BURNS 45 (2019) 1102–1111

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/burns

An effective procedure for skin stiffness measurement to improve Paediatric Burn Care

Julia Elrod [a,1], Bettina Müller [b,1], Christoph Mohr [a], Martin Meuli [a], Edoardo Mazza [b,c], Clemens Schiestl [a,*]

[a] Pediatric Burn Center, Division of Plastic and Reconstructive Surgery, University Children's Hospital Zurich, Steinwiesstrasse 75, 8032 Zurich, Switzerland

[b] Institute for Mechanical Systems, Department of Mechanical and Process Engineering, ETH Zurich, Leonhardstrasse 21, 8092 Zurich, Switzerland

[c] Empa, Swiss Federal Laboratories for Materials Science and Technology, Dübendorf, Switzerland

ARTICLE INFO

Article history:
Accepted 7 February 2019

Keywords:
Paediatric
Burn
Scar
Stiffness
Cutometer
Nimble

ABSTRACT

Background: The objective evaluation of scar quality plays a crucial role in improving burn surgery and scar rehabilitation. Suction-based skin measurements were proposed as a method to objectively determine the mechanical properties of scars, yet their use is limited, in particular for paediatric burn care. A new device was developed which provides essential advantages for scar assessment. The aim of this study was to assess its reliability, intra- and interobserver variability.

Methods: The new device, "Nimble", consists of a lightweight probe that measures the negative pressure needed to obtain a predefined tissue elevation, revealing information on the stiffness of the tissue. 29 former paediatric burn patients were included. Three observers measured the tissue stiffness of a predefined location on the scar and on healthy skin using the *Nimble*, and the established suction device, the Cutometer®. The reliability of both instruments in distinguishing between healthy skin and scar was assessed by means of the intraclass correlation coefficient.

Results: The *Nimble* successfully differentiated between scar tissue and healthy skin in 92%, the Cutometer in 80% of the patients ($p < 0.05$). Inter- and intraobserver variability of the *Nimble* (ICCs) were excellent. For the majority of the calculated ICC values the *Nimble* exceeded the Cutometer®.

Conclusion: The new device enables reliable and safe measurement of the stiffness of scars. Measurements are less susceptible to patient non-compliance and observer dependency. The *Nimble* might therefore constitute an easy to use tool for the systematic assessment of scars, thus supporting decision-making in paediatric burn care.

* *Corresponding author.*
E-mail addresses: julia.elrod@kispi.uzh.ch (J. Elrod), mueller@imes.mavt.ethz.ch (B. Müller), christoph.mohr@kispi.uzh.ch (C. Mohr), martin.meuli@kispi.uzh.ch (M. Meuli), mazza@imes.mavt.ethz.ch (E. Mazza), clemens.schiestl@kispi.uzh.ch (C. Schiestl).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.burns.2019.02.004
0305-4179/

1. Introduction

Despite tremendous efforts in prevention, burns remain a global public health problem. However, thanks to advances in critical care and surgical management, mortality has decreased in the last decades [1,2]. Yet, non-fatal deep dermal or full thickness burns often have long term consequences, such as functional and aesthetic insufficiencies like disability and disfigurement [3]. The paediatric population is affected most because scars tend not to grow along with the patient.

The prevention of the formation of hypertrophic scars is approached by developing sophisticated surgical techniques, for example through advanced methods of skin transplantation, such as dermal regeneration templates [4–6], or by growing dermo-epidermal skin substitutes. However, most elaborate surgical techniques are expensive and tend to be accompanied by a considerably longer treatment phase [7–10]. Another widely used approach to impede scar formation and for scar treatment are non-surgical techniques, such as silicone ointment, pressure garments or CO2-ablative laser treatment. However, these methods are expensive and can also be demanding for patients and families [11,12]. Furthermore, there is no treatment that results in the complete resolution of hypertrophic scars. Evidence is rather poor and contradictory for most of these therapeutic options [13–17]. A recent Cochrane Report [18], on the effects of silicone gels and a review of randomized controlled studies by Friedstat [19] demonstrates the need for standardized outcome variables in order to enable scientific comparison. This outcome variable should be highly sensitive, reproducible and valid as to enable the objective evaluation of scars and the critical examination of their therapy. Biomechanical properties have been proposed as a promising assessment criterion [20,21] as they are related to tissue function and depend on the specific conditions of the extracellular matrix. Many devices have been developed to determine the mechanical behaviour of skin such as the DermaScan C®, the Cutometer® MPA 580 and the Mexameter®, but their informative qualities are partly limited by their intra- and interobserver variability, in particular for scars [20,22,23]. The Cutometer®, which uses a suction-based characterization of tissue, is one of the most widely-used devices for the assessment of burn scars. Good reliability has been demonstrated on both normal skin [24] and on scars [21,25,26]. This device, however, is not ideally suited to paediatric burn care. In fact, its dimensions and weight make it difficult to precisely control its position on the skin as well as the compression force exerted at the contact point while measuring, see Fig. 1. Recent studies [27,28] have demonstrated a notable influence of contact force on the measured mechanical parameters, possibly affecting the reliability of the test. The resulting pre-deformation of the skin may be particularly large in the highly compliant skin of young children. Müller et al. [27] also showed, that measurements can be severely affected by patients' movements. This might limit their applicability in the paediatric population. The Cutometer® and other commercially available suction devices require specific cleaning, they can only be disinfected by wiping, and cannot be sterilized due to their sensitive optical and electronic components, further limiting their usefulness in clinical work.

