seconds and FT burns in 20 seconds without a pressure application device.

Key words: model, animal, burns, porcine

## Introduction

Burns are a distressing medical condition with important consequences that are challenging to manage, both for the patients and for the medical institutions responsible for their care. According to the World Health Organization, ~11 million individuals are impacted each year by burns, resulting in an annual mortality rate of 180,000 individuals worldwide (1).

Burn wounds are a major healthcare concern, and the development of effective treatment strategies depends on the availability of reliable animal models that closely mimic human burn wound healing processes. Thus, it is imperative to evaluate and implement stateof-the-art burn treatments using preclinical models. Variations in skin structure, wound healing mechanisms and financial consequences are common among the mouse, rat and pig models, which are commonly used species (2). Rodents dominate burn research animal models. Due to their cost-effectiveness, versatility, and ease of lodging, mating, and handling, rats and other rodents are ideal for many experimental treatments. They also make the best choice for hypothesis-driven research due to their well-organized lineage system and ease of transgenic and knockout strain generation. Rats have a thick fur coat, unlike humans (3).

Among various animal models, pigs have emerged as a valuable option for studying burn wound healing due to their anatomical and physiological similarities to humans. The use of porcine models in burn research has been well established, with pig skin responding to therapeutic agents in a manner similar to human skin (4). Additionally, pig skin has been shown to share numerous characteristics with human hypertrophic scars, making it an accepted model for the study of scarring (5). The relevance of porcine models in burn research is further supported by studies demonstrating the effectiveness of using skin harvested from commercial pigs in treating patients with severe burns (6-8). Moreover, the establishment of burn models in pigs has been described in the literature, where ordinary, male Bama miniature pigs have been used to establish burn models with different burn depths (BDs) (9). These models provide valuable insights into the pathophysiology of burn wounds and the evaluation of potential treatment modalities. Porcine models have been utilized to quantify the efficacy of first-aid treatments for burn injuries, highlighting the importance of porcine models in understanding the optimal temperature for first-aid treatment of partial thickness burn injuries (10). They have been used to provide evidence for conservative surgical debridement as a burn treatment, thus emphasizing the utility of porcine models in evaluating burn wound management strategies, which has notably contributed to the current understanding of burn wound healing processes and the development of potential therapeutic interventions (11). These models not only provide insights into the pathophysiology of burn wounds but also serve as essential tools for evaluating the efficacy of burn wound treatments.

Additionally, the thickness and permeability properties of pig skin align closely with those of human skin, making pig skin a suitable membrane for studying drug delivery and skin penetration. The structural similarities between pig and human skin extend to the epidermal thickness, hair follicle morphology and overall skin architecture, further supporting the utility of pig skin as a model for human skin in research studies (12-14). Andrews and Cuttle (15) reported mean values for temperature and exposure time in their review of the literature.

The primary objective of the present study was to provide evidence of initial BD for another experiment that compares two treatment methods for burn wounds. The secondary objective was to validate the findings of a systematic review which attempted to solve the problem of standardization of porcine burn models.

## Materials and Methods

### *Animals*

The experimental study group consisted of 6 four-week-old female Large White x Landrace gilts with aa mean weight of 27.5 kg, supplied through a donation by the Smithfield Ferme company, Timisoara subsidiary, Romania. To adhere to the principles of 3Rs (Replacement, Reduction, Refinement), multiple studies were simultaneously conducted on this particular set of animals. This approach aimed to minimize the requirement for general anesthesia while conducting such studies. The initial study entailed the establishment of an animal model to simulate burns, while the subsequent study aimed to compare an innovative burn treatment with the conventional treatment used in clinical settings. Upon completion of this experiment, the pigs experienced a typical process of maturing into adulthood, at which point they were subjected to another experiment regarding their reproductive system. For that reason, the swine had not yet been euthanized at the date of article submission, but were in the process of preparation for the aforementioned experiments instead.

