# Progress in burn scar contracture treatment

## A clinimetric and clinical evaluation

C.M. Stekelenburg

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Caroline Monique Stekelenburg

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dr. P.P.A. Schellekens

Aan mijn ouders

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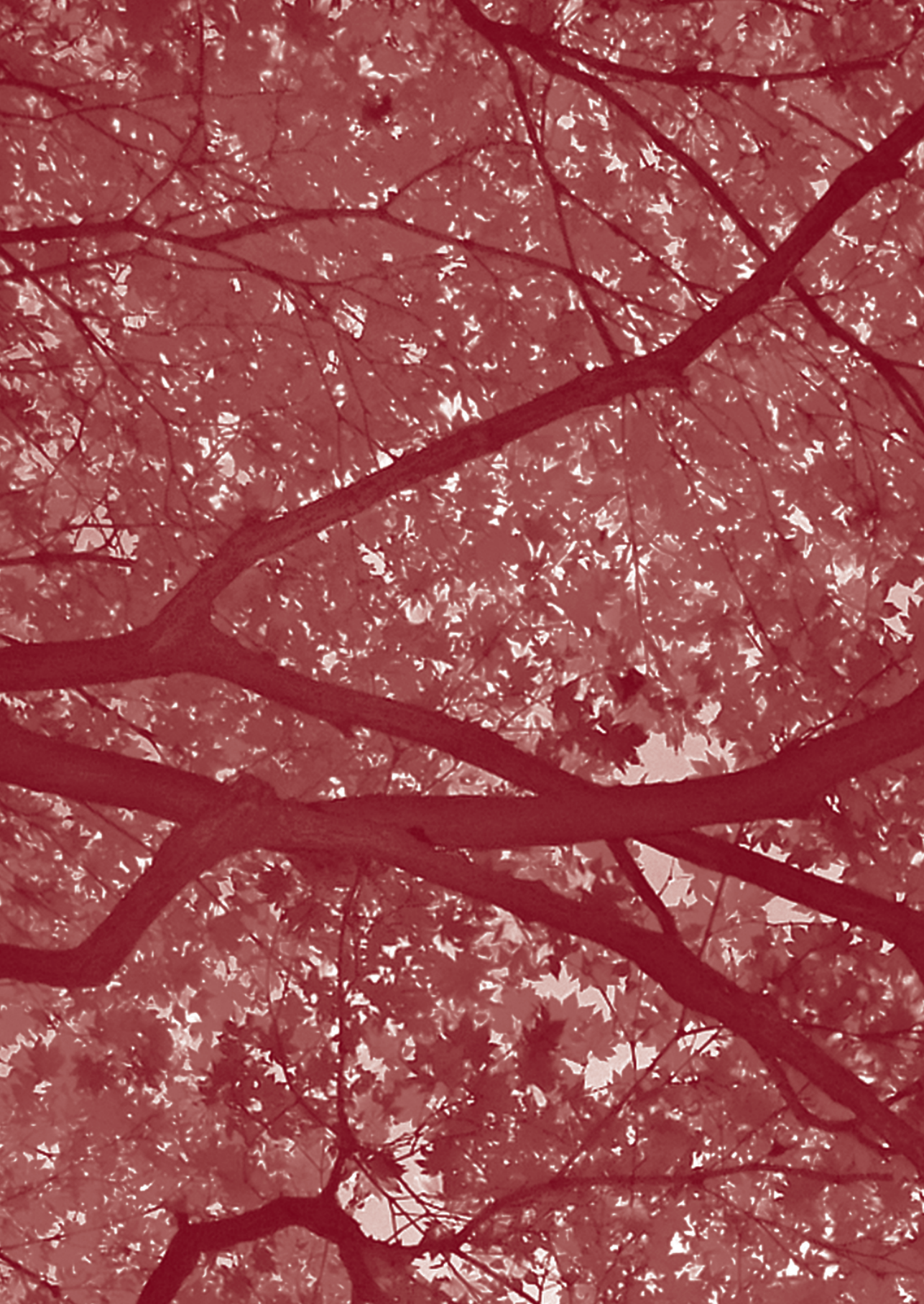

# 1

# Introduction and outline of this thesis

1

# Introduction and outline of this thesis

## Burns, scars and contractures

Advances in burn care have led to an increased survival of patients with extensive burns[1,2]. As a consequence an increased number of patients have to live with extensive disfiguring and disabling scars[3,4]. For this reason greater attention is being paid to the improvement of the quality of scars. Although scar treatment has improved significantly over the past decades, scars resulting from deep burns still result in considerable functional problems in daily life[5]. These functional problems are often caused by the contraction of scar tissue[6,7]. When the functional result of contracted tissue causes loss of range of motion (ROM) in joint areas, it is called 'contracture'[8]. *Figure 1* shows two examples of burn scar contractures. Because burn scars are often widespread and cover large areas, their treatment remains a considerable challenge in reconstructive surgery. Research in the field of burn scar reconstruction is therefore important and necessary.

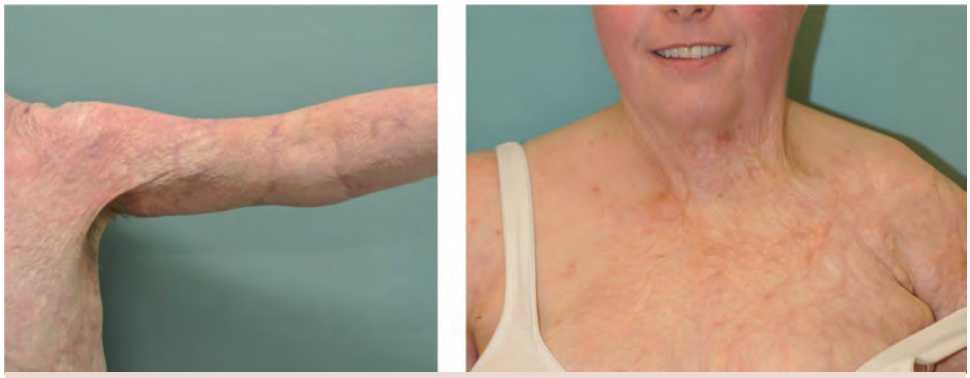

***Figure 1.*** *Left: a scar contracture of the left axilla in a 44-year-old patient and a scar contracture of the neck in a 48-year-old patient (right). Both patients survived full thickness burns and experience a limited range of motion in the arm and neck respectively.*

By means of the studies that are presented in this thesis we aim to increase the current knowledge and thereby improve the treatment of burn scar contractures. In order to do so, we will first assess the clinimetric properties of a measurement tool to measure surface area and volume of scars. Secondly, we will review the current literature on the surgical treatment of burn scar contractures to obtain a clear picture of the current state of the art. With this knowledge and the acquired clinimetric knowledge on scar evaluation tools, we will perform two clinical trials that investigate the effect of the use of perforator based interposition flaps for the treatment of burn scar contractures.

## Part I Clinimetric studies on scar surface area and volume

Evidence based medicine has become the cornerstone of today's medical practice. Evidence comes from clinical trials in which treatment techniques are compared. To be able to compare treatment techniques adequately, there is a need for clear outcome descriptions. In reconstructive surgery outcomes are often not a matter of life or death, sick or cured. We must register changes in functional and cosmetic outcome, from the viewpoint of the patient as well as the clinician. Tools to objectify these kind of outcome parameters are not readily available and have to be tested. The discipline of clinimetrics focuses on testing the quality of these tools in medical science and health care. The basic clinimetric properties are reliability and validity[9]. Reliability refers to the degree a measurement is free from measurement error[9]. Validity refers to the degree to which a measurement tool is able to measure what it is supposed to measure[9]. These clinimetric properties are the core of many chapters in this thesis. For some scar characteristics such as color and elasticity, suitable measurement tools are readily available[10]. For the scar characteristics surface area and volume however, reliable and valid measurement tools are lacking. Scar surface area is an important scar feature to measure because it enables quantifying the percentage of scar surface area that becomes hypertrophic and the extent of scar contraction[10,11]. Scar volume is an important outcome parameter in the treatment of problematic scars such as hypertrophic scars and keloids. Since the available techniques to measure scar surface area and volume have not been proven to be reliable and valid, and are at best cumbersome or not feasible, there is a need for a new measurement method[10,12]. In **Chapter 2** and **Chapter 3** we explore the clinimetric properties of 3D stereophotogrammetry for measuring scar surface area and volume respectively.

## Part II Burn scar contracture treatment: the current state of the art

Reconstructive surgery forms the foundation on which the treatment of functional disabling scar contractures is based. Although the first descriptions of reconstructive techniques date from more than 2000 years ago[13] it was not until the First World War that various surgical reconstructive techniques were developed. At that time the field of reconstructive surgery was rapidly emerging due to the high incidence of burns and injuries to the head and neck[14]. Many young soldiers suffered from large facial defects and scar contractures were often treated before they reintegrated into society. It was during that period, that doctors like Gillies and Esser, originally ear nose and throat specialist and general practitioner (and dentist) respectively, specialized in the reconstruction of facial defects[14]. They created the fundamentals of modern reconstructive surgery[15,16]. Esser described all types of flaps of which some are still being used today[15]. *Figure 2* shows Esser surrounded by his patients.

***Figure 2.*** *Johannes Esser together with his patients, which were injured during the First World War. Illustration from the archives of medical historian L. van Bergen, VU University.*

At the same time, burns were rarely treated surgically and the treatment of acute burns with the use of skin grafts was still in its infancy[17]. Although Thiersch stated already in 1886 that autografts could be used for the treatment of burns, also to cover larger wound areas, their use in burn surgery was not implemented in burn surgery for decades[13,18]. This changed during the Second World War when the pioneering plastic surgeon Archibald McIndoe introduced revolutionary methods for burn treatment including the use of skin grafting[17]. Many of the reconstructive techniques used today in patients with burn injury and hand surgery are highly influenced by his work.

Nowadays, plastic and reconstructive surgery has evolved and established itself as an individual specialism. Over the years, many studies on reconstructive surgical procedures for scar contractures have been performed. Studies on the effectiveness of the treatment of these scar contractures present new techniques or adaptations of previously established techniques. However, examining the current literature does not provide us with recommendations on the appropriate reconstructive procedure or clear algorithms for their treatment. Therefore, **Chapter 4** presents a systematic review on the effectiveness of the available reconstructive techniques for burn scar contracture release.

The goal of surgically treating burn scar contractures is improving the functional limitations that patients are experiencing in daily life. Scar contracture release is performed by incising the scar in such a way that it allows optimal mobility. Tissue is used to 'fill up' the defect that was created by incising the scar, which we refer to as 'interposition' in this thesis. Narrow contracture bands are mostly corrected by use of local plasties, such as Z-plasties[19]. Scar contractures resulting form burn wounds though, are often wide and cover large body areas. This thesis focuses on these wide contractures. Their treatment represents a greater challenge because when a release is performed it is often required to create a large defect.

In clinical practice full thickness skin grafts (FTSGs) are regularly used to treat wide scar contractures. FTSGs are preferred over split thickness skin grafts (STSGs), as STSGs are known to have a considerable risk of future scar contraction[20,21]. Remarkably, the extent of contraction of FTSGs has never been objectified for burn patients[22,23]. Moreover, the available studies on the contraction rate of FTSGs in other patient groups use a relatively short follow-up period and use non validated surface area measurement techniques[22,23]. Therefore, in **Chapter 5** we assess the long-term contraction rate of FTSGs by using 3D stereophotogrammetry. This chapter gives insight in the potential predictive factors that influence the surface area of FTSGs over time.

Besides FTSGs, local flaps are an alternative in the treatment of scar contractures[1,24]. Local flaps derive from adjacent tissue and are brought to the defect by advancement or rotation. As they contain local (healthy) tissue including the subdermal fat layer, they are of a superior quality. A disadvantage is that they are supposed to have a restricted length-to-width ratio. Ratios ranging from 1:1 for the extremities to 2:1 for the trunk, and even greater ratios for the face are described[21,25-27]. When the length-to-width ratio is exceeded, these random flaps may encounter vascular limitations[21].

## Part III Progress in burn scar contracture reconstruction by perforator-based interposition flaps

Perforator-based flaps are flaps where the blood supply of the flap is based on perforators[28]. Perforators are the vessels in the subcutical tissue that 'perforate' different layers (fascia or muscle and subcutis) providing the blood supply to the skin. By including a perforator in the design of the flap the vascularization of the flap is improved and larger flaps could be raised with less restrictions concerning length-to-width ratios. *Figure 3* visualizes a perforator and its course to the skin. In the early nineteen eighties, tissue (including fascia and/or muscle) was transferred based on cutaneous branches of large arteries such as the ulnar, radial and humeral arteries[28]. Extensive basic research on the vascular anatomy

resulted in the concept of angiosomes and their source arteries (the perforators)[29]. We know now that the body contains a few hundred perforators with a diameter of > 0.5 mm[29]. Their discovery was an important breakthrough in the utilization of flaps and the term perforator flap was first used by Koshima and Soeda in 1989[30]. During the past decades, many perforator locations have been identified and proven suitable to base a flap on, such as the deep inferior epigastric artery perforator flap (DIEAP), the superior gluteal artery perforator flap (SGAP), the lateral circumflex femoral artery perforator (LCFAP) flap and the thoraco-dorsal artery perforator flap (TDAP).

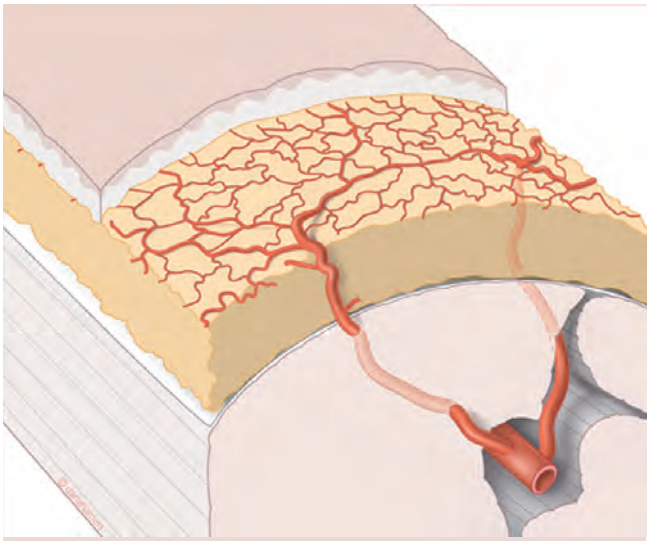

***Figure 3.*** *illustrates the course of a perforator. Originating from a deeper axial artery, the perforator 'perforates' subsequent structures (fascia or muscle and subcutis) to flow into the subdermal plexus. Illustration designed by Dana Hamers.*

A new development is the use of *ad hoc* perforator-based interposition flaps. These flaps are established on any perforator capable of an adequate blood supply that is situated adjacent to the location where the release is needed. Thus, any skin surface of the body can be considered as a potential perforator flap donor site. This type of perforator-based interposition flap is not yet routinely applied for burn scar reconstructions. The application of perforator-based interposition flaps augments the armamentarium for the reconstructive surgeon considerably because it offers a solution for scar contractures, irrespective of the anatomical location. Two small cohort studies have described their safe, reliable and sustainable use[31,32]. Perforator flaps can be designed as an islanded or a non-islanded flap. The latter implies that the skin base of the flap is left intact, hereby

protecting the perforator bundle and supporting the venous outflow. Originating from the principles of free flap surgery, perforator-based flaps are most frequently islanded. However recently, some groups have described the use of non-islanded flaps[31,33,34]. **Chapter 6** introduces an algorithm for the treatment of scar contractures that includes the design of the flap. This chapter also assesses the safety and effectiveness of the perforator-based flaps for the treatment of scar contractures. Furthermore, the true effectiveness of perforator-based interposition flaps is studied in a randomized controlled trial comparing this technique to FTSGs (**Chapter 7**).

The location of perforators varies significantly between patients[35]. Perforators can easily be located by Doppler sonography prior to surgery, which facilitates the planning and safety of the flap design[35]. We anticipated finding sufficient evidence to support the use of the hand held Doppler device to locate perforators. However, literature showed a lack of clinimetric studies adequately testing the reliability. The available studies focus mainly on the validity of this technique, and yield conflicting results[36-42]. Since the Doppler device is regularly used in the upcoming field of perforator flaps, **Chapter 8** focuses on both the reliability and validity of the hand held Doppler for the detection of perforators.

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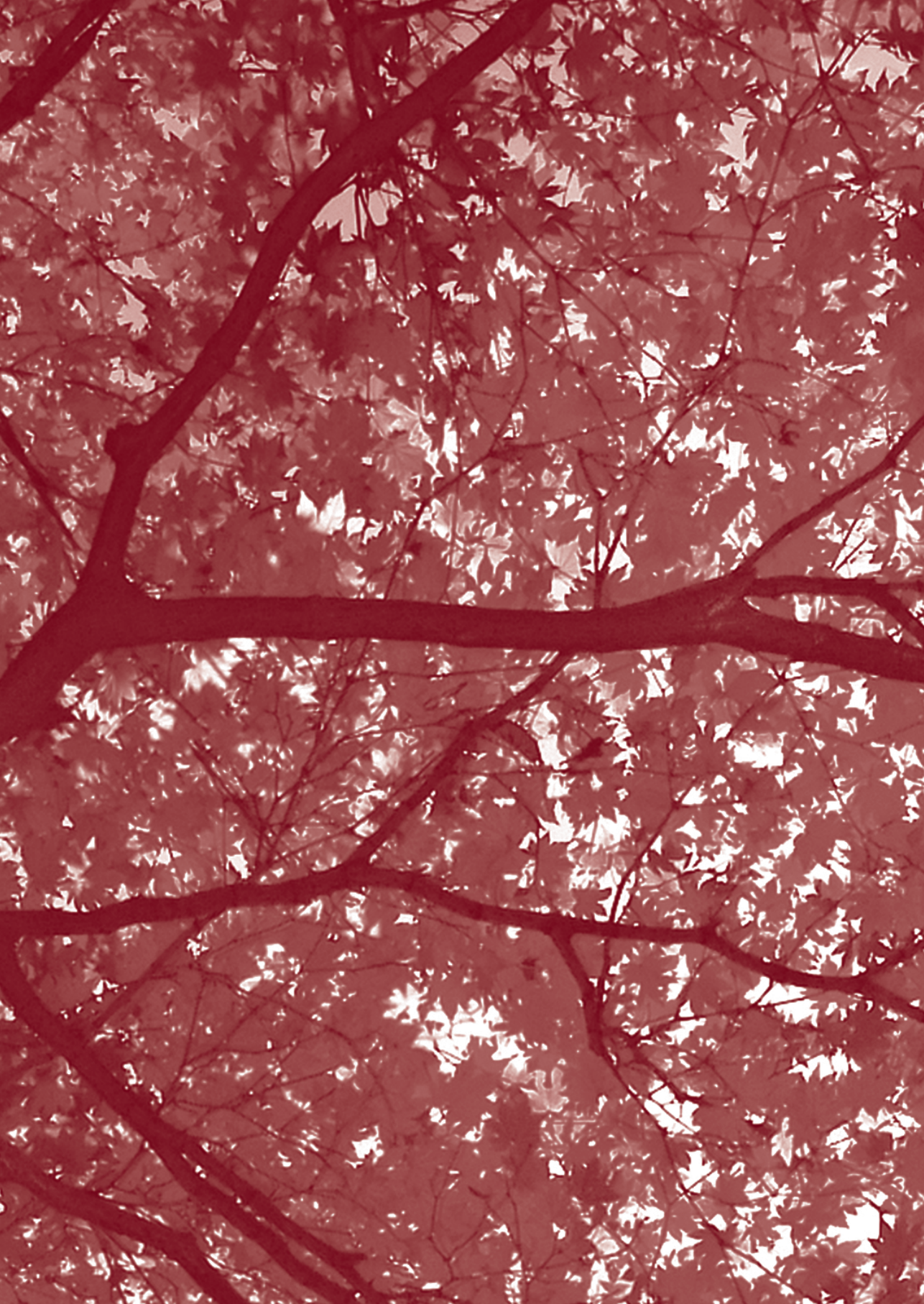
# 1

# PART I

## Clinimetric studies on scar surface area and volume



# 2

# Three-dimensional digital stereophotogrammetry: a reliable and valid technique for measuring scar surface area

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Martijn B.A. van der Wal
Dirk L. Knol
Henrica C.W. de Vet
Paul P.M. van Zuijlen

*Plast. Reconstr. Surg. 2013 Jul; 132(1): 204-11*

## Abstract

**Introduction:** The surface area of scars is an important outcome parameter in scar assessment. It is often used to quantify the extent of scar features such as pigmentation disturbances, hypertrophy, and contracture. Currently available techniques for measuring the surface area are known to be cumbersome or do not meet the basic clinimetric criteria (i.e., reliability and validity). Three-dimensional (3D) stereophotogrammetry is a technique that may improve the quality of surface area measurements. The aim of this study was to investigate the reliability and the validity of 3D stereophotogrammetry for measuring scar surface area.