A new suction device, "Nimble", developed at ETH Zurich, might provide essential advantages for an effective evaluation of scars. The small dimensions and ultra-low weight (3.5 g) make it particularly suitable for paediatric use, see Fig. 1. Control of its position and its contact interaction with the skin surface is simpler. Its mechanics – a so-called "displacement controlled" mechanical test makes it intrinsically safer for application on fragile tissue, than the pressure-driven "force controlled" suction devices. Furthermore, all components in contact with the patient are made of inexpensive parts and are thus disposable. A recent study [27] has demonstrated that the *Nimble* allows accurate characterization of the mechanical response of healthy skin in adults. Altogether, this evidence motivated the present investigation to assess the safety, reliability, validity and usability of the *Nimble* for assessing paediatric burn scars. Specifically, this study aimed at determining the ability of the new device to distinguish between normal skin and scar, and at quantifying the corresponding intra- and interobserver variability. For comparison, measurements were also performed with the Cutometer®. The long-term goal is to develop a tool that allows for objective assessment of scar maturation, that helps to guide surgical decision making in the future and that enables a critical review the efficacy of scar therapies.

An interventional study was conducted at the University Children's Hospital in Zurich. Ethical approval was obtained from the local ethics committee (Kantonale Ethikkommission Zurich, KEK-ZH-Nr. 2017-02015) and from the Swiss Agency for

Fig. 1 – Exemplary assessment of scar stiffness in a small child. Tissue stiffness is measured on a predefined location (a) with the Cutometer® (b) and the Nimble (c) in a 28-month-old child. The images demonstrate facilitated handling and positioning of the Nimble on small and strongly heterogeneous scars in young patients. Conversely, precise relocation of the Cutometer is considerably more difficult due to its large size.

Therapeutic Products (Swissmedic, 2017-MD_0039). After written consent was obtained, 29 paediatric patients with a history of a burn or scald underwent repetitive measurements of skin stiffness using both devices, carried out by three blinded observers, on scars and on corresponding areas of unaffected skin.

2. Methods

Skin stiffness was measured with the investigational aspiration device, *Nimble*, and with the aspiration device, Cutometer® (Courage and Khazaka Electronic GmbH).

2.1. *Investigational device "Nimble"*

The investigational device is a suction device with a lightweight probe, aimed at improving the control of contact conditions during suction measurements. The design is based on a previous instrument, the Aspiration device, developed for biomechanical characterization of the uterine cervix during pregnancy and used trans-vaginally for over 1000 measurements on pregnant women [29–31]. The new apparatus was optimized in order to achieve an easy-to-use ultra-lightweight suction instrument. The device consists of a circular probe (6mm opening) connected to a pump. Negative pressure draws the skin into the probe up to a certain height (h=0.5mm). The pressure necessary to reach 0.5mm is recorded and referred to as the closing pressure *pcl*. From this, the tissue stiffness k (mbar/mm) is calculated as follows:

$$k^{nimble} = \frac{p_{cl}}{h} = \frac{p_{cl}}{0.5\,\mathrm{mm}}$$

The time required for a measurement typically varied from 2–15s, depending on the *pcl*. Further technical details on the device and protocol are documented in27. After each measurement, all components in contact with the patient were plasma sterilized.

2.2. *Cutometer® dual MPA 580*

The Cutometer® with its 6mm aspiration probe was used for comparison [21]. In contrast to the *Nimble*, the Cutometer® is pressure controlled, i.e. a predefined negative pressure is generated, resulting in tissue deformation and leading to a certain elevation of the skin that depends on the specific skin properties. In this study, the ramp load (Mode 2) was set to 15mbar/s and a maximum suction pressure of p_{max}=250mbar was applied. This led to a measurement duration of 34s. The elevation height, in response to p_{max} can be extracted, referred to as *R*0. Several other parameters can be extracted from the readings but prior studies [25,26] have indicated that the value of R0 is sufficient to characterize skin tissue [22,32]. In order to facilitate comparison with the *Nimble*, the corresponding tissue stiffness k^{R0} (mbar/mm) was calculated:

$$k^{R0} = \frac{p_{max}}{R0} = \frac{250\,\mathrm{mbar}}{R0}$$

As mentioned before, placing the probe (weight 165g) on the skin leads to a certain pre-deformation of the tissue [27] even before applying the negative pressure. This pre-deformation was recorded by the Cutometer® software for each measurement and referred to as *Offset*. After each measurement the inside of the probe was cleaned with a small brush and designated disinfectant [33].

2.3. *Measurement procedure*

The recruitment of patients with a history of deep dermal or full thickness burns, ≥1 month and ≤10years, was performed by the investigator. In a total of 29 patients, three independent observers measured the skin stiffness as follows: First, a measuring point on the scar was determined in a standardized manner (location 2), see Fig. 2, left side; next, a measuring point on the corresponding normal (uninjured) skin was determined, located either adjacent to the scar (see Fig. 2, left side) or on the contralateral side of the body (location 1), see Fig. 2,

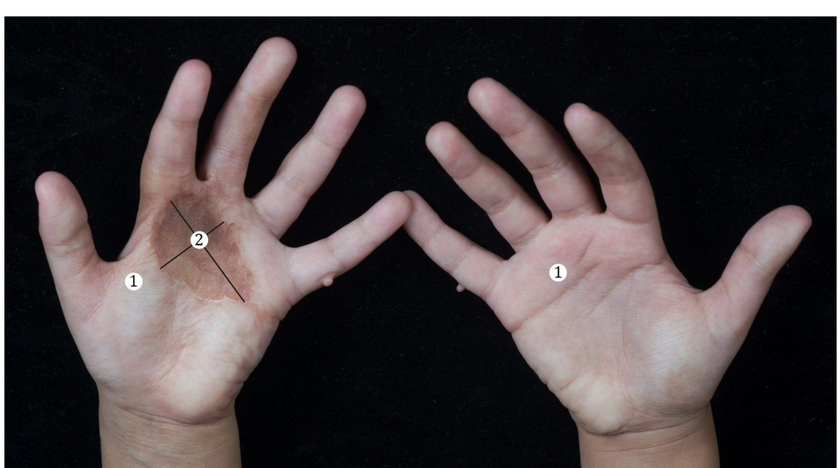

Fig. 2 – Allocation of the points 1 (healthy skin) and 2 (scar). Point 1 is either positioned on the contralateral side (a) or on the adjacent healthy skin (b), adapted from Ref. [34].

right side [34–36]. The first observer placed the *Nimble* on location 1 and location 2 alternately. A pause of at least 30 seconds was guaranteed between two measurements at the same location, thus avoiding measurement-induced alterations of the mechanical properties of the skin as shown in Refs. [37,38]. Measurements were repeated three times at each location. For each measurement, the tissue stiffness values were generated. Next, the same observer repeated the same measurements using the Cutometer®. Subsequently, the second and third observers (blinded from each other) repeated the same procedure at the marked locations.