### *Animal Welfare*

The animals underwent a 10-day acclimatization process, where they were housed in a closed structure with a controlled temperature, all 6 together in a fenced area, provided with concrete floor covered with hay, proper feeding and ad libitum access to water. The polypropylene covering of the housing structure ensured a physiological light/dark cycle. When the experiment commenced, the wounds were covered in bandages, followed by a textile-foam covering and a hydrophobic material to protect the wound from infection and scratching. During the experiment, the animals were kept in single housings, in the above-mentioned structure, with the same accommodation (*Fig. 1A*).

### *Wound Infliction Protocol*

Every burning procedure and tissue harvesting was performed under general anesthesia. For induction ketamine (1 mg/kg) and Sedanol (1 mg/kg) were used, while, for maintenance, isoflurane (2 mg/ml/h with a target concentration of 1%) and O2 (4 l/min). was used. Analgesia was achieved with meloxicam (0.4 mg/kg) (15,16). The animals received two doses of prophylactic antibiotic therapy consisting of a mixture of penicillin and streptomycin solution after the harvesting procedure. Analgesic medication was administered during each intervention, on days 1 and 2 after every procedure, with a total of 3 days of analgesic medication administration (on the day of the procedure plus 2 days after the procedure).

The device used to produce the injuries consisted of a round 2.5 cm diameter copper plate, welded to an aluminum rod with a wooden handle (*Fig. 1B*). The copper plate was heated by contact transfer from a dehorner device. The temperature was controlled with a contact thermometer. When the temperature decreased to 111°C, the thermometer was removed and the burning device was applied to the pig's skin, thus ensuring a contact temperature of 110°C. The aim was to produce a superficial partial thickness burn with the plate heated at 110°C applied for a period of 10 sec (group 10s), and a deep-thickness (DPT) burn with the plate heated to the same temperature but with a period of exposure of 20 sec (group 20s). No stabilizing or pressure control device was used to apply the hot plate. Pressure was applied by the weight of the device. After applying the device, wet gauzes were placed on the wound and refreshed with 50 ml saline solution every 2 min, Subsequently, they were covered with an occlusive dressing and harvested 24 h later.

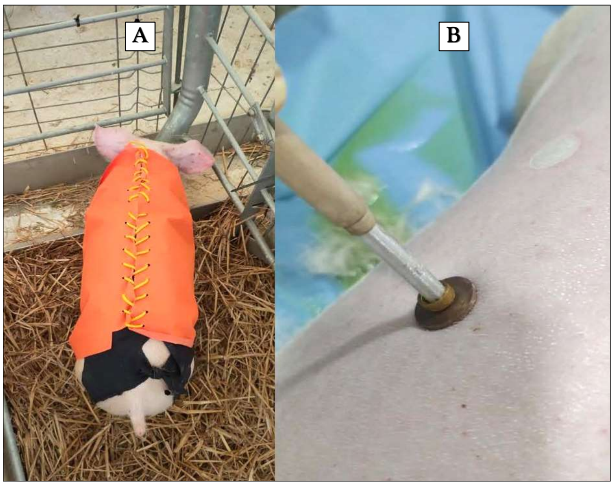


**Figure 1.** **(A)** Animal housing and dressing pattern; **(B)** Copper plate device used to inflict burn wounds

### *Histological Analysis*

The harvested specimens were fixed in 10% formalin and two representative central sections were embedded in paraffin. Sections of 4-µm thickness were cut and stained according to a standard hematoxylin and eosin (H&E) staining protocol (16). The following regents were used: Mayer's hematoxylin (cat. no. 05-06002/L) and eosin Y alcoholic solution (cat.

no. 05-100009/L), both from Bio-Optica Milano Spa.

The resulting slides were then scanned on a Leica Aperio AT2 slide scanner (Leica Biosystems), and morphometric analysis was performed with QuPath v0.5(JASP Team (2024). JASP (Version 0.18.3)[Computer software]) (17).