**Materials and Methods:** In a cross-sectional study, two independent clinicians photographed and measured 50 scar areas of 32 patients with a handheld stereographic camera, to assess the reliability. Subsequently, using planimetry, the scar surface was traced on a transparent sheet (considered the accepted standard) to assess validity.

**Results:** 3D stereophotogrammetry showed good reliability, with an intraclass correlation coefficient of 0.99 and a coefficient of variation of 6.8%. To visualize the differences between the two observers, data were plotted and the limits of agreement were calculated at $0 \pm 0.19 \times$ *mean surface area*. Also, excellent validity was found with a concordance correlation coefficient of 0.99.

**Conclusion**: This study showed that 3D stereophotogrammetry is a reliable and valid tool for research purposes in the field of scar surface area measurements.

## Introduction

Scars are acquired each year by millions of people, primarily because of trauma or surgical interventions[1,2]. Many scars develop abnormally. They can be characterized by different scar features such as an aberrant color, increased thickness, irregular surface area, and contraction. Accurate scar assessment permits quantification of scar evolution and is key to evaluating the effectiveness of applied modulating therapies and treatments[3].

Surface area measurement enables the quantification of scar contraction and the percentage of the scar surface area that becomes hypertrophic or hyperpigmentated[4]. Several methods are available to perform surface area measurements. The most simple and commonly used technique is planimetry by manually tracing the scar on a transparent grid paper[5,6]. A more refined technique is computer-assisted planimetry, in which the manual tracings are scanned and transferred to a software program or traced on an electronic tablet[7-10]. Another technique is photogrammetry, which uses photographic images to determine the geometric properties of an object[11]. Moreover, stereophotogrammetry, based on the same principle but with the use of two or more cameras, has been found to be a reliable surface area measurement technique[12,13].

Although useful, the above-mentioned techniques have their limitations. Tracing the surface of the scar, which is considered the accepted standard because of good reliability and validity, has its flaws mainly in feasibility[11]. Tracing the scar onto a transparent sheet may be subject to difficulty in fixating the sheet and determining the irregular boundaries of a scar through the transparent sheet. Furthermore, photogrammetry is not valid or reliable for extremely curved body parts[11]. Finally, traditional stereophotogrammetry, using two separate cameras to correct for these curvatures, is cumbersome in clinical practice because it is time-consuming and requires special skills[4].

Recently, the use of 3D digital stereophotogrammetry has been introduced, mainly in the field of craniofacial surgery and anthropometry[14-17]. With this technique, two or more digital images are obtained from several cameras at different angles and reconstructed in a 3D image. Measurements such as surface area can be extracted from these digital images. As this device is even more sizeable and therefore less applicable in daily practice, 3D digital stereophotogrammetry, using a single device, was developed. This may be a feasible and practical method for measuring the surface area of scars.

Before implementing a novel assessment tool into clinical practice, it is appropriate to test its clinimetric properties first. Clinimetric principles of interest are reliability and measurement error (to what extent does the device obtain the same value for repeated measurements?) and validity (does the device measure what it should measure, in this

case, the surface area?). These properties of 3D stereophotogrammetry for the purpose of measuring scar surface area have never been tested. The objective of this study was to assess the reliability and validity of 3D digital stereophotogrammetry in measuring the surface area of scars.

## Materials and Methods

### Patients

Patients with scars were recruited from both the scar outpatient clinic and the general surgery outpatient clinic of the Red Cross Hospital, in Beverwijk, the Netherlands. Patients with scars that did not exceed the measuring frame of the 3D camera (diameter ≤20cm) were eligible and included after informed consent was obtained. According to the clinical research legislation, ethical approval was not necessary. The principles outlined in the declaration of Helsinki were followed.

### The 3D camera

For 3D stereophotogrammetry, the 3D LifeViz™ (DermaPix® software; QuantifiCare S.A., Sophia Antipolis, France) was used. This system is based on a high-resolution single-lens reflex camera (Canon, Tokyo, Japan) with a customized lens splitter and dual light pointer camera system of 15.1 megapixels and 39-mm lenses. Through the lens splitter, the camera takes one photograph consisting of two images from different angles. The incorporated light pointers, which converge at a distance of 60 cm, ensure that the photograph is taken at the appropriate distance *(Figure 1).*

Photographs were taken perpendicular to the center of the scar and subsequently imported into the Dermapix software program, which allows the user to construct 3D images of the photographed surface area and to perform surface area measurements *(Figure 2)*.

### Planimetry by tracing

To test validity, planimetry by tracing was used as the accepted standard for comparison. Because this technique has been shown to be reliable and valid for surface area measurements, only one observer traced the margins of the scar[11]. Tracing was done directly onto a transparent, pliable plastic sheet, which was subsequently scanned and measured using digital image analysis software (NIS-Elements; Nikon Instruments, Inc., Melville, N.Y.).

### Procedure

In this study, two photographs were taken by two experienced clinicians (M.B.A. vdW. and C.M.S.), resulting in four photographs per scar. In addition, the scar was manually traced

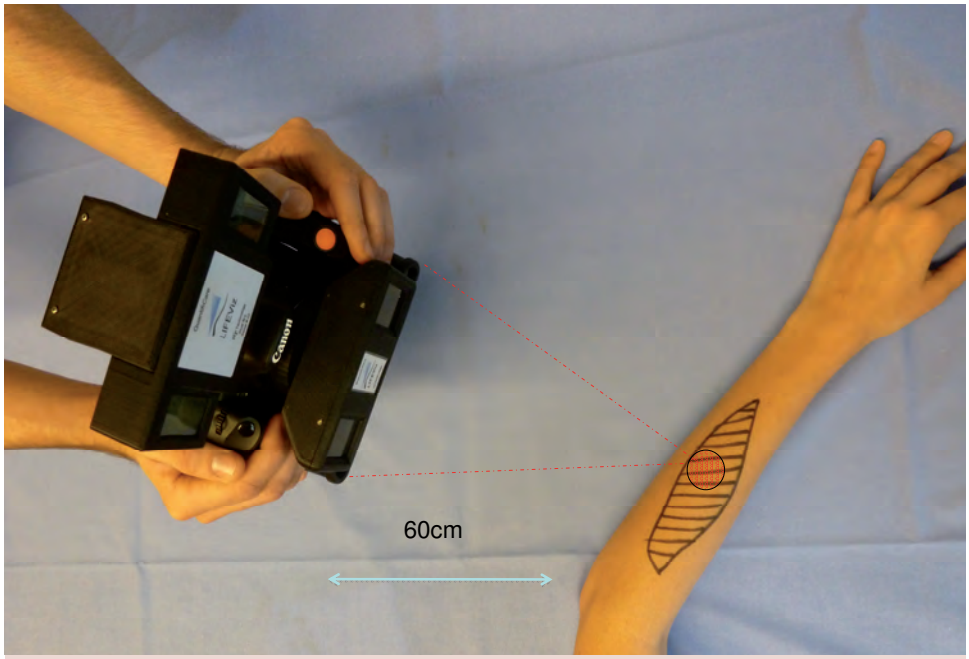


***Figure 1.*** *A simulated composition of the process of making a 3D photograph.*

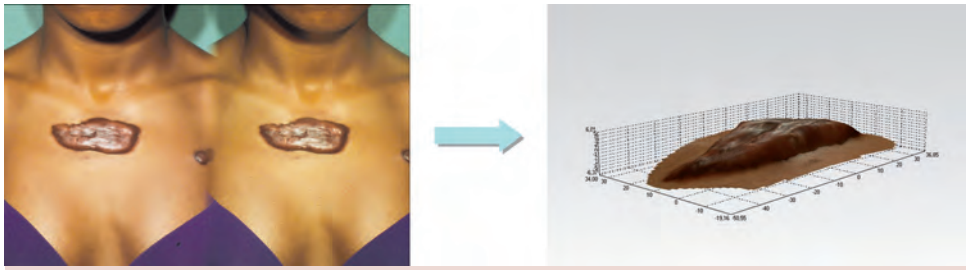

***Figure 2.*** *An example of the retrieved photograph (left) and a processed 3D image (right).*

and processed as described above. After importing the photographs into the Dermapix software program each clinician independently performed surface area measurements of each photograph, resulting in eight surface area measurements per scar.

## Statistical analysis

First, the interobserver reliability was calculated based on the eight measurements of two observers, each scoring four images per scar, made by two photographers. The reliability can be expressed as a ratio of variance components of a linear mixed or random model, and hence as an intraclass correlation coefficient (ICC). To test the interobserver $ICC_{inter}$, the variance components of a linear random effects model were estimated, with random

factors scars, photographers and observers completely crossed, and images nested within scars and photographers. Because of the skewed distribution of the measurements, data were log-transformed to approximate a normal distribution[18]. The $ICC_{inter}$ was defined as the correlation between the surface area ratings of the same scar by two observers based on the images obtained by different photographers[19]. As shown in *Appendix 1.1* (see Appendix), the $ICC_{inter}$ equals the ratio of the scar variance and the total variance. Also, the coefficient of variation (CV) of the data on the original scale was calculated in order to express the reliability as the variation between measurements in relation to the mean value. A low CV represents a more reliable measurement than a high CV. Essentially, in case of log-transformed data, the same information as the CV can be displayed by a Bland and Altman plot [i.e., plotting the differences between pairs of measurements of the same scar (*y* axis) against the mean of the measurements (*x* axis), together with the limits of agreement (LoA)][20]. The LoA are drawn in such a way that 95% of the differences between pairs of measurements lie within these limits. The LoA give an indication of the absolute agreement between the observers. *Appendix 1.1* describes in detail the statistical method used to analyze reliability. The formulas for the $ICC_{inter,}$ the standard error of the mean, and the limits of agreement are given. Also, the variance estimates of all possible variance components are included in the *Appendix, Table A. Appendix 1.2* gives adjusted formulas for the standard error of the mean and the limits of agreement in case two observers assess the scar surface.

Second, to analyze the validity, the scores of both the 3D stereophotogrammetry and planimetry by tracing were expressed on a log scale and compared using the concordance correlation coefficient (CCC)[21]. The CCC was chosen for this analysis because it reflects both the degree of correspondence and agreement among the two measurement techniques. For each of the eight measurements, the CCC was calculated, and these eight values were averaged. Finally, the method of inverse prediction was used to calculate a 95% prediction interval for the accepted standard based on one measurement (see *Appendix 2*)[22]. The data were analyzed using SPSS 15.0 software (SPSS, Inc., Chicago, USA) and Mplus 6.1 (Muthén & Muthén, Los Angeles, California)[23]. *Appendix 2* describes in detail the statistical method used to analyze the validity. The method of inverse prediction is given, as well as the formula used to calculate the limits of agreement.

# Results

## Patient and scar characteristics

Fifty scars were included from 32 consecutive patients. Patient demographics and scar characteristics are shown in *Table 1*. The mean surface area, measured using planimetry by tracing, of the photographed scars was 2058 $mm^2$ (SD: 2440 $mm^2$).

| Characteristics | Value |
|---|---|
| No. of scars | 50 |
| No. of patients | 32 |
| Gender | |
| Male | 20 (62.5%) |
| Female | 12 (37.5%) |
| Age, yr | |
| Mean (SD) | 27 (22) |
| Minimum | 1 |
| Maximum | 79 |
| Scar type, no. of scars | |
| Burn | 38 (76%) |
| Keloid | 10 (20%) |
| Linear | 2 (4%) |
| Scar location | |
| Head and neck | 6 (12%) |
| Trunk (anterior) | 5 (10%) |
| Trunk (posterior) | 16 (32%) |
| Upper extremities | 15 (30%) |
| Lower extremities | 8 (16%) |

***Table 1.*** *Patient demographics and scar characteristics of the included patients.*

## Reliability

The log-transformation resulted in an approximate normal distribution of the scores obtained. The $IC_{inter}$ was 0.99, corresponding to the correlation between surface ratings of the same scar, produced by two different observers based on photographs made by different photographers. The estimates of all variance components can be found in the *Appendix, Table A*. Because in general the intraobserver reliability is considered to be higher than the interobserver reliability, this parameter was not analyzed[24]. The CV was found to be 6.8%. In this study, the parameters ICC and CV indicate a high reliability. To illustrate the agreement, Bland and Altman plots are presented in *Figure 3* (displaying all data) and *Figure 4* (for surfaces up to 5200 $mm^2$), in order to provide a more precise overview of the distribution of the data on the smaller surface areas. The limits of agreement were 0 ± 0.19 × *mean surface area* and are proportional to the mean, because of the log transformation. When the surface area is assessed by a second observer and the mean value of two observers is taken, the CV can be reduced to 5.9%, corresponding with limits of agreement of 0 ± 0.16 x *mean surface area* (*Appendix 1.2*).

## Validity

A CCC of 0.99 was found between measuring scar surface using 3D stereophotogrammetry and doing so using planimetry by tracing. The data on the validity are plotted in *Figure 5*, with the accepted standard measurement on the y axis and the values obtained by 3D stereophotogrammetry on the x axis. In *Figure 5*, the 45-degree line represents exact equality of both measurements. Using the formula: 0.70 x 3D measurement$^{1.04}$, an estimate

of an accepted standard value can be calculated from a given 3D measurement, with its corresponding 95% prediction interval *(Figure 5)* (details are presented in *Appendix 2*). The 95% prediction interval again, increases with increasing surface area.

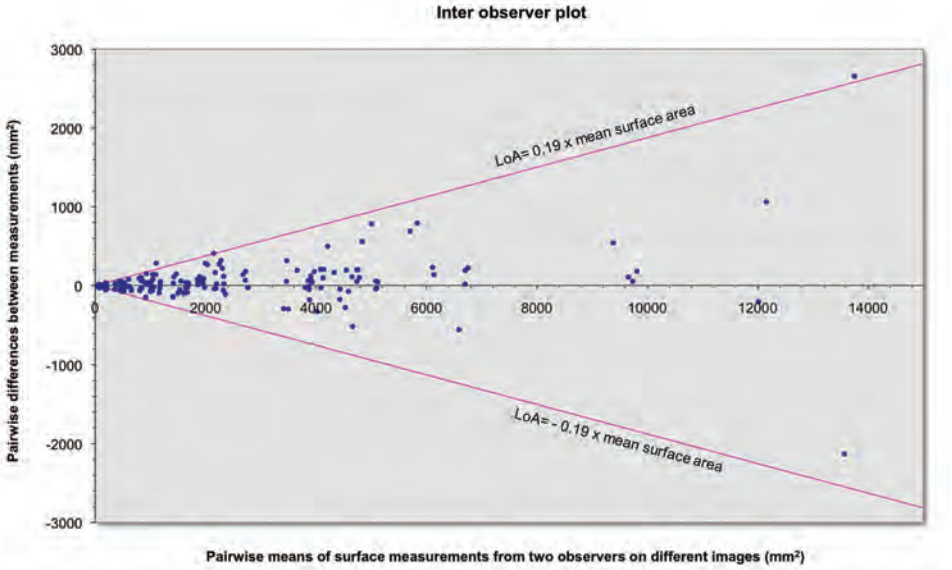


***Figure 3.*** *A Bland and Altman plot, presenting the interobserver agreement between the two observers.*

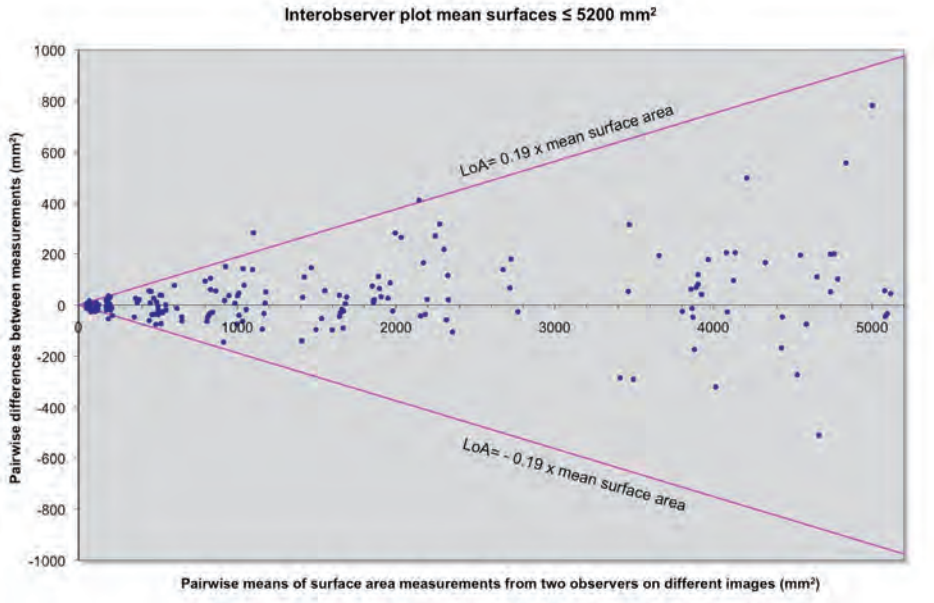


***Figure 4.*** *A Bland and Altman plot, presenting the interobserver agreement between the two observers for mean surface areas of ≤ 5200mm².*

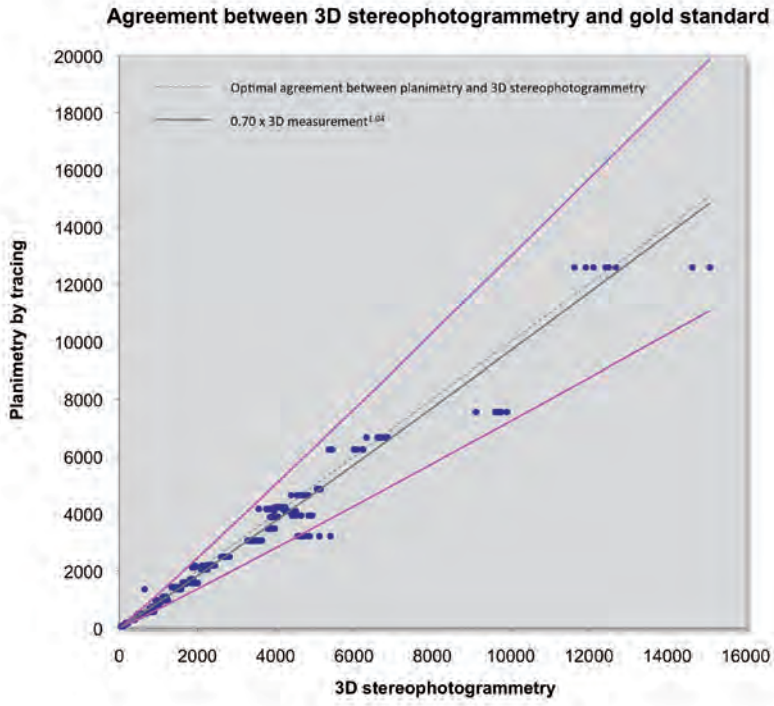


***Figure 5.*** *A plot visualizing the agreement between 3D stereophotogrammetry and planimetry by tracing. The grey solid line signifies the expected planimetry value calculated from a given 3D measurement, using the formula G (Gold standard) = 0.70 x 3Dmeasurement$^{1.04}$, with the accompanying 95% prediction interval (pink lines). The dotted grey line is the 45° line which represents the 100% agreement between the two measurement methods. Please note that the expected line runs close to the 45° line.*

## Discussion

In the present study, we tested the reliability and validity of 3D stereophotogrammetry combined with Dermapix software measurements for the quantitative assessment of scar surface area. The reliability of 3D stereophotogrammetry, indicated by the ICC was very high. Typically, an ICC of 0.70 or higher is considered acceptable for research and 0.90 to 0.95 or higher is considered acceptable for use in clinical practice[25]. The high ICC can be explained by different mechanisms. First, photographs are taken in a standardized way (i.e., perpendicular to the scar surface and at a distance of 60 cm). Second, tracing of the surface area is performed digitally, which allows the observer to carefully trace the area of interest, unhindered by movement of the patient, poorly illuminated patient rooms, or reflectance of tracing papers. Also, the software program enables the user to enlarge the image, so more precise tracing can be performed. The CV was found to be 6.8%, which we consider to be an acceptable error to take into account when measuring

the surface area. Furthermore, 3D stereophotogrammetry appeared to be a valid tool for scar surface area measurements. Excellent validity, as indicated by the high CCC of 0.99, was found for the 3D stereophotogrammetry when compared with planimetry by manual tracing. In other words, the two surface area measurement methods were shown to give comparable results. This was clearly visualized in *Figure 5*, in which the estimation line runs close to the 45-degree line.