Offsets (pre-deformation) of the Cutometer® were always recorded. The relative stiffness of scars (q^N and q^C, for *Nimble* and Cutometer® respectively) was determined by dividing the stiffness of the scar (k_{SCAR}) by the stiffness of the corresponding healthy skin ($k_{HEALTHY}$).

The patients were asked to rate the pain on a visual analogue scale (0=worst pain imaginable, 100=no pain) unless the patient was too young.

2.4. Statistical analysis

Statistical analysis was performed using the python library scipy.stats (Python Software Foundation). Results were plotted in a descriptive manner, means and standard deviations were calculated. The reliability to discriminate between different tissues was determined with a two-sided t-test (stats.ttest-ind), with a level of significance $p<0.05$, and by means of an intraclass correlation coefficient ICC(2,1) and ICC(2,k), class 2 ICCs, where each observer evaluated all patients. The ICC(2,1) is based on a random single measurement of one observer and the ICC(2,k) is based on the measurements averaged over three observers. Inter- and intraobserver variability were examined by means of the ICC (2,1). For interobserver calculations, the respective average of the three repetitions of each observer was calculated, providing a single value per observer per patient, whereas each of the three repetitions per patient was used for the intraobserver calculations.

3. Results

3.1. Patients and operability

29 patients participated. In three patients, measurements could not be completed due to significant non-compliance or technical difficulties, resulting in 26 evaluable patients (see Table 1). Upon injury mean age was 5 years (range 9 months–14 years). Measurements were conducted at a mean of 3 years (range 4 months to 14 years) after the injury, resulting in a mean age of the patient upon measurement of 9 years (range 2 years–18 years).

Mean TBSA was 13% (range: 1–55%). 28% (n=8) were scalds and 72% (n=21) were burn injuries. 28% (n=8) had been treated conservatively, 62% (n=18) had undergone split thickness skin transplantation and 7% (n=2) transplantation of full thickness skin at the site of measurement, as reported in Table 1. This resulted in a heterogeneous group of scars, including hypertrophic, eutrophic and hypotrophic ones. Keloids however were not included into the investigation.

Table 1 – Study participants and characteristics of burned areas.

Characteristics	Participants n=29 (100%)
Gender: female (%)	11 (38%)
Mean age of patient at time of injury (range)	5 years (9 months–14 years)
Race	
Black	7 (24%)
Caucasian	20 (69%)
Asian	2 (7%)
Mean age of patient on day of measurement (range)	9 years (2 years–18 years)
0–3 years	4
4–9 years	13
10–18 years	12
Mean age of scar on day of measurement (range)	3 years (4 months–14 years)
0–3 years	19
4–9 years	8
10–18 years	2
Etiology (%)	
Scald	8 (28%)
Flame	21 (72%)
Scar location	
Upper extremity	13 (45%)
Lower extremity	2 (7%)
Hand or foot	7 (24%)
Head or neck	2 (7%)
Trunk	5 (17%)
Treatment of measuring site	
Conservative	8 (28%)
STSG	18 (62%)
FTSG	2 (7%)

No safety issues or adverse events arose during the course of the study. None of the patients indicated any pain; a few children indicated only a slight tickling feeling.

3.2. Tissue stiffness of healthy skin and of scars

Measurements of the stiffness of the healthy skin (H) and scar tissue (S) were conducted by three investigators in triplicates with the *Nimble* (N^H and N^S) and the Cutometer® (C^H and C^S) for each of the 26 evaluable patients. The average over all three observers and repetitive measurements for each patient is shown in Fig. 3.

The overall mean tissue stiffness and SD for healthy skin with the *Nimble* are $\overline{N^H}=48.53\pm23.67$ mbar/mm and $\overline{C^H}=234.19\pm73.73$ mbar/mm for the Cutometer®. Mean stiffness for scars was $\overline{N^S}=108.44\pm114.46$ mbar/mm for the *Nimble* and $\overline{C^S}=423.52\pm201.27$ mbar/mm for the Cutometer® respectively.