An experienced pathologist carried out the microscopic evaluation. Seven length measurements regarding primary endpoints, including depth of the dermis (DD), BD and depth of complete collagen denaturation (CDD), were obtained for each sample. Secondary endpoints included length of maximum depth (LMD) and length to maximum depth from the lateral edge of the epidermis (LTMD) (*Fig. 2*). DD was measured from the basal membrane to the dermal-subcutaneous tissue interface, while the length of the burn was measured between the edges of maxim BD. Total collagen was measured as the DD in which all collagen bundles showed full thickness basophilic staining (*Fig. 2*).

The computing of a new percentage variables considered perfected primary endpoints were calculated with the formulas (BD/DD) x 100 and (CDD/DD) x 100, respectively. The data obtained were analyzed with MedCalc® statistical software version 22.021 (MedCalc Software Ltd.) and analyzed with independent samples Welch's t-test and for smaller sample sizes a Mann-Whitney U-test was used.

### *Ethics*

The present study complied with the Declaration of Helsinki and the ARRIVE guidelines for animal studies, and was approved by the Victor Babes University of Medicine and Pharmacy ethics committee (approval no. 61/30.08.2021). Approval to perform this experiment was solicited from the Veterinary and Sanitation General Direction, which operates under the authority of the Environmental Ministry of the Government of Romania (approval no. 012/31.07.2023). The present study was part of first author's doctoral thesis; it was funded by the 'Victor Babes' University of Medicine and Pharmacy (Timisoara, Romania); and was conducted at the 'Regele Mihai I' University of Life Science (Timisoara, Romania)(Grant approved by the University's Administration Council Statement no.13/12190/30.05.2023). The pigs were provided through a donation from the Smithfield Corporation's subsidiary in Timisoara, Romania.

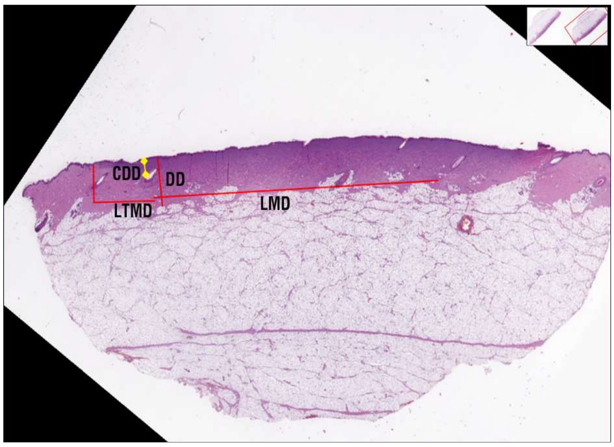


**Figure 2.** Gross representation of the various raw measurements obtained

## Results

The results (*Fig. 3*) showed full-thickness epidermal incipient coagulative necrotic

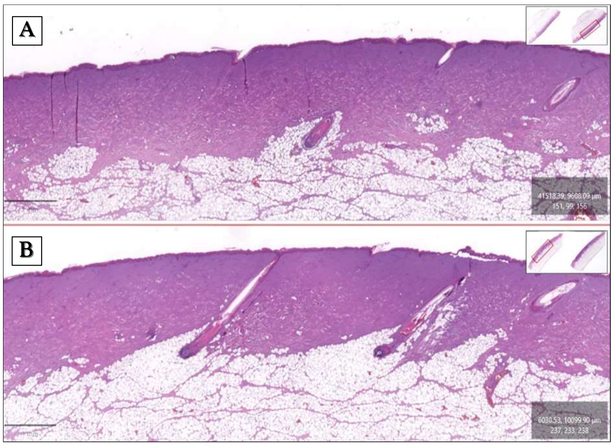


**Figure 3.** **(A)** 10 seconds exposure group; **(B)** 20 seconds exposure group

changes, while in the dermis, the depth progression occurred as a trapezoidal area, with its large base at the epidermal junction. In the dermis, necrosis was observed in all structures, involving skin adnexa, blood vessels and fibroblasts. Collagen denaturation was complete in the superficial part of the dermis, showing full-thickness basophilic change in all collagen bundles. In the deeper dermis, viable eosinophilic collagen fibers were intertwined with denatured basophilic ones. Fat necrosis, sweat gland necrosis and partial denaturation of collagen fibers were found primarily in the 20s exposure group and only in isolated areas in the 10s group. Initial inflammatory changes were identified at the interface of the burned area and healthy skin, including hyperemic blood vessels, edema and inflammatory cell influx.