The LifeViz imaging system uses a portable camera, which can also be used in the outpatient clinic and the operating room. The measurement procedure of taking a picture, processing the data, and measuring the surface area takes approximately 10 minutes. These properties make the device extremely feasible in clinical practice. Despite these practical benefits, stereophotogrammetry has its limitations. Extremely curved areas, such as fingers, helix of the ear, or top of the nose, cannot be captured in a single measurement because of the angle from which the two photographs are taken. The same problem occurs, even in less curved body parts (e.g., the forearm), with the use of other surface area measurement techniques, such as planimetry by tracing or Polaroid photographs[11]. Moreover, the device is able to image only surfaces with a diameter of 20 cm or less because of the angle configuration and the standardized distance of 60 cm. In both cases, we suggest to divide the scar area in segments using a marker or by identifying distinct features (such as anatomical landmarks) within the scar or surrounding tissue, and taking multiple photographs, all perpendicular to the different scar sections. The surface area measurements can then be added together.

In the past decades, many subjective and objective scar assessment tools have been proposed and tested for their suitability[4,26,27]. Currently, the most commonly used tools are the POSAS (the Patient and Observer Scar Assessment Scale)[28-30] and the Vancouver Scar Scale[31]. These scales provide a quantitative measure of overall scar quality by systematically assessing typical scar characteristics, but they are less useful for the quantification of scar surface area. Research on techniques that assess scar surfaces is limited. On wounds, however, several studies have described tracing techniques to evaluate sizes and contraction rates. From research on area measurements of pressure ulcers and chronic wounds, manual tracing techniques, whether or not they were combined with digital planimetry, showed overall good reliability and validity[8,32-34]. Also, stereophotogrammetry was found to be reliable and valid (Pearson's correlation coefficient of 0.96)[13]. More recently, photogrammetry using four cameras was tested for measuring linear distances on cadaver faces; results showed high reliability and validity (ICC for both was > 0.96)[35]. One study examined the validity of the LifeViz system for the purpose of measuring scar volumes and found a high association with an accepted standard (Pearson correlation coefficient of 0.98)[36]. The authors did not examine the reliability. Although they are useful, a drawback of the majority of these studies is that

they are subject to methodological deficiencies, such as small numbers of inclusions, inappropriate use of correlation to assess validity or interrater reliability, and omission to quantify the agreement[36,37].

The high ICC found in our study is comparable to that of other research in this field[37]. This means that the device is extremely reliable. Note that reliability (defined as the ability to distinguish patients from each other despite measurement errors[25]) is influenced by the heterogeneity of the study population, since it is easier to distinguish between patients with heterogeneous scar surfaces than patients with almost similar scar surfaces. The scar surface areas varied widely in our study sample. However, our study population was a good representation of the population in which 3D stereophotogrammetry is going to be used, which means that the values of ICC and CV hold for patients as seen in clinical practice.

We were also interested to consider the agreement between observers by presenting the limits of agreement. This additional analysis showed that although the 3D technique is extremely reliable, in terms of absolute agreement, there is some variation in outcomes between observers (LoA of 0 ± 0.19 x *mean surface area*). The absolute agreement still leaves room for improvement. This can be reduced when in clinical practice two observers perform the area measurements and use the mean value, resulting in LoA of 0 ± 0.16 x *mean surface area* (see *Appendix 1.2*). In clinical research, where we are interested in mean values of groups of patients, measurement errors are also reduced. Therefore, the device is more eligible for research purposes than for the individual patient follow-up in clinical practice. In addition, the value of the CCC, expressing the validity of the device, is, like the ICC, dependent on the range of measurements and is expected to be high in heterogeneous populations. The 95% prediction interval is comparable to a Bland and Altman analysis and shows the absolute agreement between planimetry and 3D stereophotogrammetry.

Besides a thorough analysis of our results, this study aimed to advocate a more critical appraisal of clinimetric research in the field of reconstructive medicine. To aid future research initiatives that investigate clinimetric properties of a device, an appendix with detailed statistical information is included.

In conclusion, we have shown that 3D stereophotogrammetry is a reliable and valid technique for the assessment of scar surface area in clinical research. The findings in this study contribute to a more evidence-based approach to scar assessment.

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# Appendix

## 1.1 Reliability

According to the design of the study, we have a linear random factor effects model with random factors scars (S), photographers (P) and observers (O) completely crossed, and images nested within S and P (I : SP). The model can be written for the naturally log-transformed data (log Y) as

$$\log Y_{spio} = \mu + v_s + v_p + v_{sp} + v_{i:sp} + v_o + v_{so} + v_{po} + v_{spo} + \varepsilon_{spio}$$

for s = 1,…,50; p = 1,2; i = 1,…,200; o = 1,2, where μ is the fixed intercept parameter, and the v-terms are the random effects identified by their subscripts, e.g., $v_{sp}$ are the random scars × photographers interaction effects. The random effects are independently normally distributed, with mean 0 and variance as denoted in *Table A*. The variance components are estimated by the method of residual maximum likelihood.

The total variance can be decomposed as

$$\sigma^2_{total} = \sigma^2_S + \sigma^2_P + \sigma^2_{SP} + \sigma^2_{I:SP} + \sigma^2_P + \sigma^2_O + \sigma^2_{SO} + \sigma^2_{PO} + \sigma^2_{SPO} + \sigma^2_E.$$

The interobserver intraclass correlation coefficient $ICC_{inter}$ is defined as the correlation between the measurements of different observers on the same scar obtained by different photographers[1]:

$$ICC_{inter} = corr(\log Y_{spio}, \log Y_{sp'i'o'}) = \frac{\text{cov}(\log Y_{spio}, \log Y_{sp'i'o'})}{\text{var}(\log Y_{spio})} = \frac{\sigma^2_S}{\sigma^2_{total}} \qquad p \neq p' \; ; \; o \neq o'.$$

The interobserver within scar variance can be shown to be

$$\text{var}(\log Y_{spio} \mid S) = \sigma^2_{total} - \sigma^2_S$$

and the square root is called the standard error of measurement (SEM).

For measurements with an absolute zero point, the coefficient of variation (CV) is a useful reliability index. It can be shown[2] that the CV of the measurements on the original scale is approximately

$$CV = SEM \times 100\%.$$

A 95% prediction interval of the ratio $Y_{spio} / Y_{sp'i'o'}$ is[2]:

$$\exp(-1.96\sqrt{2} \times SEM) \leq \frac{Y_{spio}}{Y_{sp'i'o'}} \leq \exp(1.96\sqrt{2} \times SEM)$$

and backtransformation to the original scale[2] yields the limits of agreement (LoA) for the differences $Y_{spio} - Y_{sp'i'o'}$

$$-2\bar{Y}\frac{\exp(1.96\sqrt{2} \times SEM) - 1}{\exp(1.96\sqrt{2} \times SEM) + 1} \leq Y_{spio} - Y_{sp'i'o'} \leq 2\bar{Y}\frac{\exp(1.96\sqrt{2} \times SEM) - 1}{\exp(1.96\sqrt{2} \times SEM) + 1}$$

where $\bar{Y} = (Y_{spio} + Y_{sp'i'o'}) / 2$ or $LoA = 0 \pm 2\bar{Y}\frac{\exp(1.96\sqrt{2} \times SEM) - 1}{\exp(1.96\sqrt{2} \times SEM) + 1}$.

| Random effect | Term in linear model | Variance component | Estimate ($x10^{-2}$) |
|---|---|---|---|
| Scars (S) | $V_s$ | $\sigma^2_S$ | 206.528 |
| Photographers (P) | $V_p$ | $\sigma^2_P$ | 0.006 |
| Scars × Photographers (SP) | $V_{sp}$ | $\sigma^2_{SP}$ | 0.095 |
| Images nested within S × P (I:SP) | $V_{i:sp}$ | $\sigma^2_{I:SP}$ | 0.128 |
| Observers (O) | $V_o$ | $\sigma^2_O$ | 0.008 |
| Scars × Observers (SO) | $V_{so}$ | $\sigma^2_{SO}$ | 0.065 |
| Photographers × Observers (PO) | $V_{po}$ | $\sigma^2_{PO}$ | 0.000 |
| Scars × Photographers × Observers (SPO) | $V_{spo}$ | $\sigma^2_{SPO}$ | 0.019 |
| Residual | $\varepsilon_{spio}$ | $\sigma^2_E$ | 0.141 |

***Table A.*** *Variance estimates of all possible variance components.*

## 1.2 Two observers?

When two observers assess the scar surface the following formula can be used:

$$SEM^2_{\text{inter}} = \sigma^2_P + \sigma^2_{SP} + \sigma^2_{I:SP} + \frac{\sigma^2_O}{2} + \frac{\sigma^2_{SO}}{2} + \frac{\sigma^2_{PO}}{2} + \frac{\sigma^2_{SPO}}{2} + \frac{\sigma^2_E}{2},$$

where all the variance components that include the observer component are divided by two.

To assess the limits of agreement same formula is used, with adjusted SEM values:

$$LoA = 0 \pm 2\bar{Y}\frac{\exp(1.96\sqrt{2} \times SEM) - 1}{\exp(1.96\sqrt{2} \times SEM) + 1}.$$

## 2. Validity

To obtain a prediction for the accepted standard as a function of the 3D method, we used the method of inverse prediction[3]. First, each of the eight 3D measurements was regressed on the accepted standard, both on the log transformed scale:

$$\log Y_{js} = \beta_0 + \beta_1 \log G_s + \varepsilon_{js}, \qquad j = 1,...,8;\ s = 1,...,50,$$

where $Y$ is the 3D measurement, $G$ the accepted standard, $\beta_0$ and $\beta_1$ regression parameters and $\varepsilon_{js}$ the errors, which are normally distributed with mean 0 and common variance $\sigma^2$. Using the data, the parameters $\beta_0$, $\beta_1$ and $\sigma^2$ can be estimated by Mplus[4].
Next, an estimate for $\log G$ is

$$\log \hat{G} = \frac{\log Y - \hat{\beta}_0}{\hat{\beta}_1} \quad .$$

Also, an approximately 95% prediction interval for $\log G$ can be calculated:

$$\frac{\log Y - \hat{\beta}_0}{\hat{\beta}_1} \pm 1.96 \frac{\hat{\sigma}}{\hat{\beta}_1} \quad .$$

Finally, back-transformation to the original scale yields the estimate:

$$\hat{G} = Y^{1/\hat{\beta}_1} \exp(-\hat{\beta}_0/\hat{\beta}_1)$$

and a 95% prediction interval for G:

$$Y^{1/\hat{\beta}_1} \exp(-\hat{\beta}_0/\hat{\beta}_1) \exp(-1.96\hat{\sigma} / \hat{\beta}_1) < G < Y^{1/\hat{\beta}_1} \exp(-\hat{\beta}_0/\hat{\beta}_1) \exp(1.96\hat{\sigma} / \hat{\beta}_1)$$

Substituting the parameter estimates, $\hat{\beta}_0 = 0.343$, $\hat{\beta}_1 = 0.966$ and $\hat{\sigma} = 0.144$ yields

$\hat{G} = Y^{1.04}$ x 0.70 and ($Y^{1.04}$ X 0.52, $Y^{1.04}$ X 0.94), respectively.

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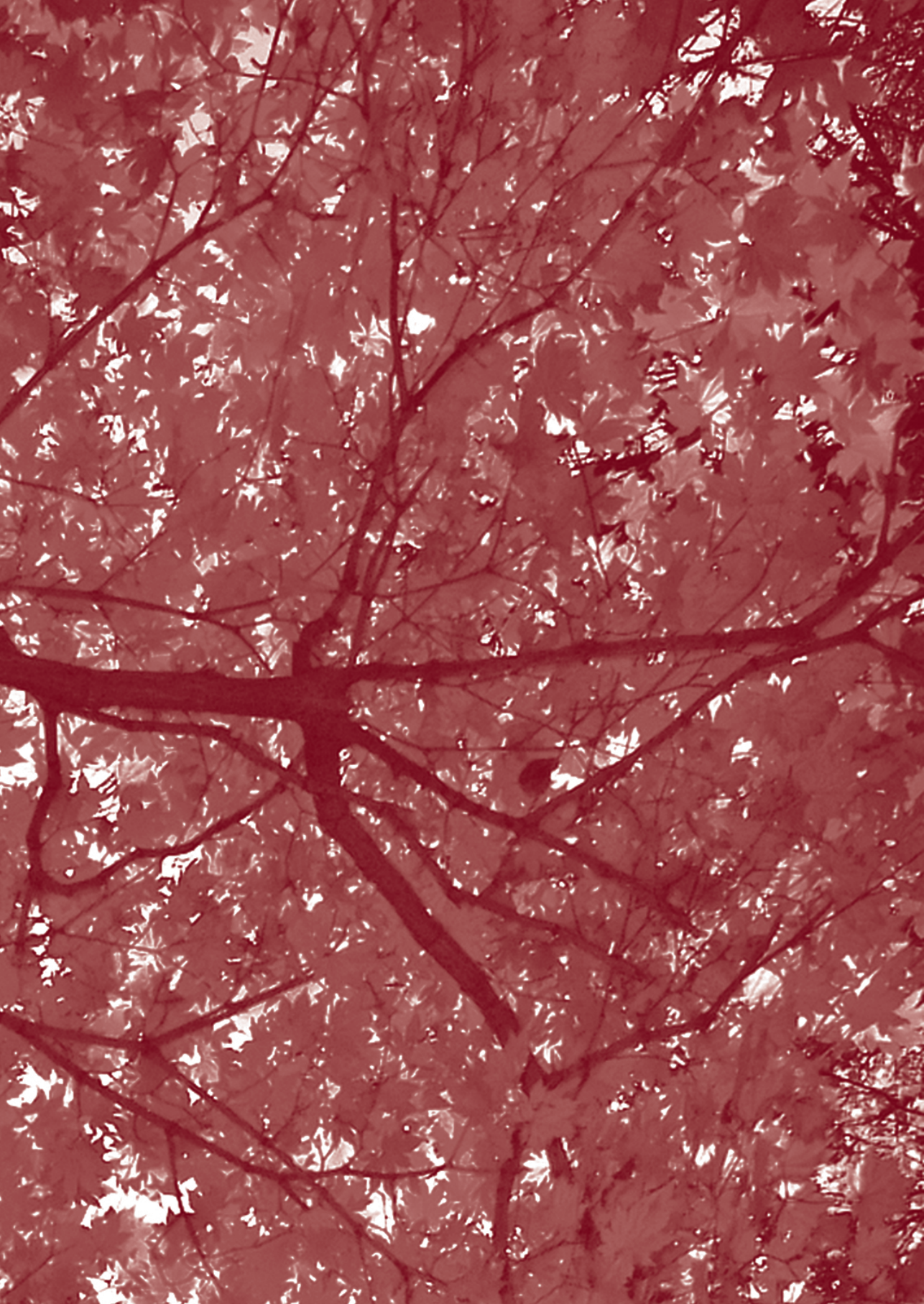

# 3

# In a clinimetric analysis, 3D stereophotogrammetry was found to be reliable and valid for measuring scar volume in clinical research

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## Abstract

**Introduction:** Volume is an important feature in the evaluation of hypertrophic scars and keloids. Three-dimensional (3D) stereophotogrammetry is a noninvasive technique for the measurement of scar volume. This study evaluated the reliability and validity of 3D stereophotogrammetry for measuring scar volume.

**Materials and Methods:** To evaluate reliability, 51 scars were photographed by two observers. Interobserver reliability was assessed by the intraclass correlation coefficient (ICC), and the measurement error was expressed as limits of agreement (LoA). To assess validity, 60 simulated (clay) scars were measured by 3D stereophotogrammetry and subsequently weighed (gold standard). The correlation of volumes obtained by both measures was calculated by a concordance correlation coefficient (CCC), and the measurement error was expressed as a 95% prediction interval.

**Results:** The ICC was 0.99, corresponding to a high correlation of measurements between two observers, although the LoA were relatively wide. The correlation between 3D stereophotogrammetry and the gold standard was also high, with a CCC of 0.97. Again, the plot of the differences and LoA showed moderate agreement for the validity.

**Conclusions:** Three-dimensional stereophotogrammetry is suitable for the use in clinical research but not for the follow-up of the individual patient.

## Introduction

Scarring after burns and after surgical and traumatic injury may lead to functional, esthetic and psychological problems. The development of pathological scars is regularly seen[1] especially after burns. One of the most distinct features of these pathological scars is that they are elevated above the surrounding skin, thereby having an increased volume. An adequate assessment of the scar property volume allows clinicians and researchers to compare the effectiveness of therapy protocols. Scar properties may be assessed by validated scar assessment scales, such as the POSAS[2,3]. There is, however, a need for objective scar assessment tools, to quantitatively measure the volume of a scar and to provide an objective patient follow-up after applied treatment[4,5].



Studies describing techniques that objectively measure scar volume are scarce. A reliable technique is taking a cast of the scar with elastomer putty (negative impression), where after the resulting mold is filled with plaster and subsequently weighed[6,7]. This casting method though has several disadvantages: it may cause patient discomfort, the plaster density may vary, and it is time consuming. Moreover, the use is limited to small scars surrounded by normal skin. The last few years, several three-dimensional (3D) imaging methods have become available for the assessment of volume in clinical and research settings[8-13]. One of these methods is 3D stereophotogrammetry, which uses digital color images that are captured simultaneously by two cameras. Especially in the field of oral and maxillofacial surgery, various studies have been performed to identify facial landmarks[13], to measure volumetric changes in cleft lip and palate nose[10], and to image facial surface area[11].

Three-dimensional stereophotogrammetry for measuring scar volume was tested in two studies with an experimental set up and found to have a good validity (both Pearson's correlation coefficient >0.97)[8,12]. Although useful, the applicability of these results is limited mainly because of the small inclusion numbers[8,12]. For assessing the appropriateness of a measurement device, both reliability (i.e., the degree to which repeated measurements provide similar results) and validity (i.e., the degree to which the device measures what it is intended to measure) are essential features[14]. The objective of this study was to evaluate the reliability and validity of 3D stereophotogrammetry for measuring scar volume.

# Materials and Methods

## Study population

Patients with clinically raised scars (hypertrophic scars and keloids) were recruited from the scar outpatient clinics in the Red Cross Hospital in Beverwijk and the VU Medical Center in Amsterdam from August until October 2012. Scars with a diameter of less than 20 cm fitted the measuring frame of the camera and were eligible for inclusion. In addition, healthy volunteers, either working as health care workers in the Burn Center or as intern at the surgery department of the Red Cross Hospital, participated in the validation part of the study. Verbal informed consent was obtained from patients and volunteers. The principles outlined in the declaration of Helsinki were followed.