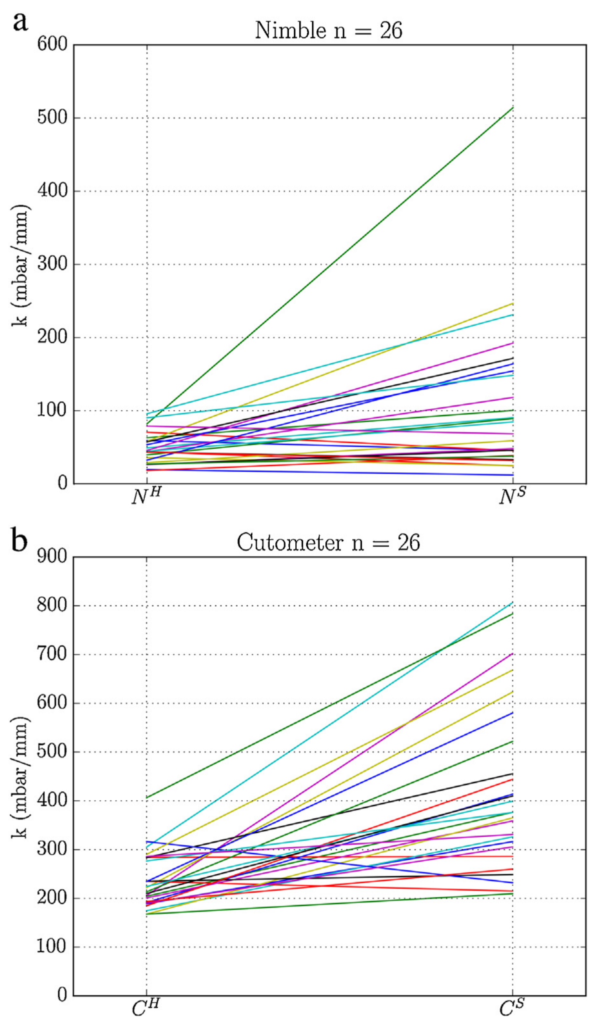

Fig. 3 – Tissue stiffness measured by Nimble and by Cutometer®. Measurements are conducted by three independent observers in triplicates each and the mean tissue stiffness (k) over all observers and repeated measurements of each of the 26 patients is indicated for healthy skin (left) and for scars (right), whereby Nimble values (N^H, N^S) are shown in (a) and Cutometer® values (C^H, C^S) are shown in (b).

3.3. *Ability to discriminate between healthy skin and scars*

In order to enhance comparability and because the skin stiffness values obtained with the two instruments differ notably, the analysis was performed based on relative skin stiffness (q^N and q^C). Data show that scars tend to be stiffer than healthy skin (q^N=2.20 fold±1.50 for *Nimble* and q^C=1.88 fold ±0.65 for Cutometer®). Yet, some scars resulted in less stiffness than the corresponding healthy skin. The reliability of the devices in distinguishing between both tissue types was assessed by means of ICC. With an ICC(2,1) of 0.98 the *Nimble* has an outstanding ability to distinguish tissue types. The same is true for the Cutometer®, (ICC(2,1)=0.99).

Fig. 4 depicts the quotients *q* for each of the 26 patients. The *Nimble* values reveal the scar to be statistically stiffer in 18 cases (69%) and less stiff than normal skin in 6 cases (23%). The Cutometer® reveals a statistically significant higher stiffness of the scar in 20 cases (76%) and a lower stiffness in 1 scar (4%).

3.4. *Interobserver and intraobserver variability*

Interobserver variability was examined by means of ICC(2,1) and ICC(2,k) (see Table 2) for both skin conditions separately. For this purpose, the mean values of the tissue stiffness of one location, measured in triplicate by each observer, were calculated. The *Nimble* provides excellent [39] values of ICC (2,1) as well as ICC(2,k) for both, healthy skin and scar. The Cutometer® had a fair ICC(2,1) for healthy skin and an excellent one for scars. The Cutometer® ICC(2,k) was excellent for both skin conditions.

Intraobserver variability was calculated separately for each observer (see Table 3). The average over all three observers of the ICC(2,1) values for the *Nimble* were excellent for both skin conditions. The Cutometer® resulted in good overall intraobserver variability. The ICC(2,k) was excellent for both devices, all observers and skin conditions.

3.5. *Comparative analysis of both devices*

As analysed in Ref. [27], a direct comparison of the Cutometer® and *Nimble* in terms of measured stiffness values is impaired because the tissue elevations induced by the Cutometer® measurements are much larger than those of the *Nimble*, as shown in Fig. 5. The maximum Cutometer® elevation is up to three times larger than the *Nimble* elevation.

Of note, the maximum elevation of the Cutometer® is composed of the sum of the pre-deformation, induced due to probe placement, and the R0 value, which is the additional elevation of the skin once the negative pressure of the Cutometer® is applied. Fig. 5 illustrates well, that the pre-deformation of the Cutometer® is in a similar range as the *Nimble* maximum elevation.

In order to evaluate the correlation among the stiffness values measured with the *Nimble* and the Cutometer®, the Pearson's correlation coefficient was calculated for the mean stiffness of healthy skin (Table 4). The correlation between k^{nimble} and k^{R0} is weak for healthy skin. This confirms the finding from [27], where r– values obtained for measurements with the *Nimble* and the Cutometer® on the healthy skin of adults are similar to the present values. The Pearson's coefficient between q^N and q^C demonstrates a stronger correlation as compared to the stiffness values, see Table 4. This indicates that differences between healthy and scar tissue affect the mechanical response to both, small and large deformations, although to a different extent for different patients. In Ref. [27] a correction scheme was proposed to reduce the influence of the pre-deformation in the Cutometer® measurements. According to the definition in Ref. [27] a corresponding corrected stiffness parameter ($k^{cuto}{}_{corr}$ (h=1mm), for a tissue elevation of 1mm) was now calculated. Interestingly, the correlation improved significantly, and the r – value (r=0.62) was comparable to the one found in [27] (r=0.66).