### *Statistical Analysis*

A total of 77 valid measurements were obtained, out of 84 possible, for each variable. One sample had artefactual detachment of the epidermis prior to paraffin embedding and therefore reliable measurements could not be performed.

To evaluate sampling bias, an independent samples Student's t-test was conducted to assess if there were any differences between the two groups regarding total DD, and a significant difference was found (P<0.01). A mean of 1,800.50 μm [standard deviation (SD)=195.04 μm] for the 10 s group and a mean of 1,646.73 μm (SD=163.22 μm) for the 20s group were observed (*Fig. 4*).

The analysis of raw BD showed statistically significant differences between the two groups (P<0.01), with a mean of 1,522.15 μm (SD = 245.24 μm) for the 10s group and a mean of 2,053.52 μm (SD=389.71 μm) for the 20s group (*Fig. 4*). Next, the depth of total collagen denaturation was compared between the two groups and no statistically significant difference was found (P=0.078). The mean for the 10s group was 385.51 μm (SD=150.97μm), and the mean for the 20 s group was 493.41 μm (SD=322.36 μm) (*Fig. 4*).

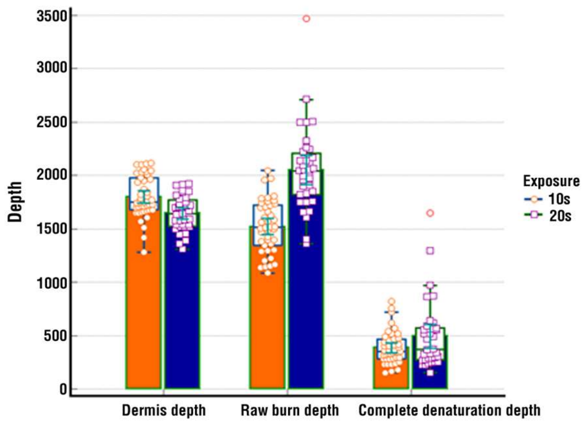


**Figure 4.** Raw measurements of different sample characteristics

Since there was a significant difference between the two groups in regards to DD, two new variables were computed: (Raw BD/DD) x 100 (expressed as %) and (CDD/DD) x 100 (expressed as %). For the BD/DD% formula, the tests showed a statistically significant difference (P<0.01) (*Fig. 5*), with a mean of 85.61% [95% confidence interval (CI)=80.62-90.61] involvement of the dermis for the 10s group and a mean of 123.71% (95% CI=114.91-132.50) involvement for the 20s group.

For the CDD/DD% formula, the results revealed a statistically significant difference between the two groups (P<0.05), with means of 21% (95% CI=18.96-23.49) involvement of the dermis for the 10s group and 30.04% (95%

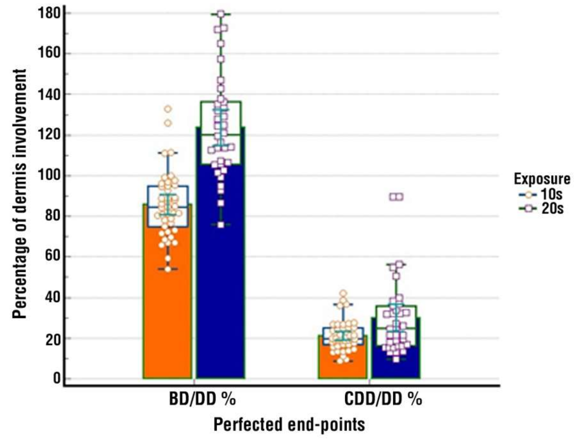


**Figure 5.** Percentage transformation of raw measurements

CI=23.33-36.76) for the 20s group (*Fig. 5*).