## The imaging system

The stereophotographic system 3D LifeViz (Canon 500D body, Dermapix software, Quantificare, Sophia Antipolis, France) was used. This system includes a customized Canon 500D, 15.1 megapixel digital reflex camera with a 39-mm-bifurcated lens. Photographs were taken from a standardized distance of 60 cm by the use of two light beams that converge at one spot when the camera is held perpendicular at the correct distance from the targeted point (*Figure 1a*). The camera captures two images simultaneously by taking a photograph from different angles (*Figure 1b*). The software program Dermapix automatically integrates the stereo images and produces a three-dimensional reconstruction in the 'fine analysis' mode. The margin of the scar was manually marked in the software program Dermapix, using a computer mouse. To do so, the image can be pictured from above in a 2D manner. After the margin was defined, the 3D reconstruction shows a black surrounding line (*Figure 1c*). Thereafter, the software program automatically defines the cutoff plane at the bottom of the scar (i.e., the closing surface), using the curvature of the surrounding skin as a reference. It is possible to adjust the sigma, which defines to what extend 'the closing surface' follows this curvature. In this study the sigma was set to 1 to perform volume measurements. Finally, the software program automatically calculates the scar volume by height x width x depth dimensions displayed in a grid (*Figure 1c*).

## Gold standard

To obtain a gold standard, scars with a random form and random volume were created with self-hardening modeling clay (DAS Terracotta, modeling material, Fila Group, Italy). The specific gravity of the clay ($\rho$ = 1.66 g/cm$^3$; range 1.63-1.71 g/cm$^3$) was calculated by averaging five repeated gravity measurements, performed under standard laboratory conditions. The scar models were weighed with a high precision scale (Sartorius MC1 Analytic AC 120S) to provide the actual volume by the formula: volume (mm$^3$) = mass/ specific gravity.

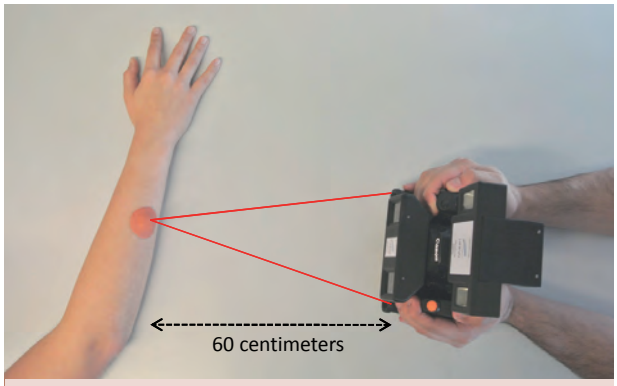


***Figure 1a.*** *Camera held at a fixed distance of 60 cm from the scar.*

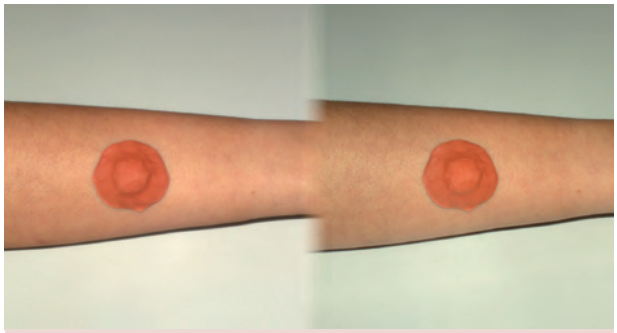

***Figure 1b.*** *Stereographic images captured from different angles.*

***Figure 1c.*** *Three-dimensional reconstruction by the use of Dermapix software. The black line indicating the scar contour, marked manually.*

## Study procedure

To assess the reliability, the scars of the patients were photographed by two observers. Both observers were experienced in taking the photographs and using the software to calculate the volumes. Each observer independently performed a volume measurement of the photograph made by the other observer, resulting in two volume measurements per scar. This procedure was expected to simulate the routine clinical practice best: someone else than the photographer may perform volume analysis. To establish the reliability, both 3D measurements were compared.

The validity was tested by applying the scar models to three different body sites of the volunteers (thorax, upper leg, and lower arm), which represented a flat, moderate, and strong curvature of the body, respectively. Subsequently, two observers took one photograph of the simulated scars, and volume measurements were performed crosswise.

## Statistical analysis

Data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, USA) and Mplus 6.1 (Muthén & Muthén, Los Angeles, California, USA)[15]. General patient and volunteer characteristics were documented. For the statistical analysis, a similar approach was used as described in a previous study by Stekelenburg et al[16] where the device was tested for measuring scar surface area. We refer to the appendix of this study for a detailed description of the statistical calculations[16]. All analyses were performed with the scars as unit of analysis. Because of the skewed distribution of the measurements, data were transformed using a cube root transformation to approximate a normal distribution and constant error variance best. The interobserver reliability was defined as the correlation between the measurements of the two observers and expressed through the interobserver intraclass correlation coefficient ($ICC_{inter}$). The $ICC_{inter}$ was calculated using the estimated variance components of a scars × observers random-effects model without replications (on the transformed data): scar variance ($\sigma^2_{scar}$), observer variance ($\sigma^2_{obs}$), and the error variance ($\sigma^2_{error}$). The ICC is the ratio between the scar variance and the total variance[17]: $ICC = \sigma^2_{scar}/(\sigma^2_{scar} + \sigma^2_{obs} + \sigma^2_{error})$. The standard error of measurement (SEM)was obtained using the formula: $SEM = \sqrt{(\sigma^2_{obs} + \sigma^2_{error})}$ [18]. To give an indication of the absolute agreement between observers, Bland and Altman plots were obtained in which limits of agreement were indicated[19]. These plots show the mean of measurements of two observers on the x-axis against the difference between the two measurements on the y-axis, accompanied by the Limits of Agreement (LoA)[19]. The LoA were derived from a backtransformation of the data (X) and calculated as: $LoA=0\pm(\sqrt[3]{X} \pm 1.96\sqrt{2} \times SEM)^3$ . The LoA were expressed in the units of measurement and indicate that 95% of the differences between two measurements lie between these limits.

In order to assess the validity, the measurement data of 3D stereophotogrammetry and of the gold standard were compared by using the concordance correlation coefficient

(CCC)[16]. For each of the two measurements, the CCC was calculated, and these two CCC's were averaged. To quantify the difference between both methods expressed in $mm^3$, again LoA were calculated. In this way, a (nonlinear) regression line and a corresponding 95% prediction interval for the gold standard based on one 3D measurement was calculated using the method of inverse prediction[16,20].

# Results

## Reliability

Fifty-one clinically raised scars of 31 patients were included. Patient demographics and scar characteristics are shown in *Table 1*. The mean volume, obtained by 3D measurement, was 1619 $mm^3$ [standard deviation (SD): 4120 $mm^3$]. After cube root transformation of the data, the $ICC_{inter}$ was found to be 0.99, corresponding to the correlation between the cross 3D volume measurements of two photographs produced by two observers. The variance components were estimated at 25.35 (scars), 0.00 (observers) and 0.10 (error). The SEM was calculated at 0.32. Acquired from the reasonably high SEM, also the LoA are quite wide. Transformation to the traditional Bland-Altman format yields *Figure 2*, which represents the volumes up to 3000 $mm^3$.

| Characteristics | Value | Characteristics | Value |
|---|---|---|---|
| Scars, n | 51 | Cause of scar, n | |
| | | Burn injury | 11 (22%) |
| Patients, n | 31 | Trauma | 2 (4%) |
| | | Operation | 13 (25%) |
| | | Injection | 6 (12%) |
| Gender, n | | Acne | 13 (25%) |
| Male | 16 | Cause unknown | 6 (12%) |
| Female | 15 | | |
| Age, years | | Scar location, n | |
| Mean (SD) | 33 (16) | Face | 7 (14%) |
| Minimum | 2 | Presternal | 12 (23%) |
| Maximum | 73 | Deltoid region | 8 (16%) |
| | | Extremities | 14 (27%) |
| Scar type, n | | Back/scapula | 6 (12%) |
| Hypertrophic | 15 (29%) | Ear(lobe) | 4 (8%) |
| Keloid | 35 (69%) | | |
| Mixed | 1 (2%) | | |

***Table 1.*** *Patient characteristics.*

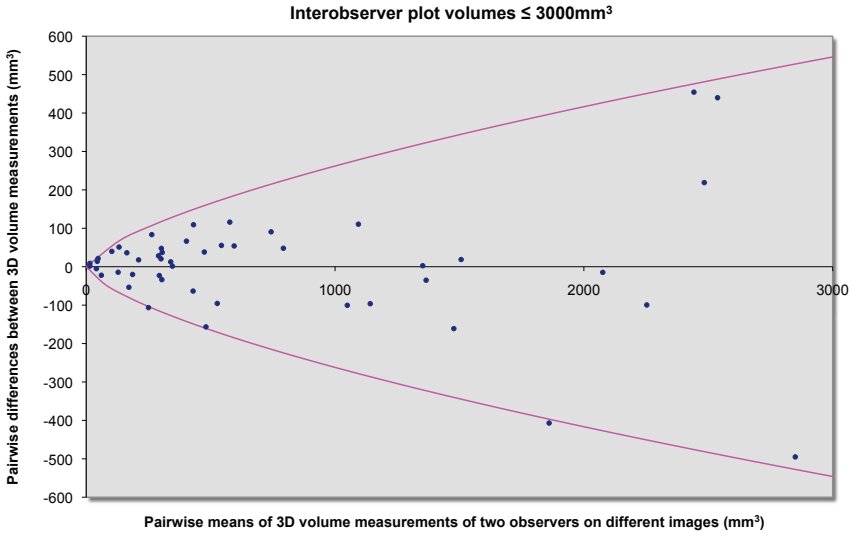


***Figure 2.*** *Bland and Altman plot with the back transformed limits of agreement (pink lines), indicating the inter-observer agreement between the two observers of mean scar volume ≤3000 mm³.*

## Validity

Sixty scar models were applied to 20 healthy volunteers. The mean scar volume by weighing the clay and calculating the volume was 5550 mm³ (SD: 4042 mm³). The mean volumes and standard deviations measured by two observers using 3D stereophotogrammetry were, respectively, 5459 mm³ (SD 4256 mm³) and 5629 mm³ (SD 4322 mm³). The mean CCC was 0.97, corresponding to the correlation between 3D stereophotogrammetry measurement and by weighing the clay. The data of validity are plotted in *Figure 3*, with the gold standard (G) on the y-axis and 3D stereophotogrammetry values (X) on the x-axis. Inverse prediction yielded the (nonlinear) regression line $G = (0.93\sqrt[3]{X} + 0.12)^3$ and $(0.93\sqrt[3]{X} + 0.12 \pm 1.74)^3$ for the accompanying LoA. With the regression line, a gold standard value can be calculated from a given 3D measurement. Also, a 45° line (i.e., the line of equality) is plotted, representing 100% agreement between the two methods for measuring scar volume. Note that the prediction line is positioned below the 45° line and that the LoA are again considerably wide.

# Discussion

In this study, 3D stereophotogrammetry was found to have a very high reliability expressed by a high $ICC_{inter}$ (0.99). Moreover, the CCC that was found for the correlation between 3D

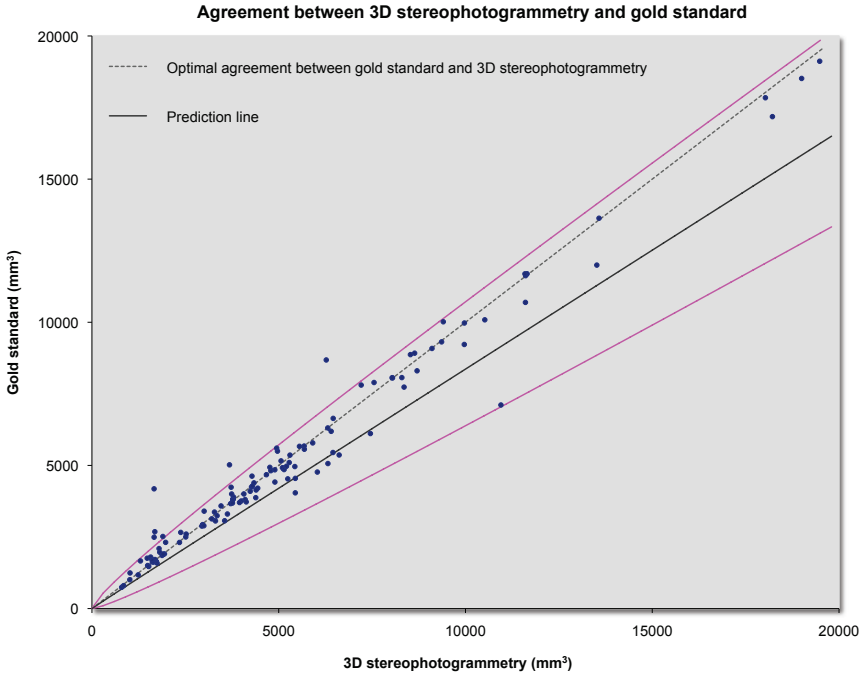


***Figure 3.*** *Plot of the 3D stereophotogrammetry and the gold standard. The grey solid line signifies the regression line between these two methods (or predicted value of the gold standard). The dotted grey line is the 45° line signifying 100% agreement between the two methods.*

stereophotogrammetry and the gold standard was very high (0.97). The reliability and validity of 3D stereophotogrammetry were excellent from this perspective and correspond to other studies that described the use of 3D stereophotogrammetry in measuring volume of clinically raised skin scars. Both studies calculated and presented a very high correlation coefficient (Pearson's correlation coefficient >0.97) between volumes obtained with 3D stereophotogrammetry, and the actual volume assessed by weighing and calculating the volume of a scar model[8,12]. Therefore, it can be concluded that not only our study but also all clinimetric studies on 3D stereophotogrammetry for volume measurements of scars showed an excellent reliability and validity measured by correlation statistics. However, although the correlation coefficient is rather a widely accepted and common parameter to assess the reliability and validity, it is not very informative. ICC as well as a Pearson's correlation coefficient, are relative measurements of correlation and do not provide direct information about the absolute measurement error. For the clinical follow-up of patients, we are interested in the absolute measurement error of an individual measurement because that determines the change that can be detected beyond the measurement error. The SEM's we found are too large for use in clinical practice. For research purposes,

(i.e., group comparisons), measurement errors are much smaller as these are leveled out in groups because the error is divided by the square root of the number included in the study[14].

Because we were interested in applications of 3D stereophotogrammetry in both research and clinical practice, we additionally studied the absolute agreement between observers as well as the agreement between stereophotogrammetry and the gold standard. This analysis showed that the agreement between observers, in terms of measurement error and LoA, was moderate, which can be concluded from the relatively broad LoA in the Bland and Altman plot. Also, the true agreement between 3D stereophotogrammetry and the gold standard was moderate, which can be interpreted from the considerable width of the LoA. These findings are similar to those of a study that was previously performed by our research group, where the reliability and validity of 3D stereophotogrammetry for the measurement of scar surface area was studied: a high ICC in combination with a moderately good agreement[16]. In most studies on reliability and validity, including those previously mentioned, no additional agreement analysis is done[8,12]. Likely, the same discrepancy would be found in these studies if additional agreement analysis was performed. For clinimetrical studies, we therefore advocate the use of both ICCs, measurement error, and Bland and Altman plots with LoA to have a better (true) understanding of the clinimetric quality.

The discrepancy between the high correlation values and the moderate agreement can be explained by the heterogeneity of the study population. Reliability refers to the question to what extent the scar volumes can be distinguished from each other by the two observers. It is obvious that it is easier to distinguish scars with a wide range of volumes than scars with equal volumes. The ICC is a parameter that is dependent on the heterogeneity of scar volumes in the study population[17]. The measurement error refers to absolute differences between the estimation of the volumes, expressed in $mm^3$. We chose a study population with a wide range of scar volumes because this matches the patient population that is seen in clinical practice. In cases where a high ICC is possibly due to a heterogenic study population, it is important to also assess agreement parameters[16,17].

Possible explanations for the moderate agreement are multiple. First, it was found that scars on extremely curved body parts could not be captured in a single photograph. From a single position of the camera, the edges of the scar were not seen. The 3D reconstruction that was obtained subsequently showed a deformation of the scar edges, resulting in an aberrant volume measurement. Second, it was seen that in some scars, especially keloids, a volumetrically smaller base could not be captured with one photograph. Because the camera was held perpendicular to the scar and the angle of the lenses was predefined, it was not possible to picture the small base resulting in a deformed 3D reconstruction.

For both situations, we suggest taking multiple pictures of a scar from more than one angle and identifying the different segments of a scar with a marker. This will result in a better quality of the photographs without deformation. Subsequently, the volumes of the segments derived with 3D measurement can be summed. Third, another possible reason for the moderate agreement is the three-dimensional aspect of volume measurements. For measuring scar surfaces, quadratic units are used, and for scar volumes, cubic units. This means that measurement errors may occur in three dimensions instead of one. This hypothesis is supported by the finding that a cube root transformation of the data results in an approximate normal distribution of the volume values[16]. Fourth, although we optimally standardized the method of taking the pictures and measuring the volumes, measurement errors may arise when taking a photograph. These measurement errors may arise from differences in distance to the object and the exact angle in which the photograph is taken. Technical adjustments to the device might overcome this source of possible measurement error and could be food for future research. Finally, regarding the moderate validity of the device, this could be partially due to the difficulty in determining the exact cutoff point on the backside of the scar. Although we standardized the cutoff point for each scar, the actual curve of the scar, underneath the skin, remains unclear. This difficulty applies though, for all other types of photographic 3D imaging, but also for the gold standard.

In summary, 3D stereophotogrammetry is suitable for the use as measurement instrument in research settings. This is a valuable finding in the search for objective tools to monitor the effect of different treatments. For the use in clinical practice, where we are interested in the individual follow-up of patients in time, the agreement should be improved.

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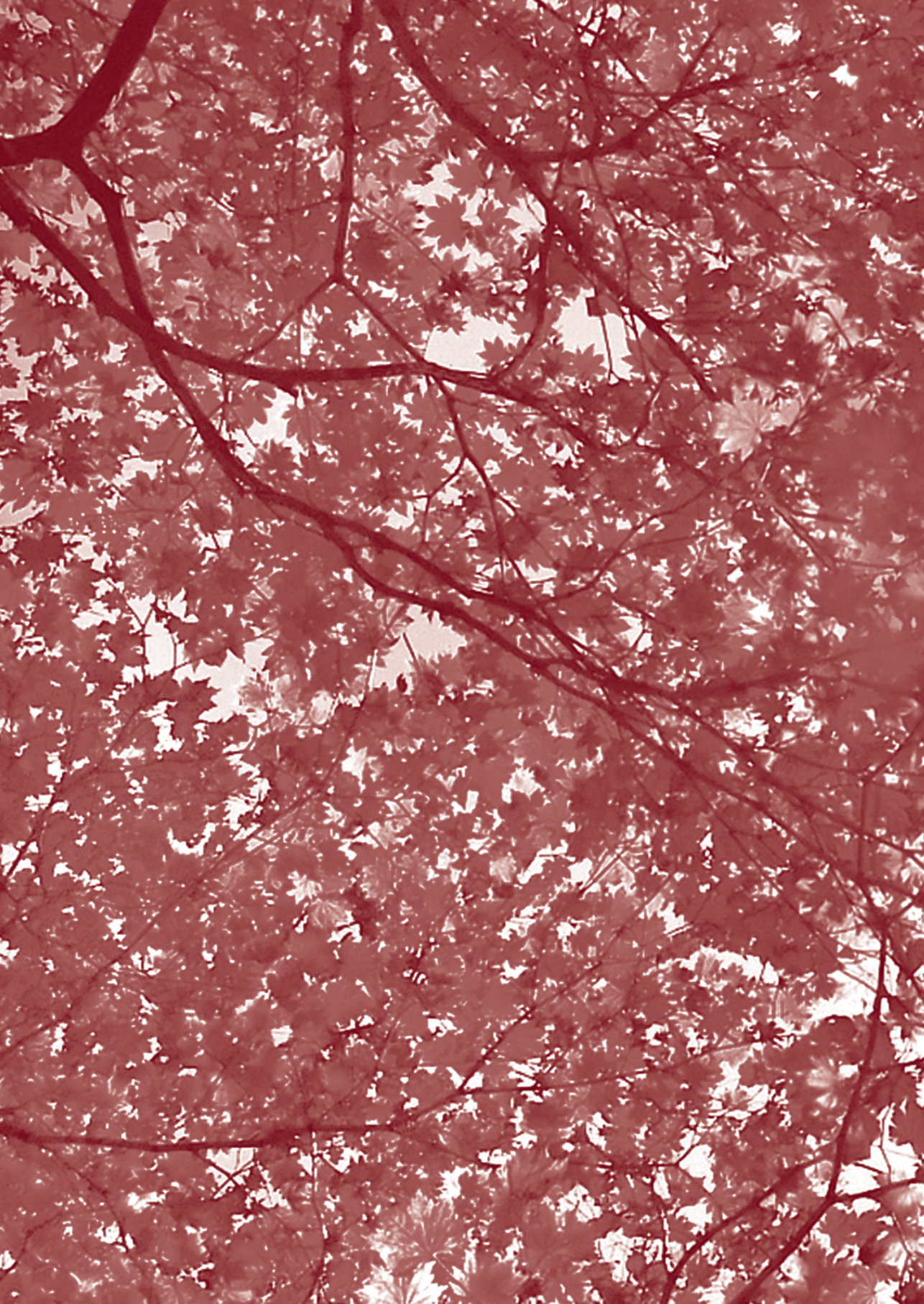
3

# PART II

## Burn scar contracture treatment: the current state of the art



# 4

# A systematic review on burn scar contracture treatment: searching for evidence

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## Abstract

**Introduction:** Treating burn scar contracture remains a challenging problem for reconstructive surgeons. At present, no consensus exists on when to use what kind of technique. Therefore, a systematic review was performed on the effectiveness of the different surgical techniques after burn scar contracture release.