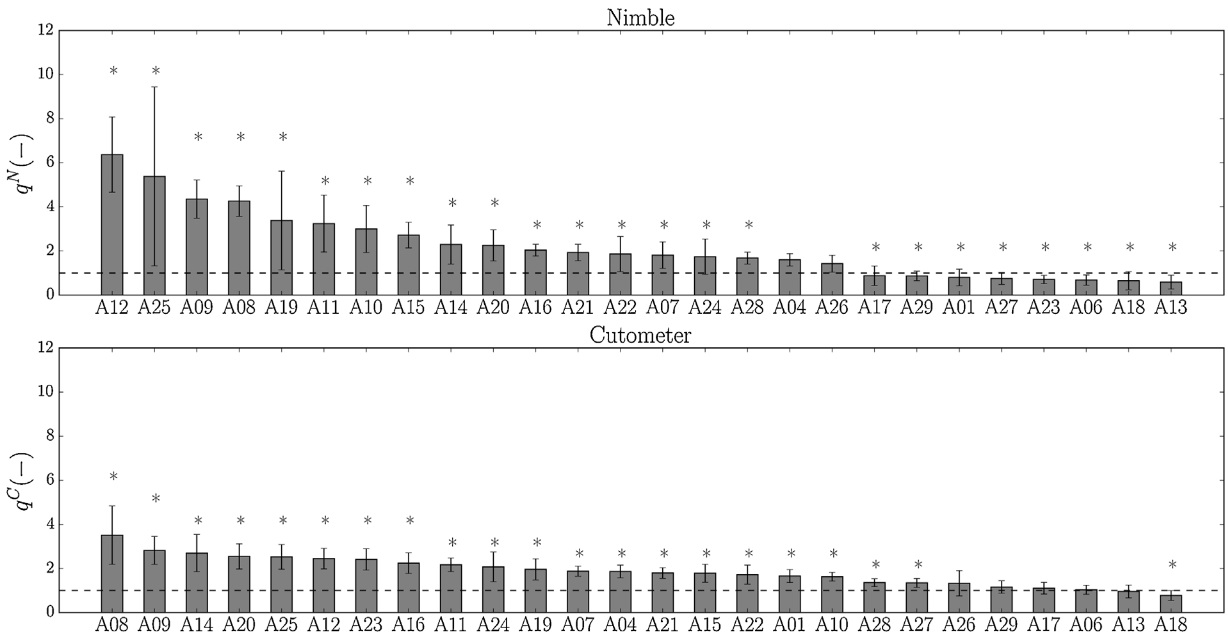

Fig. 4 – Relative tissue stiffness (q^N and q^C) as measured by Nimble and Cutometer®. Measurements are conducted by three independent observers in triplicates each. Relative tissue stiffness is determined by calculating the quotient of the according scar stiffness and the respective healthy skin. Results depicted separately for each of the 26 subjects, mean and SD indicated. Dashed line indicates a quotient of 1 implying healthy tissue and scar to be equally stiff. Statistically significant difference between scar and healthy skin is indicated for each patient with *. This is the case for 24 patients (92%) for the Nimble and 21 patients (80%) for the Cutometer®.

Table 2 – Interobserver variability assessed by means of ICC (2,1) and ICC (2,k).

Interobserver variability – ICC	HEALTHY		SCAR	
	Nimble	Cutometer®	*Nimble*	Cutometer®
ICC(2,1)	0.88	0.56	0.87	0.75
ICC(2,k)	0.95	0.79	0.95	0.90

4. Discussion

4.1. *Patients and operability*

The 29 patients in the study resulted in 26 evaluable subjects, i.e. only 3 cases of patient non-compliance or a technical difficulty. The former was due to age-appropriate non-compliance in 2 toddlers. When defining the inclusion criteria for this clinical trial, children as young as 2 years of age were included to ensure realistic diagnostic conditions, allowing feasibility to be tested.

The safety of *Nimble* measurements was confirmed as no pain or irritation was reported in the 468 measurements performed in the present study. Because the aspiration probe of the *Nimble* consists of robust and inexpensive components, it can be used as a disposable probe or can be plasma sterilized. Conversely, the Cutometer® probe, including a fragile optical measurement system, can merely be wiped with a disinfectant and cleaned internally with a small brush. This might limit its use with chronic wounds and emerging multi-resistant germs, where disposable or sterilisable devices might be indispensable

The main advantage of the *Nimble*'s small probe is the ability to position the device precisely on the area of interest and with negligible contact force, see Fig. 1.

Table 3 – Intraobserver variability was determined by means of ICC (2,1) and ICC (2,k).

Intraobserver variability – ICC	HEALTHY						SCAR					
	Nimble			Cutometer®			*Nimble*			Cutometer®		
Observer	O1	O2	O3	O1	O2	O3	O1	O2	O3	O1	O2	O3
ICC(2,1)	0.77	0.70	0.84	0.61	0.70	0.82	0.92	0.80	0.95	0.53	0.84	0.88
ICC(2,k)	0.91	0.88	0.94	0.82	0.87	0.93	0.97	0.92	0.98	0.77	0.94	0.96

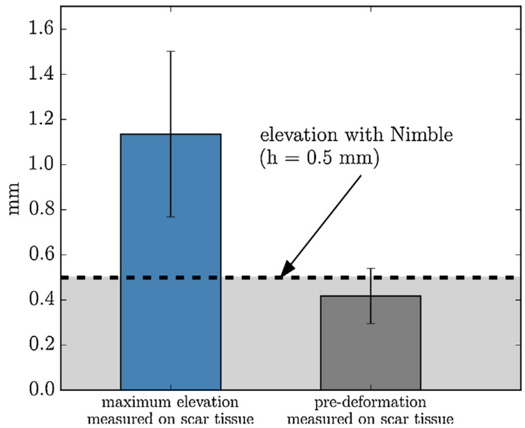

Fig. 5 – Maximum elevation of scar tissue (left bar) with the Cutometer® and according pre-deformation (right bar) (mean and SD indicated). The maximum elevation is composed of the sum of the pre-deformation, which is induced when the Cutometer® is placed on the skin, and the R0 value, which is achieved once the negative pressure of the Cutometer® is applied. The pre-deformation is shown separately. The horizontal dashed line indicates the maximum elevation of the Nimble. Importantly, the latter is only slightly higher than the mean pre-deformation generated with the Cutometer®.

Table 4 – Pearson's correlation coefficient between stiffness measured with Nimble and Cutometer® (corrected and non corrected) for healthy skin measured on 26 patients.

Pearson's correlation coefficient						
		k^{R0}		q^{C}		k^{cuto}_{corr}
r	k^{nimble}	0.18	q^{N}	0.56	k^{nimble}	0.62
p		1.07E-02		9.71E-08		1.69E-09

Finally, due to its small size and light weight, the *Nimble* moves along with the child's movements. Within limits [27], the outcome is not significantly affected by these movements. This is of paramount importance when dealing with children.

4.2. *Absolute tissue stiffness of healthy skin and of scars*

Since the Cutometer® operates load controlled whereas the *Nimble* operates displacement controlled, the level of elevation at p_{max}=250 mbar for Cutometer® and h=0.5 mm for *Nimble* diverge, as shown in Fig. 5. This data confirms that the two devices interrogate the tissue for different levels of deformation, see Fig. 3. As a consequence, they provide very different stiffness values.