Secondary endpoints were LMD involvement and LTMD involvement. For both types of determinations, a single value for each sample was measured, leading to 12 readings for each variable. To compensate for the small sample size, a Mann-Whitney U test was performed.

For LMD (*Fig. 6*), the results showed no statistical difference between the two groups (P=0.79, U=13), and similar results were obtained for LTMD (P=0.08, U=5; *Fig. 7*).

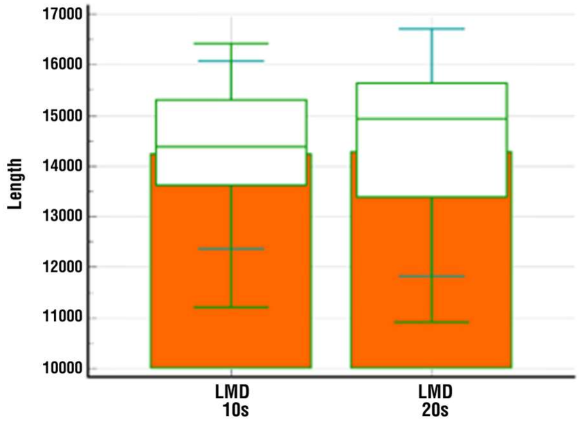


**Figure 6.** Analysis of the length of maximum depth involvement between the two groups

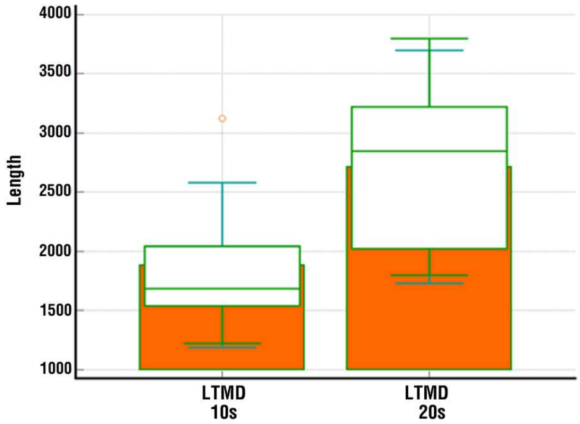


**Figure 7.** Analysis of the length to maximum depth involvement between the two groups

## Discussion

Animal models play a crucial role in burn injury research by providing a platform to replicate burn injuries. While human or humanized models have been employed in certain studies to investigate local events at the injury site, the use of animal models remains essential due to ethical considerations that prevent the development of severe burn injury models in humans (18,19). Animal models offer a way to study burn injuries comprehensively, considering factors such as wound progression, tissue-specific glucose metabolism changes and modulation of post-burn hypermetabolism (20-22).

Standardization is crucial for ensuring the reproducibility and reliability of experimental results. The development of a consistent and reproducible porcine burn model has been advocated to address the variability in burn severity and depth, enabling researchers to compare and validate findings across different studies (23,24). Moreover, the establishment of a standardized burn model using a multi-parametric histological analysis of BD has been proposed to facilitate standardization and comparison within future burn studies, emphasizing the importance of uniformity in burn models (23). The lack of standardization in pig burn models not only affects the internal validity of individual studies but also hinders the translational potential of research findings into clinical applications.

Inconsistencies in burn models may impede the development and evaluation of novel therapeutic interventions, as the variability in experimental conditions may lead to conflicting outcomes and hinder the identification of effective treatments for burn injuries (15,25). Therefore, addressing the standardization of pig burn models is essential for advancing the field of burn research and improving clinical outcomes for patients with burns.

The present pilot study aimed to evaluate the morphological changes when comparing two-time exposures on a porcine model. The burns were produced on a homogenous group of experimental animals, using the standardized protocol of our group for conditions and methods. The sample markers shown in *Fig. 4* revealed limited extreme values or outliers, which was an unexpected result, since our group had not previously employed a standardized device for pressure application. Therefore, there was less interference than originally expected with the experimental outcome.