**Materials and Methods:** Electronic databases were searched using a predefined search strategy. Studies evaluating the outcome of surgical techniques for the treatment of burn scar contractures were included. The methodological quality was tested and data was summarized.

**Results:** 1649 papers were identified of which 17 met the inclusion criteria. Three papers reported on a controlled trial, 14 were cohort studies, including 10 of a pre-post operative design and 4 of a comparative design. The papers described outcomes of grafts, flaps with random or defined vascularization, and dermal substitutes. All studies had methodological shortcomings and most used inappropriate statistical methods.

**Conclusions:** The current evidence on the effectiveness of reconstruction techniques for burn scar contractures was summarized. Due to the scarcity and low quality of the included studies, no definitive conclusions could be reached about the effectiveness of different techniques. Therefore, no direct implications for daily practice could be made. However, recommendations could be given for improvement of the quality of further primary research on the effectiveness of surgical treatment strategies for burn scar contracture release.

# Introduction

Patients with burn scars often experience functional problems because of scar contractures[1]. A contracture describes the condition in which contraction of scar tissue results in a decrease in range of motion and/or instability of the scar. This problem is considerable in burn patients because burns often cover large areas. Although various efforts have been made to prevent the development of contractures in the acute phase of burn treatment, the contraction rate of burn scars is still a poorly controlled process and reconstructive surgery is often indicated.

The purpose of surgery is releasing the contracture to improve the function of an underlying joint by incising a scar in such a way that it allows optimal mobility. This often leads to a defect that needs closure for which various techniques are available. Many established surgical techniques are available such as split thickness skin grafts (STSG), full thickness grafts (FTG), V-Y plasties, V-M plasties, dermal substitution and free flaps. Also, new techniques mainly in the field of defined vascular supplied flaps and dermal substitution are rapidly developing, gaining importance in the treatment of burn scar contractures.



Worldwide many types of reconstructive procedures are performed for scar contractures every day, yet there is still no systematic review on the effectiveness of different treatment techniques. Therefore, we performed a systematic review on this relevant topic. We looked at the methodological and statistical quality of the available primary studies and summarized the evidence to clarify the efficacy of different techniques and the outcome parameters used.

# Materials and Methods

## Types of studies

All types of studies that evaluated the effect of different types of reconstruction techniques after burn scar contracture release were included. Also, studies that evaluated the effect of a single intervention (a pre-post comparison) were eligible next to studies that compared two interventions (cohort studies and RCTs). This was done because we expected it to be unlikely to find a sufficient number of randomized controlled trials concerning this subject. We realized that, as a consequence, potential biases were likely to be greater and therefore careful assessment of the risk of biases, especially the potential for selection bias and confounding, was performed.

## Types of participants

All studies concerning reconstructive procedures for burn scar contractures were included.

## Types of interventions

Studies examining the effect of any type of reconstruction technique after burn scar contracture release were included. If a comparator intervention was described, it could be any other reconstruction technique, placebo intervention or no intervention.

## Types of outcome measures

Only studies that described long-term outcomes i.e. ≥ 3 months were included, because we were interested in lasting functional results. Studies with a shorter follow-up period predominantly describe the direct effect of the operation such as survival rate and percentage of necrosis of the intervention. Typical outcome measures were functional improvement, surface area measurements and scar quality. As outcomes are often described in different ways, this broad term strategy was chosen in order to include all articles concerning this subject.

## Other aspects of eligibility

Studies were excluded if they were not (only) on burns or (only) on the treatment of contractures, there was no abstract available or it concerned a narrative description instead of an outcome description of a reconstructive technique. We decided to include studies with an inclusion number of at least 15 procedures to avoid inclusion of small, possibly selective patient series.

## Search methods for identification of studies

*Electronic searches*

The following databases were searched until November 2012:

- Cochrane CENTRAL Trial register;
- PubMed; from inception;
- Ovid EMBASE - 1980 to date; and
- Clinical Trials Registry Platform Search Portal (www.who.int/trialsearch).

We conducted the PubMed, EMBASE and Cochrane search using the search strategy illustrated in *Table 1* of the *Appendix*. No date or language restrictions were applied and citation lists within all studies were checked in an effort to identify additional relevant studies.

## Data collection and analysis

Two authors (Carlijn Stekelenburg and Roos Marck) independently screened the titles and abstracts identified from the search against the inclusion criteria. The full text articles were reviewed; data extraction and quality assessment were performed independently

by the same two authors (Carlijn Stekelenburg and Roos Marck). As different types of studies were included, different types of criteria based on different assessment forms were applied. For (randomized) controlled trials the Cochrane Risk of Bias criteria[2] were used (*Table 2, Appendix*), for cohort studies the Newcastle-Ottawa quality assessment scale[3] was used (*Figure 1, Appendix*). The studies were judged on three broad perspectives: selection, comparability and outcome. Any discrepancies in judgment between the two authors were again resolved by discussion between the review authors.

### Statistical analysis

The included studies were summarised using a structured narrative description. The studies were grouped according to their primary outcome parameter. Of each study effect sizes (with 95% confidence intervals) were calculated if possible using the standardised response mean[4]. For this analysis, comprehensive meta-analysis Version 2, Biostat, Englewood NJ (2005) was used. Statistical pooling of the data per outcome would only be undertaken for studies that are comparable (concerning study design, type of intervention, outcome description and statistical analysis) and that present sufficient data to perform pooling.



## Results

### Search results

After de-duplication 1649 references were identified from electronic databases. Checking titles and abstracts on the inclusion and exclusion criteria resulted in 327 papers. The exclusion of studies with an insufficient outcome description and studies with a sample size of less than 15 persons left only 17 studies for full evaluation[5-21]. *Figure 1* illustrates the flow of studies throughout the review process.

### Main description of studies

No randomized controlled trials were identified. Three manuscripts, describing the follow-up of the same controlled trial[7,18,19], and 14 cohort studies met the review inclusion criteria. Of the included cohort studies 4 compared different therapies[5,6,9,16] and 10 had a pre-post operative design[8,10-15,17,20,21]. The patients were measured before operation and at a predefined time period after operation. The follow-up period varied from 3 months to 12 years. The controlled trial analyzed the same cohort at multiple time points, so each parameter could only be evaluated once[7,18,19]. The same was true for 2 cohorts which were analyzed twice in different papers[5,6,10,11]. Overall, the patient groups studied in the different papers were small with a median of 27 patients (range 10-103).

The included articles describe different operative techniques that could be divided in 4 main groups: skin grafts, flaps based on random vascularization (such as Z-plasties and

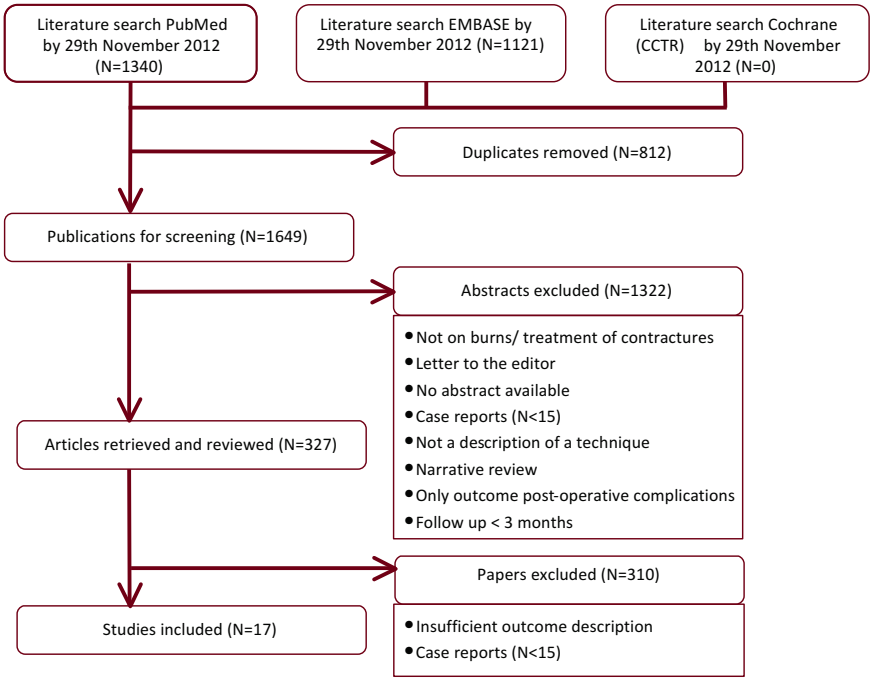


***Figure 1.*** *Flow diagram of study selection process.*

V-Y plasties flaps), flaps based on defined vascularization (perforator based flaps, free flaps), and dermal substitutes. This division seemed to cover the different treatment modalities best.

## Outcome measures

Methods for measuring the effect of surgical interventions included goniometry, planimetry, scar assessment scales and 3D video-based goniometry (*Table 1*). Most studies that used range of motion as outcome measure, used goniometric measurements, but did not describe the measurement technique[5,6,8,13,16,17,21]. Only one study used a semi-validated system to measure different movements[15]. Planimetric measurements were performed by tracing (surface area)[19,20] and/or measuring (width)[14,20]. In the dermal substitutes group scar scales were used to measure the scar quality as outcome measure. The Vancouver scar scale[10-12,18] and the POSAS (Patient and Observer Scar Assessment Scale)[7] were used.

## Effect of Interventions

### *Skin grafts*

Four studies assessed the outcome of skin grafts after burn scar contracture release[5,9,15,16], of which 3 used the range of motion (ROM) as primary outcome parameter to assess the functional results[5,16]. The detailed descriptions of the outcomes can be found in *Table 1*.

*Flaps with random vascularization*

All papers that studied the effectiveness of plasties used ROM as outcome parameter[5,6,13,16]. *Table 1* gives a detailed description of the different flaps and their outcome.

*Flaps with defined vascularization*

Five studies described the outcome of different flaps on various anatomic locations[8,14,17,20,21]. Tsai et al[17], Woo et al[21] and Er et al[8] found an increased postoperative range of motion[17,21]. Although all the 3 studies measured an increased range of motion[8,17,21], unfortunately, none used statistical analysis to evaluate this effect. Three of the authors used planimetric measurements to evaluate the effect of treatment strategies; surface area or width during surgery was compared to the surface area or width at follow-up. However, only Verhaegen et al[20] performed statistical analysis and found no statistical difference. See *Table 1*.

*Dermal substitutes*

Six manuscripts describing the outcome of 3 trials assessed the effect of dermal substitutes in combination with an STSG[7,10-12,18,19]. Different dermal substitutes are used across studies: Integra®[10,11], Matriderm® prototype[7,18,19] and Alloderm®[12]. All the studies that measured scar quality before and after surgical procedures showed a significant decrease in Vancouver Scar Scale score[10-12]. Furthermore, no difference in surface area was found for the use of skin grafts with or without dermal substitution; both show a considerable contraction after a mean follow-up period of more than one year[19]. *Table 1* describes in detail the outcomes of the different studies relating dermal substitutes.

## Effect sizes and meta-analysis

The studies were subdivided according to the way the outcome was measured, i.e. planimetry, range of motion or scar quality. The effect sizes were calculated and plotted to allow for a comparison between the treatments per outcome parameter (*Figure 2*). Calculation of effect sizes was only done when comparison with another independent study that measured the outcome similarly was possible. *Figure 2* visualizes the effect sizes with corresponding 95% confidence intervals of different interventions. No meta-analysis of these data could be performed because this was incorrect for both clinical and statistical heterogeneity of the studies. Calculation of the effect sizes was done using mean differences, standard deviations, sample sizes and p-values retrieved from the result sections of the articles. Corresponding authors were contacted in case studies did not contain sufficient information. After repeated requests we were only able to calculate effect sizes for a small amount of studies[6,8,12,14,19,20].

| Study | Intervention | Number | Primary outcome parameter | Effect of intervention | Use of validated outcome measures? |
|---|---|---|---|---|---|
| **Controlled trials** | | | | | |
| Van Zuijlen et al (2000 and 2001) [18,19] | Dermal substitution +STSG vs. STSG | 44 | Scar quality and surface area | Surface area: no significance diff between with or without dermal substitute | Planimetry |
| Bloemen et al (2010) [7] same cohort | | 34 | | VSS : no significance diff between with or without dermal substitute<br><br>POSAS<br>12 years: significant better result for pliability, relief and general | Vancouver scar scale<br><br><br><br>POSAS |
| **Cohort studies - Comparative design** | | | | | |
| Alexander et al (1982)[5] | Skin grafts, Z plasties, Rotational flaps | Skin grafts (54 STSG, 9 FTSG)<br>Z plasty (46)<br>Rotation flap (34) | ROM | NS differences between Graft, z-plasty and rotational flap | Goniometry: retrospective chart review |
| Alexander et al (1983)[6] | V-M plasty | 36 | ROM | Significant differences in ROM and cosmetic appearance between V-M plasty and control group | Goniometry: retrospective chart review |
| Stern et al (1985)[16] | Flaps (Z-plasty,Y-V advancement, rotationflap) and STSG's | 78 | ROM | Decrease in extension contracture for Flaps and STSG's. No statistical analysis | Goniometry: retrospective chart review |
| Iwuagwu et al (1999)[9] | STSG vs. FTSG | 75 STSG<br>235 FTSG | Rereleases | Significant more rereleases in of STSG's than for FTSG's | Documentation: retrospective chart review |

***Table 1.*** *Summary of outcome in included studies.*

| Study | Intervention | Number | Primary outcome parameter | Effect of intervention | Use of validated outcome measures? |
|---|---|---|---|---|---|
| **Cohort studies- Pre-post operative design** | | | | | |
| Moiemen et al (2000 and 2006) same cohort[10,11] | Integra + STSG | 30 | Scar quality | Significant improvement in VSS pre-op vs. post-op | Vancouver scar scale |
| Woo et al (2001)[21] | Free flap | 18 | ROM | Increase in range of motion pre-op vs. post-op. No statistical analysis | Goniometry: retrospective chart review |
| Peker et al (2003)[13] | Y-V plasty combined with Z-plasty | 98 | ROM | Significant increase in ROM arc | Goniometry: retrospective chart review |
| Er et al (2005)[8] | Thoracodorsal perforator based cutaneous island flap | 15 | ROM | Increase in ROM pre-op vs. post-op<br>No statistical analysis | Goniometry: retrospective chart review |
| Tsai et al (2006)[17] | Flaps | 40 | ROM<br>Flap width | Increase in ROM for different areas in the neck<br>Increase in flap width<br>No statistical analysis | Goniometry: retrospective chart review<br>Planimetry: measuring |
| Rashid et al (2006)[14] | Supraclavicular flap | 27 | Flap width | Increase in flap width pre-op vs. post-op<br>No statistical analysis | Planimetry |
| Verhaegen et al (2010)[20] | Perforator based flaps | 22 | Flap width and area | No statistical differences in flap width and -area directly postoperative and at follow-up. | Planimetry |
| Oh et al (2011)[12] | Alloderm + STSG | 27 | Scar quality | Significant improvement in VSS pre-op vs. post-op. | Vancouver scar scale |
| Sison-Williamson et al (2012)[15] | STSG | 16 | ROM | Significant improvement in most motions that are needed for high reach, hand to head and hand to back tasks. | 3D-videobased technique using retroreflective markers attached to the patient |

***Table 1.*** *Continued.*

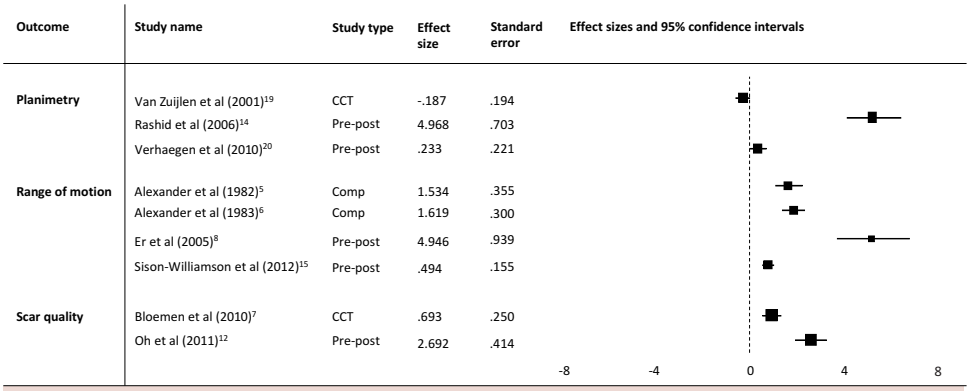


***Figure 2.*** *Effect sizes with corresponding 95% confidence interval for range of motion, planimetry and scar quality. In the* Study type *column the following abbreviations are used. CCT= Controlled Clinical Trial, Comp= Comparative cohort, Pre-post= pre-post operative cohort.*

## Assessment of the risk of bias

Information on the methodological quality of the included studies is summarized in *Table 2*. The overall risk of biases was high in all cohort studies. One of the most frequent encountered problems included insufficient description of the cohort. Only two studies satisfactorily described the cohort; a representative cohort and the presence of a comparable cohort[5,9]. Of the studies that could score on the item 'comparability'[5,6,9,16], one study performed most favorably[9] by controlling for differences between cohorts on the basis of the design. In terms of outcome assessment, the weaknesses were mainly found in an insufficient outcome measurement[8,12-14,16,21].

The key concern for the controlled trials was the absence of randomization and blinding resulting in selection, performance, and detection bias. The description of the outcome however, was done adequately with the use of reliable and valid measurement instruments[7,18,19].