The present mean values of tissue stiffness in healthy skin are not far from the average stiffness reported in the recently published study [27] on healthy adults in which two subjects were measured on different regions by three observers.

As expected, the average stiffness for scars is considerably higher than the stiffness of healthy skin for both devices. Both devices exhibit a high standard deviation. This high value is related to aggregating data from 26 patients with very disparate scars in terms of patient demographics, scar characteristics and clinical data. Large differences in measured stiffness among the whole population indicates the ability of the device to distinguish between distinct tissue conditions.

4.3. *Reliability in discriminating between healthy skin and scars*

As a primary outcome of the present study, the *Nimble* was shown to reliably distinguish between healthy skin and scars. Its ICC value was very high (ICC=0.98) and it discerned between healthy and scar tissue in 92% of the cases, similar to the performance of the Cutometer®. Large differences in measured k_{SCAR} values indicate that scars in different patients have very distinct tissue conditions and are, in some cases, softer than their corresponding healthy adjacent or contralateral control values. This finding is in line with the clinical impression of scar stiffness. For example, A18 is a 22-month-old scar in the area of the temple that appears rather soft, floppy and parchment-like.

4.4. *Interobserver and intraobserver variability*

The second outcome parameters of the study were the inter- and intraobserver variability of the new device. With high ICC(2,1) and ICC(2,k) values, the *Nimble* demonstrated excellent inter- and intraobserver repeatability for both healthy skin and scars. The present ICC values are in line with those reported for healthy skin of adults in Ref. [27]. The inter- and intraobserver variability of the *Nimble* is comparable to that of the Cutometer® and is in line with other devices used for the determination of viscoelastic parameters of skin [20], such as the DermaLab® [40] and the tissue Tonometer [41,42].

The interobserver variability of the Cutometer® was higher for healthy skin than for scars. A possible explanation is that healthy skin is more susceptible to pre-deformation (*Offset*) due to the weight of the probe applied to the tissue [27,28] (Fig. 5). Our finding is in contrast with Draaijers et al. [25], reporting a lower reliability for scars than for normal skin, suggesting that this could result from the lower deformation created in (stiff) scars than in less stiff healthy skin, which could then lead to a comparatively high error due to the relatively low resolution. The Nedelec et al. [22] intrapatient controlled study, which assessed tissue stiffness in several areas within one scar (clinically appearing more and less hypertrophic) and in healthy skin, found an equally high ICC of 0.89 for normal skin and for areas with less severe scarring. Note, however, that this paper reports a lower ICC of 0.56 in areas of very severe scarring. Fong et al. [26] estimated the ICC (2,1) to be 0.78 in 108 measurements from 12 scars assessed by the Cutometer®, in line with the present values. Yet, unlike our study, none of the above-mentioned studies included (young) children, who have a negative effect on accuracy due to their inability to sit still. Generally speaking, as opposed to the *Nimble*, the interobserver variability of the Cutometer® is negatively affected both in healthy tissue and in scars, by the difficulty of ensuring uniform handling, such as the force applied to the skin.

Intraobserver reliability was good or excellent, yet the Cutometer® again was slightly inferior to the *Nimble* for scars and for healthy skin, and also somewhat worse for healthy skin than for scars. Nedelec et al. [23] reported an intraobserver ICC(3,1) of 0.81 for healthy skin while the values for scars were lower than in the present study, with 0.62 for less severe scars and 0.12 for the most severe scars. It seems reasonable to assume that the scars assessed in the present study are most comparable to the less severe scars in Nedelec et al. [23], since the latter measured significantly younger scars, which are in a period of supreme hypertrophy/stiffness. Intraobserver reliability is affected, inter alia, by the difficulty of locating the exact same (marked) area during repeated measurements. The *Nimble* can be relocated precisely due to its small size; the Cutometer® is considerably larger, complicating this matter. In the case of heterogeneous scars, relocation can have a major impact on the tissue stiffness measured [22].

4.5. *Comparative analysis of both devices*

The devices characterize different properties of the mechanical response of skin, with the Cutometer® being associated with larger tissue deformation than the *Nimble*. As shown in Fig. 5, the maximum elevation achieved in *Nimble* measurements is in the same range as the pre-deformation in Cutometer® measurements. Thus, the pre-deformation, resulting from the uncontrolled magnitude of the contact force, has an effect comparable to the total tissue elevation applied in *Nimble* measurements. The detrimental effect of the pre-deformation is confirmed by the fact that the correlation between stiffness values measured by *Nimble* and Cutometer® improves significantly if the correction scheme from Ref. [27] is applied, introduced as a means to compensate for the effect of the variable contact force and the resulting pre-deformation.

4.6. *Limitations*

The main shortcoming of the present trial is the small sample size in combination with heterogeneous scars in terms of injury characteristics and demographics. At the same time, this heterogeneous group of patients is a strength– young children were included intentionally because this study was aimed at evaluating the capability of the *Nimble* to distinguish stiffness of healthy skin and scars in a representative, real-life cohort.

A large number of repetitions, choosing more measuring sites per scar and/or increasing the number of observers would also improve the informative value of this study, especially in heterogeneous scars, helping to capture the actual conditions of the scar. However, these optimisations would lead to an even longer measuring time, which is not realistic for the young patients.

5. Conclusion

The data obtained in the present clinical study demonstrates well that the *Nimble* measurements of the stiffness of healthy skin and scars of paediatric patients are reliable. The intra- and interobserver variability of the *Nimble* is generally better than that of the present Cutometer® measurements. Along with several advantages associated with its lightweight and small dimensions, and its usability as disposable device, these results indicate that the *Nimble* might offer a viable solution for scar monitoring in paediatric burn care.