Previous studies have focused on pressure monitoring during the development of standardized animal models (26,27).It is common knowledge that heat transfer is dictated by the laws of physics, and the progression of heat-induced changes towards deeper parts of the dermis are directly associated with the exposure time and nature of the materials involved in the process. The present data regarding the depth of full collagen denaturation showed that the levels were deeper in the 20-sec exposure group, but not statistically significant, which may appear contradictory at first. However, at this point, an important morphological confounding element was not addressed, namely the inherent variations between the samples caused by the fact that there are variations in the dermis thickness in relation to anatomical site. The 20-sec exposure samples were performed closer to the midline; therefore, the dermis thickness was analyzed. To further understand the present data, a new parameter was we calculated, namely the percentage of affected dermis in each group, and the newly formed data provided an improved image of how the burn time impacted different anatomical sites.

Subsequent analysis of the total collagen denaturation concerning the corresponding DD showed that 20 sec of exposure increased the percentage of dermis affected by almost 50% compared to 10 sec of exposure. According to the current analyses, 10-sec exposure produced effects that were visible in ≤ 85.61% of the dermis in the recorded samples, while 20-sec exposure produced thermal effects far beyond the dermal-subcutaneous tissue border. Thus, the majority of samples in the 10s group could be considered deep partial thickness burns, while the majority of samples in the 20s group should be regarded as full-thickness burns.

Total collagen denaturation depth is a critical factor in burn studies, and it is closely linked to burn severity (28,29). In the present study, there was no significant difference in the depth of total collagen denaturation across the two groups. Since this was possibly not the best way of assessing the experimental end-point, total collagen denaturation in respect to the corresponding DD was assessed instead, and it was found that 20 sec of exposure increased the percentage of dermis affected by almost 50% compared to 10 sec of exposure.

Despite certain samples from the 10s group could be considered full-thickness burns, there is currently no histological cut-off value for depth or extent of the burn in subcutaneous tissue that could help the surgeon in assessing clinical response to treatment. Therefore, the involvement of subcutaneous tissue in the categorization of patients needing a more radical treatment needs to be further investigated.

The limitations of the present study include the relatively small sample size, since only one pathologist examined the histological samples and only H&E staining was conducted in the samples without immunohistochemical analysis, which would have allowed a more in-depth assessment.

## Conclusion

In conclusion, even without a standardized pressure application device, the present study was able to produce DPT burns using 10-sec exposure and FT (full thickness) burns by prolonging the exposure to 20 sec. The mean values reported for temperature and exposure time were supposed to produce a superficial and a deep partial thickness burn, respectively; however, the current results showed deeper penetration of the thermal agent.

### *Acknowledgements*

We would like to acknowledge Victor Babes University of Medicine and Pharmacy Timisoara for their support in covering the costs of publication for this research paper.

## Author's Contributions

Conceptualization, BC and AV; Data curation, VLD, DP and BC; Formal analysis, AV and DGB; Investigation, AV, and IH; Methodology, BC; Project administration, BC and ESB; Software, FGH; Supervision, VLD and ESB; Validation, AV, VLD and IH; Visualization, DP and ESB ; Writing – original draft, BC and IH; Writing – review & editing, AV and VLD All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflicts of interest


## Funding

This experiment was funded by the Victor Babes University of Medicine and Pharmacy, 300002 Timisoara, Romania. The pigs were provided through a donation from the Smithfield Corporation's subsidiary in Timisoara, Romania (Grant approved by the University's Administration Council Statement no.13/12190/30.05.2023).


## Institutional Review Board Statement

The study complied with the Helsinki and ARRIVE guidelines for animal experimental studies and was approved by the University's Ethics Committee (61/30.08.2021). Approval was solicited from the Veterinary Authority of Romania, which operates under the authority of the Government of Romania (012/31.07.2023) to perform this experiment.

## Data Availability Statement

Data available on request from the corresponding author.

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