# Discussion

As far as we have been able to establish, this is the first systematic review on the effectiveness of reconstructive techniques after burn scar contracture release revealing that the current literature is of low methodological quality. We analyzed 1649 articles on the subject of which only 17 described a surgical treatment regimen in a sample of ≥ 15 patients. Considering the fact that we applied mild inclusion criteria regarding the year of publication and study type, this is a particularly low number of studies.

| Study | Selection * * * * | | | | Comparability * | Outcome * * * | | |
|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort | Selection of the non exposed cohort | Ascertainment of exposure | Outcome of interest not present at start | Comparability of the cohorts | Assessment of outcome | Follow-up long enough | Adequacy of follow-up |
| **Cohort studies - Comparative design** | | | | | | | | |
| Alexander 1982[5] | * | * | * | * | | * | * | |
| Alexander 1983[6] | * | | * | * | | * | * | |
| Stern 1985[16] | * | * | * | * | | | * | |
| Iwuagwu 1999[9] | * | * | * | * | * | * | * | |
| **Cohort studies- Pre-post operative design** | | | | | | | | |
| Moiemen 2000/2006[10,11] | * | | * | * | | * | * | |
| Woo 2001[21] | * | | | * | | * | * | |
| Peker 2003[13] | * | | | * | | | * | |
| Er 2005[8] | * | | | * | | | | |
| Tsai 2006[17] | * | | * | * | | * | * | |
| Rashid 2006[14] | * | | | * | | | * | |
| Verhaegen 2010[20] | * | | * | * | | * | * | |
| Oh 2011[12] | * | | | * | | | * | |
| Sison-Williamson 2012[15] | * | * | * | * | | * | * | * |

***Table 2.*** *Included studies subdivided according to the study type, presented in chronological order. Quality assessment using the New Castle-Ottowa scale for cohort studies. A star (*) indicates that a measure was adequately addressed in this study. A maximum of one star was awarded for each numbered item within the selection- and outcome categories, and two for comparability.*

The included studies were evaluated using standardized assessment scales and found to be of low overall quality. Because of these limitations, we were not able to provide sufficient evidence to draw conclusions on the effectiveness of reconstructive techniques after burn scar contracture release and developing a standardized treatment algorithm remains a challenge. Probably, the most important conclusion of this review is that there is definitively a need for more adequate research.

Several reasons may explain the difficulty in stating conclusions on the effectiveness of reconstructive techniques for burn scar contracture release. The first relates to the design of the studies: most were of a pre-post operative design without the presence of a comparative cohort. These studies reported an improvement in range of motion or scar

quality, but only a few compared the technique of interest with another technique[5-7,9,16,18,19]. As can be seen in *Figure 2*, the effect sizes of the studies with a comparative cohort are smaller than the studies of a pre-post operative design. This means that besides the improvement that was established by means of an operation, the difference between reconstructive techniques is moderate. The pre-post operative design is informative, but does not allow for strong conclusions in terms of effectiveness of one treatment method over another. Three papers reported on the same controlled trial. These papers had a superior design and used reliable and validated measurements. As these 3 papers were based on the same patient population, we could not pool the results. A second reason may relate to the considerable amount of studies that failed to perform an adequate data presentation and statistical analysis, preventing a full interpretation of the presented results. Effect sizes were only calculated in case the same construct was measured by a comparable measurement technique (*Figure 2*). Because of both the statistical and methodological heterogeneity, no meta-analysis could be performed.

Although most of the interventions have some evidence for the effectiveness in burn scar contracture release, the included studies used different outcome parameters limiting comparisons between treatments and making a meta-analysis impossible to perform. Therefore, only a rough division could be made between functional outcome parameters and scar quality parameters. Furthermore, most studies did not describe the type of contracture. This is important because broad contractures reasonably need a different treatment than linear contractures. A final difficulty relates to the fact that burn scar reconstruction options are not completely interchangeable because they are subject to many different variables, such as width, location and extensiveness of the scars. This may put challenges on systematically reviewing the literature on the treatment of burn scar contractures.

This review has limitations. The methodological quality of the included studies was assessed using the New Castle Ottawa quality assessment tool in order to address the quality of non randomized studies[3]. Because this tool presumes the presence of a comparable cohort, all studies except for one were not awarded any stars for comparability. Other tools for assessing the risk of biases were considered; however, to our knowledge no validated tools for assessing the methodological quality of pre-post design studies were available[22]. Second, we chose to use a broad search strategy to include all types of treatment modalities. Although this offers an overview of the available literature on burn scar contracture release, it also results in an inability to compare data because of the heterogeneity of the included studies.

Despite the low number of eligible studies and the poor quality of the included studies, strength of this study is the profoundness of reviewing the data: an extensive search of 4 databases, no restriction regarding language and year and study type, and the independent reviewing by two researchers. Hereby, this review uncovers the weaknesses

of the currently available scientific literature offering a starting point for future research. We believe this to be a unique opportunity to bundle all the lessons learnt so far in the field of treating burn scar contractures and more specifically in the hurdles and challenges that one faces when performing studies in this field. Therefore it is paramount that we make good use of these lessons when setting up future studies.

We make a plea to use the findings of this review and its implication for future research. The first step is the design of a sound study set up; preferably a design that uses a comparator intervention. Only then the treatment effect can be distinguished from the clinical course and from the treatment with other surgical techniques. Also, a relevant sample size should be chosen. Comparative studies with a too small sample size are not informative and a realistic power calculation is needed for determining the numbers required in a trial, depending on the expected effect of the intervention in a specific patient population[23]. Studies should include a clear description of the patient groups including the type of contracture. The outcome assessment should be carefully linked to a relevant clinically expected outcome. Reliable and valid measurement techniques should be used to assess the outcome, which allows for comparison between study results[24]. The introduction of new measurement tools without validating them is not preferred[24]. Finally, an adequate data presentation and statistical analysis should be considered. Of the studies included in our review, many contain information to perform statistical analysis, but fail to present statistical important information such as standard deviations, p-values and confounders. Further primary research in collaboration with experts in research methodology and biostatistics is highly recommended. This review aims to encourage and inspire research initiatives on reconstruction techniques after burn scar contracture release.



## Conclusions

This review has brought to light that the current literature on the effectiveness of reconstructive techniques after burn scar contracture release is below par in both quantity and quality of the studies performed. Due to the lack of evidence we were not able to provide definitive conclusions on the effectiveness of different techniques or make specific recommendations on treatment algorithms. However, in view of the currently available literature future research initiatives are strongly encouraged. It is of the essence that such studies include methods of high quality, use of comparative outcome measures and adequate statistical analysis to ensure they contribute to a better understanding in the optimal treatment of burn scar contractures.

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4

# Appendix

| Nr | Subject | PubMed | EMBASE | Cochrane |
|---|---|---|---|---|
| 1 | **Burns** | MesH descriptor Burns (explode all trees) | burn/ | (burn OR burns OR scald* OR postburn* OR (thermal AND injur*)):ti,ab,kw |
| 2 | | Burn OR burns OR burned OR scald*[tiab] | burn or burns or burned or scald* or postburn.ti,ab,kw. | |
| 3 | | Thermal AND injur*[tiab] | thermal and injur*.ti,ab,kw. | |
| 4 | **Scar/ Contracture** | Mesh Cicatrix [noexp] | skin scar/ or scar/ | (contractur* OR scar* OR cicatri* OR hypertroph*):ti,ab,kw |
| 5 | | Mesh cicatrix, hypertrophic | burn contracture/ or contracture/ or flexion contracture/ or joint contracture/or (contractur* or scar* or cicatri* or hypertroph*). ti,ab,kw | |
| 6 | | Contractur* OR scar* OR cicatri* OR hypertroph*[tiab] | exp SCAR FORMATION/ or exp BURN SCAR/ or exp HYPERTROPHIC SCAR/or | |
| 7 | **Reconstruction** | MesH descriptor Reconstructive Surgical Procedures (explode all trees) | reconstruct* or releas*.ti,ab,kw. | ((axial OR perforator OR random OR rotation OR advancement OR transposition OR free) AND flap*) OR reconstructive surg* OR z plasty OR v y plasty OR y v plasty:ti,ab,kw |
| 8 | | MesH descriptor Surgical Flaps (explode all trees) | exp island flap/ or exp transverse rectus abdominis musculocutaneous flap/ or exp vertical rectus abdominis musculocutaneous flap/ or exp perforator flap/ or exp forehead flap/ or exp skin island flap/ or exp radial forearm flap/ or exp anterolateral thigh flap/ or exp adipofascial flap/ or exp thoracodorsal artery perforator flap/ or exp latissimus dorsi flap/ or exp scapular flap/ or exp superior gluteal artery perforator flap/ or exp skin transposition flap/ or exp skin flap survival/ or exp superficial inferior epigastric artery flap/ or exp deep inferior epigastric perforator flap/ or exp inferior gluteal artery perforator flap/ or exp lateral arm flap/ or exp muscle flap/ or exp myocutaneous flap/ or exp pedicled skin flap/ or exp gracilis flap/ or exp deltopectoral flap/ or exp skin flap/ or exp inguinal flap/ or exp paraumbilical perforator flap/ or exp tissue flap/ or exp fasciocutaneous flap/ | ((skin OR dermal OR full thickness OR split thickness OR split skin) AND (flap* OR graft*)) OR STSG OR ftg OR artificial skin* OR matriderm OR integra OR alloderm OR dermagraft OR oasis:ti,ab,kw |

***Appendix, Table 1.*** *Detailed search strategy for MEDLINE and EMBASE.*

| Nr | Subject | PubMed | EMBASE | Cochrane |
|---|---|---|---|---|
| 9 | | reconstructive surg*[tiab] | Reconstructive surg* .ti,ab,kw. | (reconstruct* OR releas*):ti,ab,kw |
| 10 | | z plasty OR v y plasty OR y v plasty | z plasty or v y plasty or y v plasty.ti,ab,kw | |
| 11 | | Axial OR perforator OR random OR rotation OR transposition OR advancement OR transposition OR free AND flap*[tiab] | axial or perforator or random or rotation or transposition or advancement or pedicled or free) and flap*.ti,ab,kw. | |
| 12 | | skin OR dermal OR full thickness OR full-thickness AND (flap* OR graft*) [tiab] | skin or dermal or full thickness and graft*:ti,ab,kw. | |
| 13 | | split thickness OR split-thickness OR split skin AND graft*[tiab] | split skin or split thickness and graft*:ti,ab,kw. | |
| 14 | | STSG OR FTG[tiab] | STSG or ftg:ti,ab,kw. | |
| 15 | | MeSH descriptor Skin, Artificial (explode all trees) OR integra artificial skin [Supplementary Concept] | artificial skin/ | |
| 16 | | artificial skin OR Matriderm OR integra OR Alloderm OR Dermagraft OR oasis[tiab] | artificial skin or matriderm or integra or alloderm or dermagraft or oasis.ti,ab,kw. | |
| 17 | | #12 OR #13 OR #14 OR #15 OR #16 AND (reconstruct* OR releas*) | #12 OR #13 OR #14 OR #15 OR #16 AND #7 | (#8 AND #9) |
| 18 | | (#7 OR #8 OR #9 OR #10 OR #11) OR #17 | #8 OR #9 OR #10 OR #11 OR #17 | (#1 AND #4 AND ( #7 OR #17 )) |
| 19 | | (#1 OR #2 OR #3) AND (#4 OR #5 OR#6) AND #18 | (#1 OR #2 OR #3) AND (#4 OR #5 OR#6) AND #18 | |

***Appendix, Table 1.*** *Continued.*

| Domain | Description | Review authors' judgment |
|---|---|---|
| Sequence generation | Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. | Was the allocation sequence adequately generated? |
| Allocation concealment | Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. | Was allocation adequately concealed? |
| Blinding of participants, personnel and outcome assessors | Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective. | Was knowledge of the allocated intervention adequately prevented during the study? |
| Incomplete outcome data | Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors. | Were incomplete outcome data adequately addressed? |
| Selective outcome reporting | State how the possibility of selective outcome reporting was examined by the review authors, and what was found. | Are reports of the study free of suggestion of selective outcome reporting? |
| Other sources of bias | State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry. | Was the study apparently free of other problems that could put it at a high risk of bias? |

***Appendix, Table 2.*** *The Cochrane Collaboration's tool for assessing risk of bias*[1].

## NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
## COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

**Selection**

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community *
   b) somewhat representative of the average _____ in the community *
   c) selected group of users e.g. nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) secure record (e.g. surgical records) *
   b) structured interview *
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes *
   b) no

**Comparability**

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) *
   b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

**Outcome**

1) Assessment of outcome
   a) independent blind assessment *
   b) record linkage *
   c) self report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow-up period for outcome of interest) *
   b) no
3) Adequacy of follow-up of cohorts
   a) complete follow-up - all subjects accounted for *
   b) subjects lost to follow-up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow-up, or description provided of those lost) *
   c) follow-up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

***Appendix, Figure 1.*** *The Newcastle-Ottawa quality assessment scale[2].*

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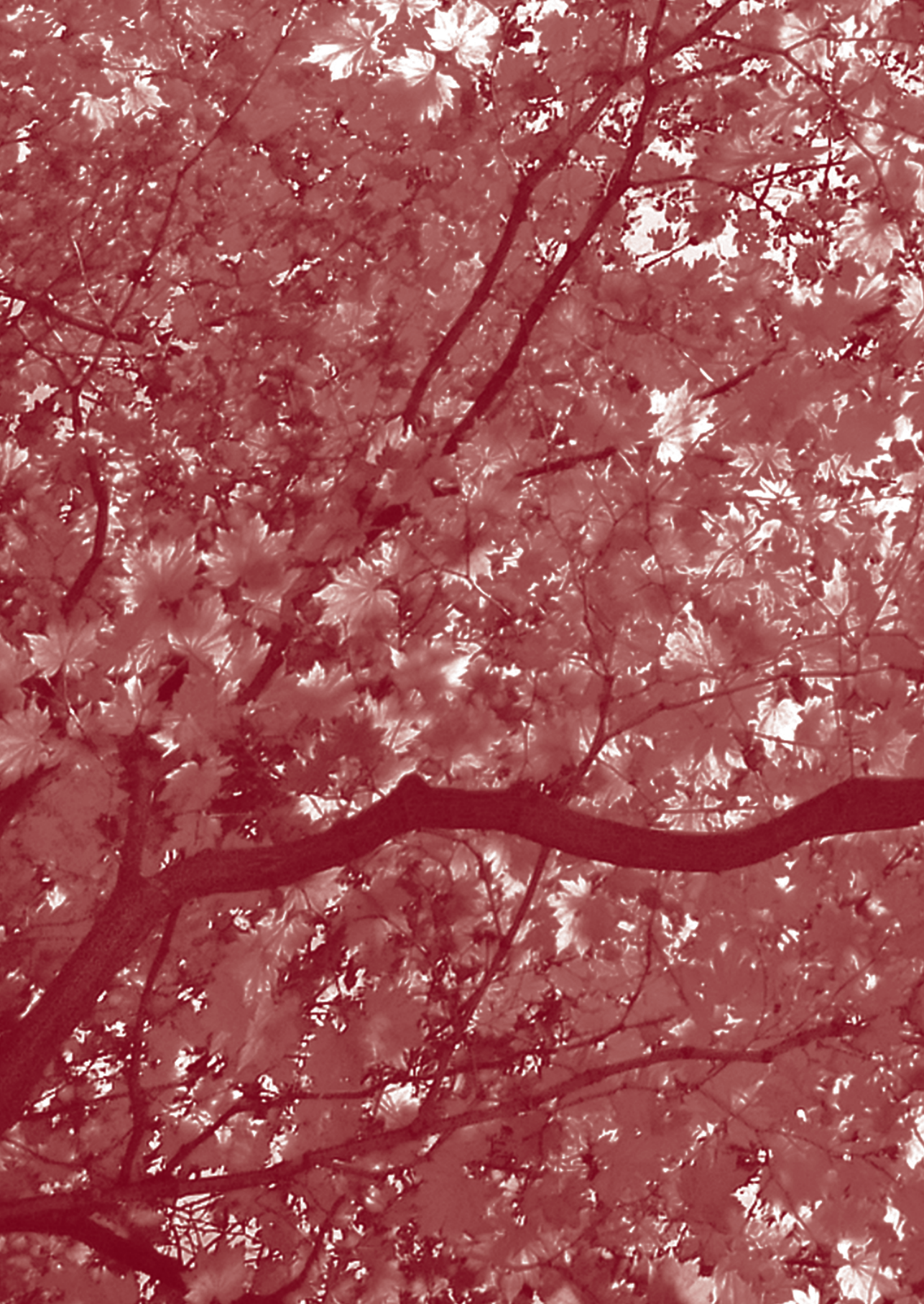
4



# 5

# Analyzing contraction of full thickness skin grafts in time: choosing the donor site does matter

Carlijn M. Stekelenburg
Janine M. Simons
Wim E. Tuinebreijer
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*Burns. In press*

## Abstract

**Introduction:** In reconstructive burn surgery full thickness skin grafts (FTSGs) are frequently preferred over split thickness skin grafts because they are known to provide superior esthetic results and less contraction. However, the contraction rate of FTSGs on the long term has never been studied.

**Materials and Methods:** The surface area of FTSGs of consecutive patients was measured during surgery and at their regular follow-up (at approximately 1, 6, 13 and 52 weeks postoperatively) by means of 3D stereophotogrammetry. Linear regression analysis was conducted to assess the influence of age, recipient and donor site and operation indication.

**Results:** 38 FTSGs in 26 patients, with a mean age of 37.4 years (SD 21.9) were evaluated. A significant reduction in remaining surface area to 79.1% was observed after approximately 6 weeks (p= 0.002), to 85.9% after approximately 13 weeks (p= 0.040) and to 91.5% after approximately 52 weeks (p=0.033). Grafts excised from the trunk showed significantly less contraction than grafts excised from the extremities (94.0 % vs. 75.7% p=0.036).

**Conclusions**: FTSGs showed a significant reduction in surface area, followed by a relaxation phase, but remained significantly smaller. Furthermore, the trunk should be preferred as donor site location over the extremities.

## Introduction

Despite new developments in acute and reconstructive burn surgery, such as dermal substitution and perforator-based interposition flaps[1], full thickness skin grafts (FTSGs) are regularly needed as first choice for reconstruction[2]. Usually FTSGs are preferred over split thickness skin grafts (STSGs) because they give a superior esthetic result and less contraction[2,3]. Remarkably, the extent of contraction of FTSGs in burn patients has never been objectified. Most often burn patients are treated with a FTSG to improve the range of motion. Therefore, the extra tissue that is inserted should retain its initial surface area to result in a successful procedure. FTSGs that are used for scar contracture release are positioned in scar tissue, which differs considerably from healthy tissue in terms of elasticity and contractile forces. The graft that is inserted in the defect is subject to these contractile forces and this could affect the contraction rate of FTSGs.

Several other factors may influence the contraction rate of FTSGs such as the age of the patient and the location where the skin is harvested[3]. It has been reported that FTSGs on the nose and peri-orbital area demonstrate more contraction than other recipient areas[4]. As differences in contraction rates according to the recipient location were found, likely differences in donorsite location may as well be present, which has only been observed in animal studies[5]. Furthermore patient characteristics like age of the patient at time of surgery have been assumed to influence the contraction rate of grafts[3,6]. Skin laxity is thought to increase with age and thereby older patients might show less contraction than younger patients[7].



Literature up to now, though providing some information on potential influencing parameters, does not suffice in a clear understanding of the contraction rate of FTSGs on the long term and its potential predictive factors. Two studies describe contraction of FTSGs in reconstructive procedures over time[4,8]. One study found a significant reduction in surface area within the first month after surgery, but no significant difference was found beyond the first month[8]. Another study stated that FTSGs undergo a significant amount of contraction; a mean remaining surface area of 62% was found[4]. As these studies use a relatively short follow-up period[4] and non validated surface area measurement techniques[8], results from these studies are less applicable for interpretation in clinical practice. To measure the outcome of a treatment technique objectively, the use of reliable and valid measurement instruments is important. 3D stereophotogrammetry is one of the most recent advances in the field of surface area measurement and has been proven to reliably and validly measure surface area[9]. The aim of this study was to evaluate the surface area of FTSGs over time using a reliable and valid measurement tool and to identify potential predictive factors that influence the surface area over time.

# Materials and Methods

## Patients

In this clinical observational study, we analyzed a cohort of consecutive patients that received FTSGs as a reconstructive procedure between April 2011 and November 2013 at the department of plastic, reconstructive and hand surgery in the Red Cross Hospital (Beverwijk, the Netherlands). Patients were seen at their regular follow-up moments as part of the medical treatment. *Figure 1* represents a flow chart. Also patients participating in other clinical studies were included. All patients of 12 years and older with scars that are treated in our clinic, undergo a standard scar evaluation protocol at follow-up. This scar evaluation protocol was approved by the local medical ethical committee and includes scar surface area measurements. From all patients informed consent was obtained. The following data were collected: age of the patient, the donor site, the recipient site, the indication for operation and the presence of risk factors such as diabetes mellitus or smoking were registered for each patient. These characteristics were registered to include in the analysis as potential risk factors.