Competing interests

Coauthor Edoardo Mazza is coinventor of the related technology, explained in the patent: Aspiration Device and Method for Determining Viscoelastic Properties of Biological Tissues and Synthetic Materials, EP16197195.7. The patent is filed but not yet granted.

Financial disclosure

This project is supported by grants from “Helmut Horten Stiftung”. Funding was received by EM and BM.

The project also received financial support from the “Forschungsfond” of the University Children’s Hospital.

Neither of the funders had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Clinical trial registration

DRKS-ID: DRKS00014031; German Clinical Trials Register (DRKS); www.drks.de.

Acknowledgments

“This project is supported by grants from “Helmut Horten Stiftung”. This work was conducted as part of the SKINTEGRITY flagship project of University Medicine Zurich (http://www.hochschulmedizin.uzh.ch/en/projekte/skintegrity.html).”

REFERENCES

[1] Bloemsma GC, Dokter J, Boxma H, Oen IM. Mortality and causes of death in a burn centre. Burns 2008;34(8):1103–7, doi:http://dx.doi.org/10.1016/j.burns.2008.02.010.

[2] Herndon DN, Spies M. Modern burn care. Semin Pediatr Surg 2001;10(1):28–31, doi:http://dx.doi.org/10.1053/spsu.2001.19389.

[3] Peck MD. Epidemiology of burns throughout the world. Part I: distribution and risk factors. Burns 2011;37(7):1087–100, doi:http://dx.doi.org/10.1016/j.burns.2011.06.005.

[4] Rowan MP, Cancio LC, Elster EA, Burmeister DM, Rose LF, Natesan S, et al. Burn wound healing and treatment: review and advancements. Crit Care 2015;19(1):243, doi:http://dx.doi.org/10.1186/s13054-015-0961-2.

[5] Stiefel D, Schiestl C, Meuli M. Integra Artificial Skin® for burn scar revision in adolescents and children. Burns 2010;36(1):114–20, doi:http://dx.doi.org/10.1016/j.burns.2009.02.023.

[6] Schneider J, Biedermann T, Widmer D, Montano I, Meuli M, Reichmann E, et al. Matriderm® versus Integra®: a comparative experimental study. Burns 2009;35(1):51–7, doi:http://dx.doi.org/10.1016/j.burns.2008.07.018.

[7] Nyame TT, Chiang HA, Leavitt T, Ozambela M, Orgill DP. Tissue-engineered skin substitutes. Plast Reconstr Surg 2015;136(6):1379–88, doi:http://dx.doi.org/10.1097/PRS.0000000000001748.
[8] Sheridan RL, Hegarty M, Tompkins RG, Burke JF. Artificial skin in massive burns– results to ten years. Eur J Plast Surg 1994;17(2):91–3, doi:http://dx.doi.org/10.1007/BF00176923.
[9] Boyce ST, Simpson PS, Rieman MT, Warner PM, Yakuboff KP, Bailey JK, et al. Randomized, paired-site comparison of autologous engineered skin substitutes and split-thickness skin graft for closure of extensive, full-thickness burns. J Burn Care Res 2017;38:61–70, doi:http://dx.doi.org/10.1097/BCR.0000000000000401.
[10] Chua AWC, Khoo YC, Tan BK, Tan KC, Foo CL, Chong SJ. Skin tissue engineering advances in severe burns: review and therapeutic applications. Burn Trauma 2016;4(1):3, doi:http://dx.doi.org/10.1186/s41038-016-0027-y.
[11] Alster TS, Tanzi EL. Hypertrophic scars and keloids: etiology and management. Am J Clin Dermatol 2003;4(4):235–43, doi:http://dx.doi.org/10.2165/00128071-200304040-00003.
[12] Lee HJ, Jang YJ. Recent understandings of biology, prophylaxis and treatment strategies for hypertrophic scars and keloids. Int J Mol Sci 201819(3), doi:http://dx.doi.org/10.3390/ijms19030711.
[13] Cruz-Korchin NI. Effectiveness of silicone sheets in the prevention of hypertrophic breast scars. Ann Plast Surg 1996;37(4):345–8, doi:http://dx.doi.org/10.1097/00000637-199610000-00001.
[14] Ahn ST, Monafo WW, Mustoe TA. Topical silicone gel for the prevention and treatment of hypertrophic scar. Arch Surg 1991;126(4):499–504, doi:http://dx.doi.org/10.1001/archsurg.1991.01410280103016. http://www.ncbi.nlm.nih.gov/pubmed/2529659%0A.
[15] Momeni M, Hafezi F, Rahbar H, Karimi H. Effects of silicone gel on burn scars. Burns 2009;35(1):70–4, doi:http://dx.doi.org/10.1016/j.burns.2008.04.011.
[16] Silverberg R, Johnson J, Moffat M. The effects of soft tissue mobilization on the immature burn scar: results of a pilot study. J Burn Care Rehabil 1996;17(3):252–9. http://www.ncbi.nlm.nih.gov/pubmed/8736373.
[17] Niessen FB, Spauwen PHM, Robinson PH, Fidler V, Kon M. The use of silicone occlusive sheeting (Sil-K) and silicone occlusive gel (Epiderm) in the prevention of hypertrophic scar formation. Plast Reconstr Surg 1998;102(6):1962–72, doi:http://dx.doi.org/10.1097/00006534-199811000-00023.
[18] O'Brien L, Jones DJ. Silicone gel sheeting for preventing and treating hypertrophic and keloid scars. Cochrane Database Syst Rev 20132013(9), doi:http://dx.doi.org/10.1002/14651858.CD003826.pub3.
[19] Friedstat JS, Hultman CS. Hypertrophic burn scar management: what does the evidence show? A systematic review of randomized controlled trials. Ann Plast Surg 2014;72(Suppl. 2 (6)):S198–201, doi:http://dx.doi.org/10.1097/SAP. 0000000000000103.
[20] Lee KC, Dretzke J, Grover L, Logan A, Moiemen N. A systematic review of objective burn scar measurements. Burn Trauma 2016;4(1):14, doi:http://dx.doi.org/10.1186/s41038-016-0036-x.
[21] Verhaegen PDHM, Van Der Wal MBA, Middelkoop E, Van Zuijlen PPM. Objective scar assessment tools: a clinimetric appraisal. Plast Reconstr Surg 2011;127(4):1561–70, doi:http://dx.doi.org/10.1097/PRS.0b013e31820a641a.
[22] Nedelec B, Correa JA, Rachelska G, Armour A, LaSalle L. Quantitative measurement of hypertrophic scar: interrater reliability and concurrent validity. J Burn Care Res 2008;29(3):501–11, doi:http://dx.doi.org/10.1097/BCR.0b013e3181710881.
[23] Nedelec B, Correa JA, Rachelska G, Armour A, LaSalle L. Quantitative measurement of hypertrophic scar: intrarater reliability, sensitivity, and specificity. J Burn Care Res 2008;29(3):489–500, doi:http://dx.doi.org/10.1097/BCR.0b013e3181710869.
[24] Pierard GE, Nikkels-Tassoudji N, Pierard-Franchimont C. Influence of the test area on the mechanical properties of skin. Dermatology 1995;191(1):9–15.
[25] Draaijers LJ, Botman YAM, Tempelman FRH, Kreis RW, Middelkoop E, Van Zuijlen PPM. Skin elasticity meter or subjective evaluation in scars: a reliability assessment. Burns 2004;30(2):109–14, doi:http://dx.doi.org/10.1016/j.burns.2003.09.003.
[26] Fong SSL, Hung LK, Cheng JCY. The cutometer and ultrasonography in the assessment of postburn hypertrophic scar: a preliminary study. Burns 199723:, doi:http://dx.doi.org/10.1016/S0305-4179(96)00095-2.
[27] Müller B, Elrod J, Pensalfini M, Hopf R, Distler O, Schiestl C, et al. A novel ultra-light suction device for mechanical characterization of skin. PLoS One 2018;13(8):e0201440, doi:http://dx.doi.org/10.1371/journal.pone.0201440.
[28] Bonaparte JP, Ellis D, Chung J. The effect of probe to skin contact force on Cutometer MPA 580 measurements. J Med Eng Technol 2013;37(3):208–12.
[29] Mazza E, Nava A, Bauer M, Winter R, Bajka M, Holzapfel GA. Mechanical properties of the human uterine cervix: an in vivo study. Med Image Anal 2006;10(2):125–36.
[30] Badir S, Bajka M, Mazza E. A novel procedure for the mechanical characterization of the uterine cervix during pregnancy. J Mech Behav Biomed Mater 2013;27:143–53.
[31] Badir S, Mazza E, Zimmermann R, Bajka M. Cervical softening occurs early in pregnancy: characterization of cervical stiffness in 100 healthy women using the aspiration technique. Prenat Diagn 2013;33(8):737–41, doi:http://dx.doi.org/10.1002/pd.4116.
[32] Jaspers MEH, Brouwer KM, van Trier AJM, Middelkoop E, van Zuijlen PPM. Sustainable effectiveness of single-treatment autologous fat grafting in adherent scars. Wound Repair Regen 2017;25(2):316–9, doi:http://dx.doi.org/10.1111/wrr.12521.
[33] Courage+Khazaka electronic GmbH, "Courage+Khazaka electronic GmbH", 09 May 2012.
[34] Jaspers MEH, Brouwer KM, Van Trier AJM, Groot ML, Middelkoop E, Van Zuijlen PPM. Effectiveness of autologous fat grafting in adherent scars: results obtained by a comprehensive scar evaluation protocol. Plastic Reconstr Surg 2017;139:212–9, doi:http://dx.doi.org/10.1097/PRS. 0000000000002891.
[35] Goei H, van der Vlies CH, Hop MJ, Tuinebreijer WE, Nieuwenhuis MK, Middelkoop E, et al. Long-term scar quality in burns with three distinct healing potentials: a multicenter prospective cohort study. Wound Repair Regen 2016;24(4):721–30, doi:http://dx.doi.org/10.1111/wrr.12438.
[36] Verhaegen PD, van der Wal MB, Bloemen MC, Dokter J, Melis P, Middelkoop E, et al. Sustainable effect of skin stretching for burn scar excision: long-term results of a multicenter randomized controlled trial. Burns 2011;37(7):1222–8, doi:http://dx.doi.org/10.1016/j.burns.2011.04.018.
[37] Weickenmeier J, Jabareen M, Mazza E. Suction based mechanical characterization of superficial facial soft tissues. J Biomech 2015;48(16):4279–86.
[38] Pensalfini M, Weickenmeier J, Rominger M, Santoprete R, Distler O, Mazza E. Location-specific mechanical response and morphology of facial soft tissues. J Mech Behav Biomed Mater 2018;78:108–15, doi:http://dx.doi.org/10.1016/J.JMBBM.2017.10.021.
[39] Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess 1994;6(4):284–90, doi:http://dx.doi.org/10.1037/1040-3590.6.4.284.
[40] Anthonissen M, Daly D, Fieuws S, Massagé P, Van Brussel M, Vranckx J, et al. Measurement of elasticity and transepidermal water loss rate of burn scars with the Dermalab®. Burns 2013;39(3):420–8, doi:http://dx.doi.org/10.1016/j.burns.2012.07.026.

[41] Corica GF, Wigger NC, Edgar DW, Wood FM, Carroll S. Objective measurement of scarring by multiple assessors: is the tissue tonometer a reliable option? J Burn Care Res 2006;27(4):520–3, doi:http://dx.doi.org/10.1097/01.BCR.0000225963.41796.54.

[42] Lye I, Edgar DW, Wood FM, Carroll S. Tissue tonometry is a simple, objective measure for pliability of burn scar: is it reliable? J Burn Care Res 2006;27(1):82–5, doi:http://dx.doi.org/10.1097/01.bcr.0000194531.93753.c5.