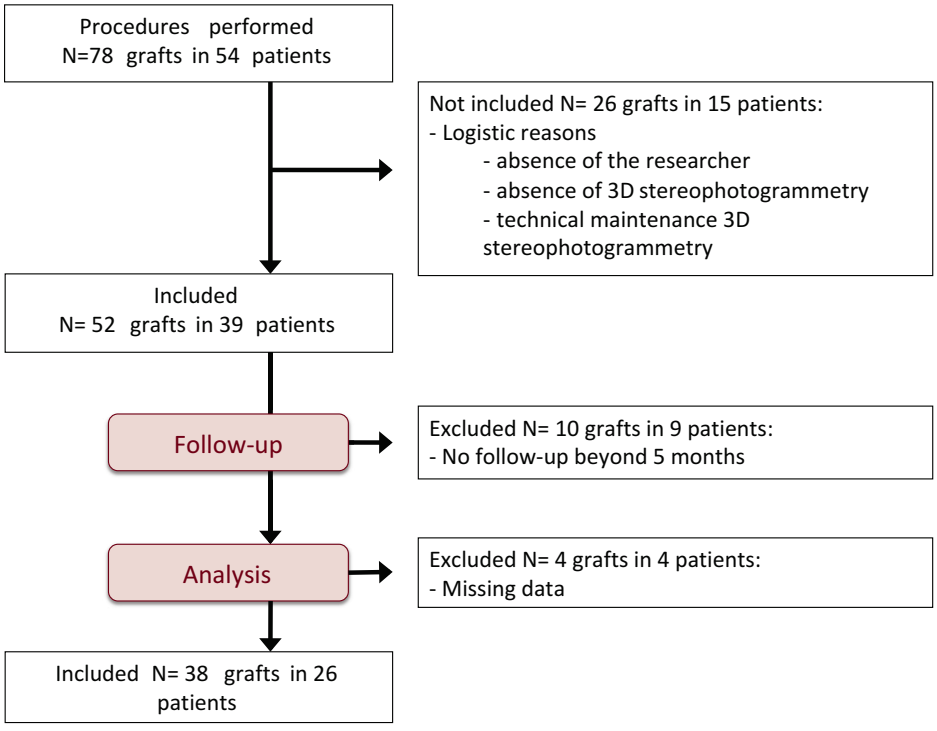


***Figure 1.*** *Flow chart representing the drop outs, due to lack of follow-up.*

## Operation technique

The FTSGs were applied using the following technique. The skin together with a thin layer of subcutaneous fat was harvested. Defatting of the subcutaneous fat from the dermis was performed adequately to facilitate survival of the graft. The graft was fixated using synthetic absorbable polyglactin suture. A tie-over was applied and removed after approximately seven days.

## Procedure

Measurement of the surface area of the graft was performed by means of 3D stereophotogrammetry, for which the 3D LifeViz (DermaPix software; QuantifiCare S.A., Sophia Antipolis, France) was used. This is a reliable and valid measurement method to measure surface area of scars which was proven in a validation study, previously published by our group[9]. Surface area measurements were performed during surgery and at follow-up. At surgery the FTSG was photographed and measured directly after being sutured on the recipient location (before applying the tie-over). This measurement was the baseline measurement for comparison with the follow-up measurements and is referred to as the initial measurement. Follow-up surface area measurements were performed at each planned visit of the patient to the outpatient clinic. Care was taken that during each measurement of the graft the patient adopted the same position. Postoperative complications were registered. Necrosis was subdivided in complete and partial necrosis. Patients were excluded from analysis in case no photographs were taken beyond 5 months follow-up (*Figure 1*).



## Statistical analysis

Statistical analysis was performed using SPSS 21.0 (IBM Corp., Armonk, NY, USA). Normal distribution was tested by calculating the skewness and kurtosis, evaluating frequency histograms, and performing the Shapiro-Wilcoxon test. To compare repeated measurements over time, a linear mixed effects model with a random intercept and analysis of covariance was used. The covariance structure was set to variance components. The surface area at surgery and at different follow-up moments was used as dependent variable in the models. Time from surgery was divided into categories and set as fixed effect. Five follow-up categories (C0w, C1w, C6w, C13w and C52w) were created (*Table 1*). The categories were chosen in a way they were considered clinically relevant and provided a substantial number of measurements. The first group (C0w) represented the measurements performed directly after surgery, the second group the measurements within the first three weeks after surgery (C1w), the third group (C6w) the short term follow-up measurements (around 6 weeks), the fourth group (C13w) the measurements from approximately 13 weeks, and the fifth group (C52w) the long term (i.e. about 1 year) follow-up measurements.

In the linear mixed effects model absolute values of surface areas were used. However,

because of the different compilations of the groups, also the means of the differences in percentages were calculated and presented per group. The main effects of age, reason for reconstruction, recipient and donor site location were included in a separate linear regression model. The significance criterion was set to 0.05.

| Category | Phase | Time | Range | Description |
|---|---|---|---|---|
| 1. C0w | At surgery | 0 weeks | - | Surface area directly after surgery |
| 2. C1w | Graft survival | Approximately 1 week | 1-21 days | The viability of the FTSG / presence of necrosis is assessed after approximately 1 week |
| 3. C6w | Contraction - short term | Approximately 6 weeks | 21-84 days | After 6 weeks, the FTSG has definitely taken and the first signs of contraction may be visible |
| 4. C13w | Contraction phase | Approximately three months | 84-168 days | End of the contraction phase. Entering the transition phase to relaxation and maturation |
| 5. C52w | Maturation phase - end | Approximately one year | 168-1095 days | End of the maturation phase |

***Table 1.*** *Time categories of the linear mixed effects model.*

# Results

## Demographics

Thirty-eight grafts, in 26 patients (13 male and 13 female) with a mean age of 37.4 years (SD 21.9 years), were included. Five patients were smokers and none had a history of vascular disorders such as diabetes mellitus, peripheral arterial disease or vascular malformations. The indication for grafting was burn scar contracture release in 27 cases. The mean age of the scar at time of surgery was 11.9 years (SD 15.5 years). In 11 cases the indication of grafting was wound closure, of which 6 were small burn wounds, 4 defects were non-healing wounds after regular surgery and 1 defect was due to excision of instable scar tissue. Recipient locations were: the face and neck (N= 20), the upper extremity (N= 11), the lower extremity (N= 5) and the trunk (N= 2). Donor sites were located on the trunk (N= 25 of which 2 from the thorax, 7 from the groin, 9 from the abdomen and 7 from the back), the upper extremity (N= 12) and the lower extremity (N= 1). Two grafts suffered from partial necrosis consisting of respectively 23.6 and 39.4% of the surface area.

## Surface area reduction

Contraction was observed in 28 of the 38 FTSGs (74.0%). Two grafts suffered from partial necrosis, but no re-operation was needed to close the defect. The linear mixed effects model showed that within the first three weeks after surgery the surface area of the grafts does not change substantially. A significant reduction in surface area to 79.1% was observed in category C6w (short term follow-up) (p= 0.002). In category C13w, a reduction to 85.9% (p= 0.040) was seen and in category C52w a reduction to 91.5.0% (p=0.033). *Figure 2* shows the change in mean remaining surface area (absolute values) at the different follow-up moments. *Figure 3 and 4* show two examples of contraction in FTSGs.

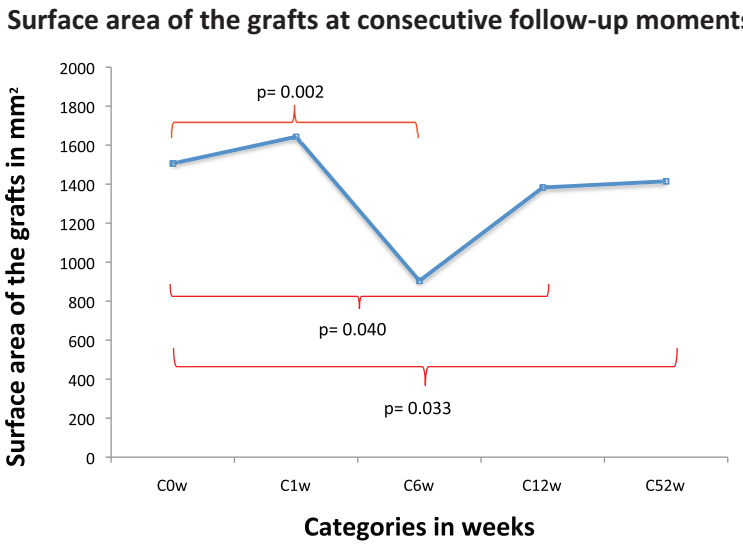


***Figure 2.*** *Graph of the mean remaining graft surface area in mm² of the grafts over time from surgery. Data points on the x-axis represent the different "time from surgery" categories. The means and ranges for the different time categories are as follows: C0w: 1506.1 (48.6 – 10438.4), C1w: 1642.7 (47.1-8472.5), C6w: 903.8 (29.1-2138.6), C12w: 1382.7 (164.8-4524.0) and C52: 1414.6 (32.8-9491.8).*



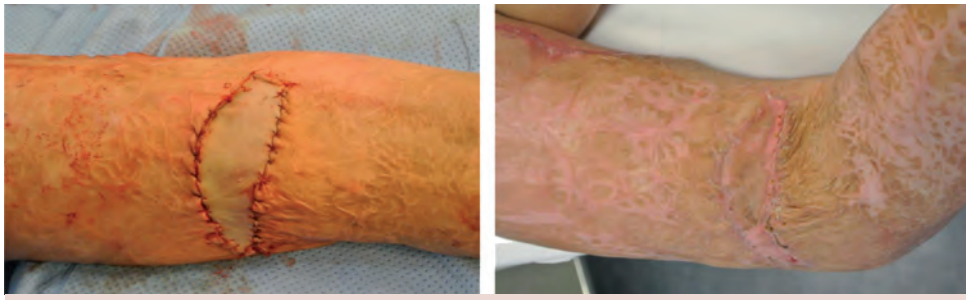

***Figure 3.*** *An example of 22-year-old patient that suffered from a contracture of the elbow. The contracture was surgically released with a FTSG (left). The photograph on the right was taken 4 weeks postoperatively.*

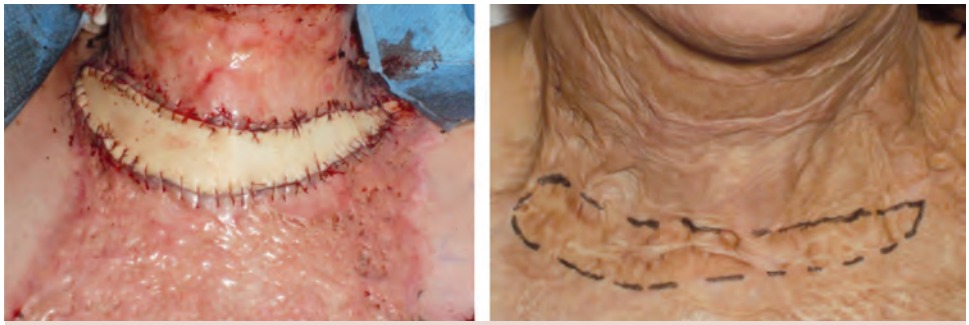

***Figure 4.*** *An example of a patient that suffered from a functional disabling contracture in the neck. The contracture was released with a FTSG, which is shown on the left. The photograph on the right was taken 12 months after the surgical release.*

## Predictive factors

The linear regression model with the analysis of possible predictive factors showed that only the donor site location significantly influenced the surface area at final follow-up (*Table 2*). Grafts excised from the trunk showed less contraction than grafts that were excised from the extremities (p=0.036 95% CI 1.054 to 31.321), with a mean contraction rate of 94.0% compared with 75.7%

| Parameter | Regression coefficient | 95% Confidence interval | | Significance |
|---|---|---|---|---|
| | | Lower | Upper | |
| Reason for operation | -10.15 | -26.22 | 5.92 | 0.22 |
| Donorsite | 16.19 | 1.05 | 31.32 | 0.04 |
| Recipient site | 11.65 | -20.77 | 44.08 | 0.48 |
| Age in years | 0.30 | -0.04 | 0.64 | 0.08 |

***Table 2.*** *Linear regression analysis, with different potential predictive factors: reason for reconstruction (wound covering compared to contracture release), donor site location (extremity compared to trunk), recipient site and age (trunk compared to face/neck).*

# Discussion

This is the first study that investigated the long-term outcome of FTSGs with respect to contraction. Interestingly, our results are inconsistent with the idea that FTSGs hardly contract. The strength of this research is that measurements were carried out at multiple occasions during follow-up for each patient, making it possible to visualize a trend in the contraction pattern. Also, surface area measurements were carried out by a reliable and valid 3D stereophotogrammetry measurement technique[9].

FTSGs are frequently used for the reconstruction of various defects. They are often preferred over STSGs because STSGs are known to contract considerably and moreover provide an inferior cosmetic result. The purpose of reconstruction of a defect or release of a scar contracture is to add tissue on a location where tissue is too little or of poor condition. Ideally, the added tissue remains its initial surface area or even increases in surface area, thereby anticipating the intended result. However, this study with multiple follow-up measurements within a mean follow-up period of approximately 52 weeks, showed that the surface area of full thickness grafts decreased over time. Moreover, the vast majority of the FTSGs showed contraction at final follow-up.

Literature on the contraction rate of FTSGs for scar contracture is lacking up to now. Nevertheless there is one study that describes the contraction rate in FTSGs used for reconstruction of defects caused by excision of skin tumors[4]. A remaining surface area

of 62% was observed after a mean follow-up period of 111 days[4]. It is however thought that contraction of scar tissue develops over time with a strong contraction phase in the first couple of months, followed by a relaxation phase. This pattern of contraction has been seen clinically, but has not been proven yet by clinical studies in human participants. Therefore, to approach the long-term results more adequately, the present study included participants with a mean follow-up period of approximately 52 weeks. Our results showed that within the first three weeks (C1w) after surgery, the surface area of FTSGs does not change substantially. After approximately 6 weeks (C6w), however, the surface area declined significantly (*Figure 2*). This contraction phase was then followed by a relaxation phase after approximately 13 weeks (C13w). Up to around 52 weeks (C52w) the grafts persisted to expand. They remained however significantly smaller at final follow-up compared to the initial measurements (p=0.033, *Figure 2*). A similar pattern of contraction followed by relaxation has been seen in STSGs; the grafts showed even higher rates of contraction with a mean remaining surface area of 75.4% (SD 36.8 and p= 0.004) at a final follow-up of one year[10]. Assumptions have been made about the factors that play a role in the etiology of contraction. Several studies implied an important role of the myofibroblast; a differentiated fibroblast that is a key cell for connective tissue remodeling and that has been identified in both normal and pathological tissues[11-13]. Because of its contractile structure and its strong retractile activity compared with e.g. a protomyofibroblast, the myofibroblast is thought to play an important role in wound contraction[11]. Besides this, myofibroblasts are over expressed in hypertrophic scars and these scars often exist together with contractures[11,14,15]. However, the exact role of the myofibroblast in the etiology of wound contraction and its possibility as a target for treatment remains poorly understood. Because of an increased tension in contractures, we expected grafts that were used to treat contractures to react differently in terms of contraction compared to grafts used to cover wound defects. Though our data showed that grafts used for contracture release endured more contraction on the long term (data not shown), no significant difference was found to support this assumption.

In the present study we found a significant difference in contraction rates between donor site locations. This finding is of clinical importance because it implicates that when possible the trunk should be preferred over the extremities to serve as donor site location whenever a FTSG is to be harvested. Grafts that were excised from the trunk endured less contraction than grafts excised from the extremities. This could be explained by the fact that skin of the trunk is generally thicker than skin of the extremities[16]. It may be suggested that a graft with a thicker dermis more effectively protects the graft against contraction of the underlying than a graft with a thinner dermis. Also, a thicker dermis likely contains a more extensive collagen network, which is more capable of stretching[17,18]. In the light of this hypothesis it is important to question whether contraction of the graft is caused by the graft itself or by the underlying wound bed. In the present study a significant

influence of the recipient site could not be confirmed, however this does not exclude its influence. It is our belief that the contraction of the underlying wound bed contributes to the final graft contraction. More in depth research should be performed to confirm this hypothesis. Finally, age was not found to be a predictive factor for the contraction rates of grafts, which could be caused by the relatively small inclusion number of this study.

In conclusion, this study was the first long term evaluation of the contraction patterns of FTSGs: a strong contraction phase was seen in the first 13 weeks, followed by a relaxation phase. The majority of grafts however, remained contracted after a mean follow-up period of one year or more. Understanding of the contraction patterns of FTSGs is of great help for the reconstructive surgeon. We believe that, despite our findings, FTSGs should retain an important role in the reconstruction of skin defects and contractures. However, a better knowledge on the contraction pattern allows to anticipate on the expected contraction and/or to use another reconstruction technique in cases where re-contraction is absolutely unwanted, such as scar contracture release. Based on the results that were presented in this study it should be recommended to harvest a greater FTSG than is needed on the recipient location, to anticipate the following contraction. Furthermore, considering our finding that grafts excised from the trunk endure significantly less contraction on the long term than grafts excised from the extremities, we advise to, whenever possible, use the trunk as the donorsite location of preference when an FTSG is required.

## Acknowledgements

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We gratefully thank the patients for their participation in this study.

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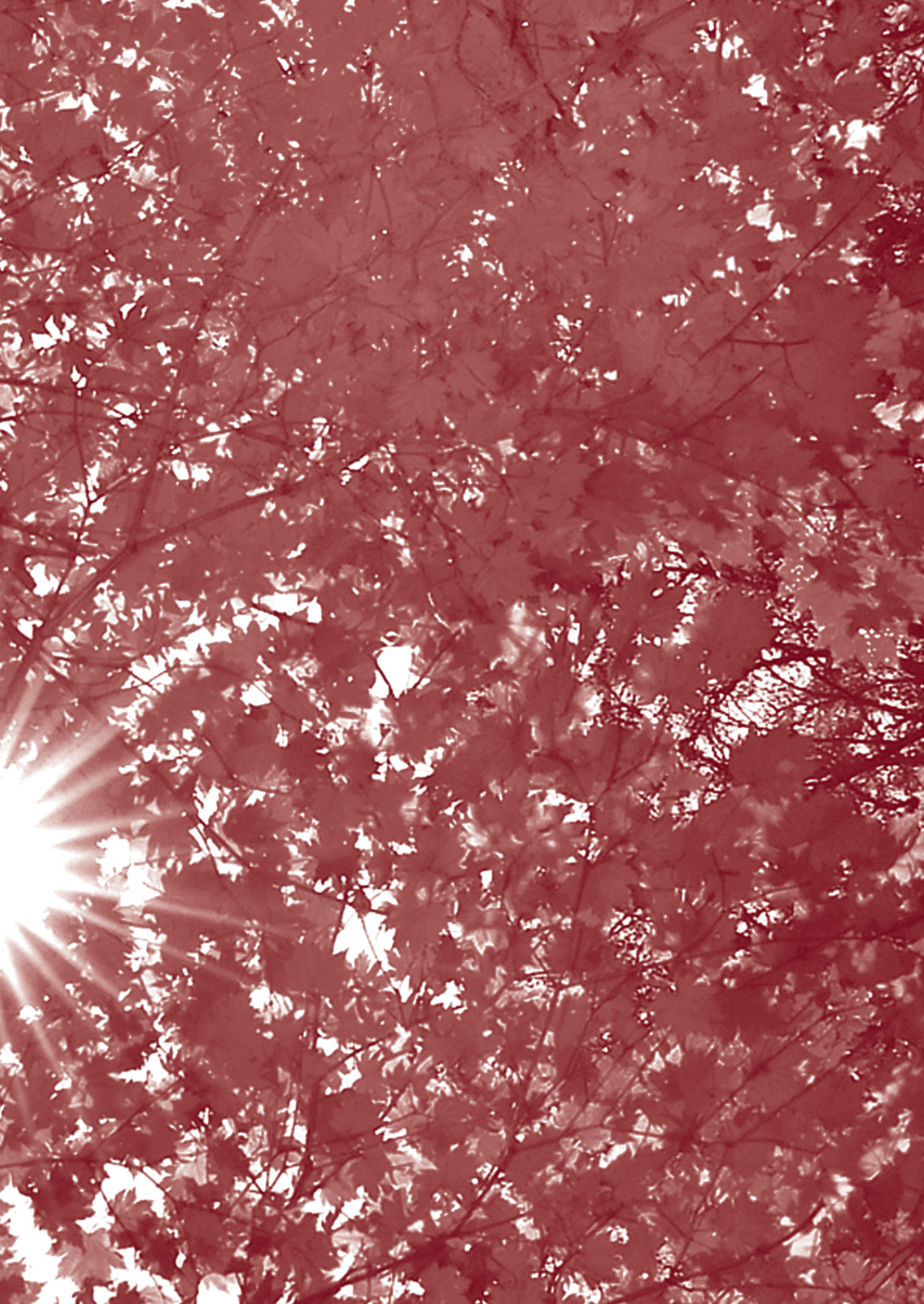
# PART III

## Progress in burn scar contracture treatment by perforator-based interposition flaps



# 6

# Perforator-based interposition flaps for sustainable scar contracture release: a versatile, practical, and safe technique

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## Abstract

**Introduction:** Problematic scar contractures are frequently observed following extensive (burn) wounds. In this study we investigated the applicability of islanded and non-islanded perforator-based interposition flaps as a technique for release of scar contracture.

**Materials and Methods:** Patients requiring surgery for scar contracture release were included. Preoperatively, a suitable perforator was identified by color Doppler sonography. The flap design was tailored according to the localization of this perforator and the anticipated defect. Flap measurements were performed intraoperatively and at follow-up. Supple scar tissue was included in the flap design when necessary, to increase the applicability of this concept in extensively burned patients. Flaps were converted into island flaps on indication to circumvent significant kinking of the flap base and compromised tissue perfusion.

**Results:** Twenty-two flaps were performed of which four were converted into island flaps. All flaps survived, but in four cases necrosis of the tip was observed. After a mean follow-up of 7.8 months the width and surface area of the flaps had expanded to 123% (40-311%) and 116% (60-246%), respectively. One flap was converted into a full thickness skin graft during the initial operation.

**Conclusions:** This concept of perforator-based interposition flaps was found to be a reliable and versatile technique for broad scar contractures. Moreover, it allows intraoperative tailoring as the flap base can be islanded when indicated. Nevertheless, additional venous outflow is warranted and operation time is saved if the flap base remains intact.

## Introduction

Patients with burn scars are frequently faced with disfigurement and functional impairment because of scar contractures. Linear scar contractures can be released with local random flaps such as Z-plasties. For the release of broad scar contractures, full thickness skin grafts (FTG) or split thickness skin grafts (SSG) frequently remain the treatment of choice. Unfortunately, the effectiveness of skin grafts is limited by scar contraction, which often necessitates additional reconstructions[1-5]. Recent advances in the field of tissue engineering and dermal substitution may create unique opportunities for burn scar reconstruction in the nearby future but still render a scar with suboptimal functional and cosmetic qualities[6].
Local flaps of preferably uninjured skin and subcutaneous tissue provide, in theory, a superior and long-lasting effect of contracture release. Many local flaps were developed on trial and error basis, as surgeons were unaware of the underlying vascularization. Random flaps are considered to have a restricted length-to-width ratio that ranges between 1:1[7,8] and 2:1[9,10] dependent on the body region. They have limited possibilities for transposition, also because they can not be converted into island flaps. When the length-to-width ratio is exceeded, these random flaps could encounter vascular limitations[10].

To provide sustainable contracture release for broad scar contractures, longer flaps are necessary. Longer flaps can be designed if the fascia is included and if adequate tissue perfusion is ascertained[11]. Similarly, longer flaps such as axial pattern flaps can be created. However, this flap design needs to be made exactly within the territory of these axial arteries[7]. The degrees of freedom for tissue transfer can be considerably increased by islanding the flap, which provides an enormous increase in possibilities for transposition.

The discovery and utilization of perforators was a breakthrough in the battle between blood supply and survival of flaps[12]. This means that a flap could be potentially based at any anatomical site as long as it incorporated a perforator artery with concomitant veins. Previous studies have demonstrated that these perforators can be easily and reliably detected by using (color) Doppler sonography[13-15]. Taylor et al. performed basic research on these vessels and their role in vascularization of the skin and showed that the body contains a few hundred of such perforating vessels with a diameter larger than 0.5mm[13].

Nowadays, free flaps and island flaps are the types of perforator flaps that are most commonly used in plastic surgical practice. Wei et al. described “free style” perforator flaps, which are free flaps based on innominate perforator vessels[16,17]. In addition, Waterston et al. presented a flap design, called the “ad hoc” perforator flap, whereby island flaps were created[18]. However, the most convenient, simplest and safest technique, a perforator-based local flap, is seldom described. Mehrotra et al. presented case studies

on perforator-based flaps which they named “perforator-plus” flaps[19,20]. This flap is based on a perforator leaving the skin base intact, providing additional vascular supply and venous outflow. It therefore resembles a random flap but has increased reliability and the potential to create a larger flap. This technique is safe and does not require extra operation time. Drawbacks of leaving the skin base intact are that this may limit flap rotation, leave dog-ears and result in kinking of the flap base and thereby compromising the blood supply.

We have experienced the advantages of islanded as well as non-islanded perforator flaps. This enabled us to come to a versatile flap design for reconstruction of broad scar contractures: the skin base is left intact when possible, while the option remains to convert this flap into an island flap (or even a FTG) if necessary. We applied and evaluated our treatment algorithm for the reconstruction of broad scar contractures by non-islanded and islanded perforator-based interposition flaps. We studied flap survival and complication rates. In addition, a quantitative analysis was performed of changes in the surface area to critically evaluate the sustainability of the contracture release over time. Although sustainability of contracture release is considered an essential component, follow-up measurements of the surface area for perforator flaps have never been performed to date.

## Materials and Methods

### Patients

All patients undergoing surgery at the department of Plastic, Reconstructive, and Hand Surgery in the Red Cross Hospital from November 2008 to November 2009, were considered. Patients older than 12 years and suffering from broad scar contractures after burns or necrotizing fasciitis were included. The perforator-based interposition flap was utilized in all patients who required flaps with a length-to-width ratio higher than 2:1. This ratio was chosen based on previously published studies which revealed problems with effective tissue perfusion for random flaps with a length-to-width ratio exceeding 2:1[7,9,10]. From all patients verbal consent was obtained. The principles outlined in the Declaration of Helsinki were followed. According to the clinical research legislation ethical approval was not necessary.

### Surgical technique *(Figure 1)*

The flap was designed on healthy skin in the vicinity of the planned release. When sufficient healthy skin was lacking for the flap design, supple scar tissue, that remained from spontaneously healed epidermal or superficial dermal burns, was included. The concept of including supple scar tissue in flaps was shown to be safe and efficient[21-23].

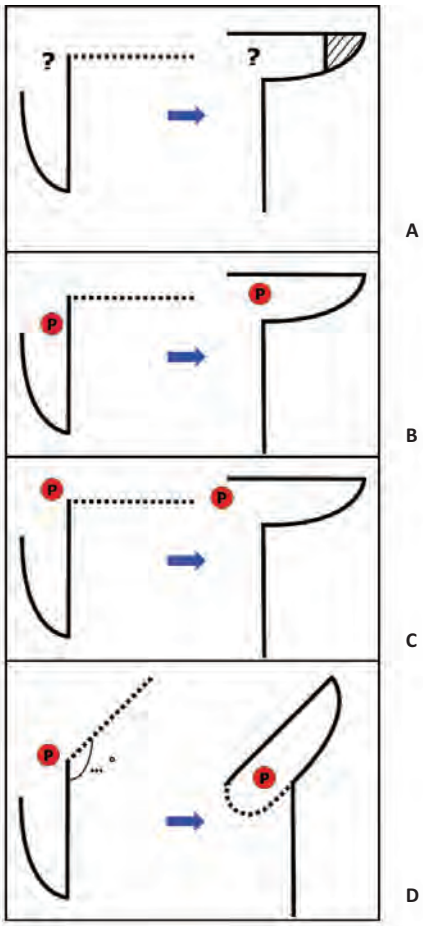


***Figure 1.*** *Abstract explanation of the design of the perforator-based flaps. The red circle indicates the perforator. A. Random flap, the marked part representing the expected necrosis. B. Non-islanded perforator flap with the perforator situated within the flap design. C. Non-islanded perforator flap with the perforator situated outwith the flap design. D. Islanded perforator flap, which is often indicated when the angle of rotation is exceeding 120˚.*

Moreover, considering supple scar tissue in the flap design increased the applicability of this concept. “Ad hoc” perforators were identified preoperatively in this area by color Doppler sonography (*Figure 2*). A more convenient and simpler option, a hand-held unidirectional Doppler, could have been used for preoperative localization[14], but has the drawback of providing less detailed information[15]. Color Doppler sonography provides additional data on the flow, calibre, and course of the perforator[24]. The flap design was tailored to a local transposition flap and possible islanding of the flap was anticipated. The flap surface area, area of scar tissue, and the angle of rotation were traced on a pliable transparent plastic sheet, which is a reliable and valid planimetry method[25]. The sheets were scanned and measured using digital image analysis software (NIS-Elements, Nikon,

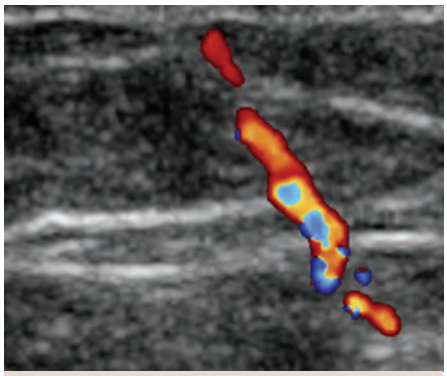

***Figure 2.*** *Example of a perforator vessel using color Doppler sonography.*

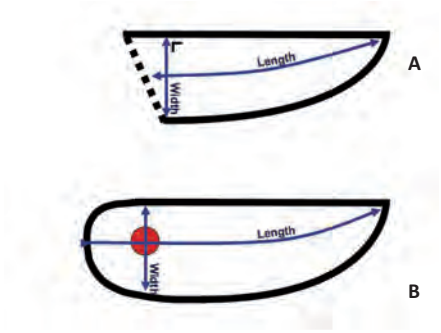


***Figure 3.*** *Geometry of local flaps (A) and island flaps (B). The red circle indicates the perforator.*

Amstelveen, the Netherlands). The width, length, and area of the flaps were measured prior to incision. It should be noted that measuring island flaps was performed differently from non-islanded flaps: the width was not measured at the base of the flap, but at the location of the perforator, and the length was measured from the edge of the flap at one side to the edge at the opposite side (*Figure 3*).

In the first 6 cases the flap design included the perforator, which was located at the base of the flap (*Figure 1b*). For these cases the perforator was identified during surgery. Subsequently, the flap design was slightly adjusted: the perforator was located outwith the flap base, thus circumventing the need to identify the perforator (*Figure 1c*). The flap was thinned to the subdermal plexus. Then a release of the contracture was performed. The flap was easily and safely converted into an island flap when an unacceptable mechanical tension or kinking of the flap pedicle occurred due to the transposition. If the flap remained congested after islanding, without other causes that could be anticipated, the flap could be safely turned into a FTG, which will result in a less optimal but still acceptable result. This treatment algorithm is represented in *Figure 4*. For closure of the donor site and for securing the flap in place, absorbable sutures were used. When the donor site had to be closed under significant mechanical tension transcutaneous non-absorbable polyester fiber sutures were used.

## Follow-up

Postoperative complications were registered. Necrosis was subdivided in superficial and full thickness necrosis. Superficial necrosis was defined as epidermiolysis, where re-epithelialisation occurred within two weeks. Full thickness necrosis was defined as necrosis resulting in an unhealed wound after two weeks with possible long-term consequences. Surface area measurements were performed at a minimum follow-up of three months.

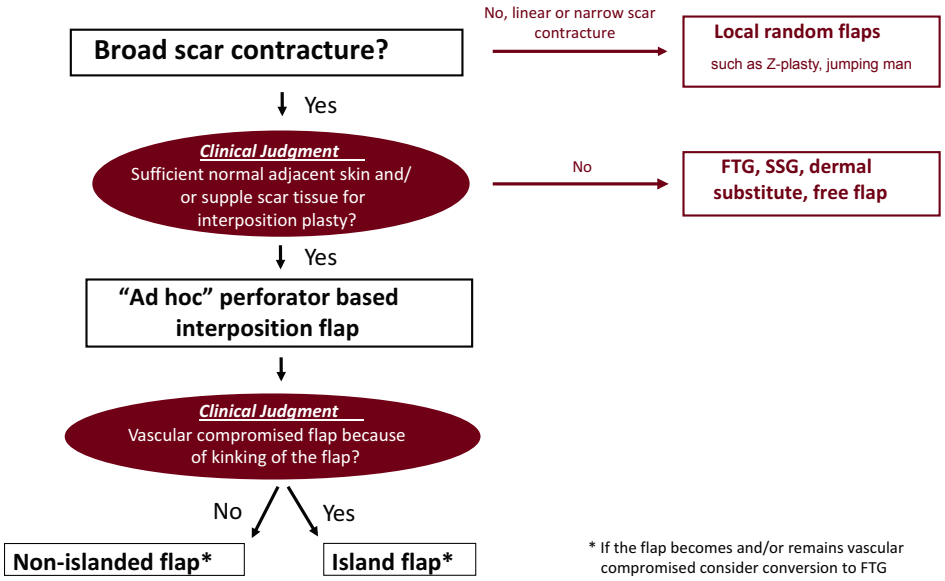


***Figure 4.*** *Treatment algorithm for broad scar contractures using "ad hoc" perforator-based interposition flaps.*

This follow-up period was chosen because split and full thickness skin grafts show the most scar contraction during the first three months postoperatively[1,26]. The percentage of necrosis, if any, was determined retrospectively by planimetry of the pictures. All measurements were performed by the same investigator.

## Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, USA). Normal distribution was tested by applying the Kolmogorov-Smirnov Test and by calculating the skewness and kurtosis. If the population was not normally distributed, the Mann-Whitney U Test (MWU Test) or, in case of paired data, the Wilcoxon signed ranks test was used. To compare categories the Fisher's exact test was used when less than five cases were observed in one category and the Chi-Square test was used when more than five cases were observed[27]. The range and P-values were given where appropriate. The significance criterion was set at 0.05.

# Results

Twenty-two flaps were performed on 18 patients (3 male and 15 female), with a mean age of 33 years (14-58 years). Twenty patients had burn scar contractures and 2 patients had contractures after necrotizing fasciitis. None of the patients had a significant medical

history of vascular diseases or wound healing disorders, such as diabetes. Of the 22 flaps, 10 were located in the head-neck region, 6 on the upper extremities, 4 on the lower extremities, and 2 on the trunk. Three patients smoked. In *Table 1* the flap characteristics are listed. Seventeen of the 22 flaps were inset into the release with their base left attached (*Figure 5*). These flaps had a mean rotation angle of 102˚ (57-163˚). Four of the 22 flaps were intra-operatively converted into island flaps (*Figure 6*). The decision to island a flap was partially based on the rotation angle. However, in all cases this remained a clinical decision which was primarily based on adequate perfusion to the flap. All donor sites could be closed primarily. One case was categorized separately: this flap was converted into a FTG. The reason being that when the flap was raised, prior to rotation, it was acutely congested and cyanosed and therefore a flap was a non-viable option.

All flaps survived, however, 2 flaps showed epidermiolysis and 4 showed full thickness necrosis of the apex (*Figure 7*). The mean percentage of necrosis for these 21 flaps was 3.8% (0-51.4%). The patient with 51.4% necrosis of the total flap area underwent a release in the head-neck region whereby an unexpected amount of subcutaneous scar tissue complicated a safe conversion to an island flap. This was the only patient in our study group who required a secondary procedure after a perforator-based flap.

Comparing the non-islanded flaps with the perforator within the flap design to the non-islanded flaps with the perforator outwith the flap design, showed no significant difference in the incidence of necrosis (Fisher's Exact Test, p=0.52) or percentage of necrosis (MWU Test, p=0.18). For the non-islanded perforator flaps, the mean angle of rotation of the flaps without necrosis was 97˚ (57-157˚) and of the flaps with necrosis was 120˚ (73-163˚). This difference was not statistically significant (MWU Test, p=0.21). The case where the flap was converted into a FTG had a complete take rate of the graft seven days postoperatively.

In 11 of the 21 flaps (52.4%) supple scar tissue was included with a mean percentage of 13.1% (n= 21, 0-49.4%) of the total flap area. No significant correlation could be demonstrated between the percentage of scar tissue and the percentage of necrosis (n=21, Spearman's Rho correlation coefficient= -0.26, p= 0.25). Furthermore no significant difference was found between flaps with and without scar tissue concerning the incidence of necrosis (Fisher's exact test, p= 0.64). The mean width of the flaps was 4.1 cm (2.8-6.0 cm) and the mean surface area, measured before incision, was 36.1 $cm^2$ (18.3-62.2 $cm^2$). After a mean follow-up of 7.8 months (3.0-13.8 months) the mean width of the flaps increased to 4.8 cm (2.4-11.8 cm) and the mean area increased to 39.2 $cm^2$ (16.3-60.8$cm^2$). The width of the flaps at follow-up was 123% (40-311%) of the original width and the area of the flaps was 116% (60-246%) of the original area. No significant decrease of the width and area was registered at follow-up compared to the original width and area at the time of surgery (Wilcoxon signed

| | All flaps (n=21) | Non-islanded flaps (n=17) | Islanded flaps (n=4) | Statistical tests (non-islanded versus islanded) |
|---|---|---|---|---|
| Mean length-to-width ratio (range) | 3.0:1 (2.0:1-4.5:1) | 2.9:1 (2.0:1-4.5:1) | 3.3:1 (2.5:1-3.9:1) | p = 0.32[1] |
| Mean surface area at time of surgery, $cm^2$ (range) | 36.1 (18.3-62.2) | 35.3 (18.3-62.2) | 39.6 (28.1-60.0) | p = 0.53[1] |
| Mean surface area at f ollow-up, $cm^2$ (range) | 39.2 (16.3-60.8) | 37.3 (16.3-60.8) | 47.1 (30.9-58.6) | p = 0.18[1] |
| Mean expansion of surface area, % (range) | 116 (60-246) | 113% (60-246) | 129 (86-208) | p = 0.46[1] |
| Mean width at time of surgery, cm (range) | 4.1 (2.8-6.0) | 4.1 (2.8-6.0) | 4.2 (3.5-5.0) | p = 0.75[1] |
| Mean width at follow-up, cm (range) | 4.8(2.4-11.8) | 4.9 (2.4-11.8) | 4.4 (3.6-5.5) | p = 0.79[1] |
| Mean expansion of width, % (range) | 123 (40-311) | 126 (40-311) | 109 (80-157) | p = 0.90[1] |
| Incidence of full thickness necrosis, % | 19.0 (4/21) | 17.6 (3/17) | 25.0 (1/4) | p = 1.00[2] |
| Mean % of full thickness necrosis (range) | 3.8 (0-51.4) | 4.7 (0-51.4) | 1.3 (0-5.2) | p = 0.90[1] |
| Incidence of scar tissue in flap, % | 52.4 (11/21) | 47.1 (8/17) | 75.0 (3/4) | p = 0.59[2] |
| Mean % of scar tissue in flap (range) | 13.1 (0-49.4) | 12.5 (0-49.4) | 15.8 (0-32.8) | p = 0.52[1] |

***Table 1.*** *Overview of the characteristics of all flaps and of the non-islanded and islanded flaps separately. The statistical tests column displays the statistical comparison of outcomes of the islanded versus the non-islanded flaps.[1] = MWU Test, [2] = Fisher's exact test.*



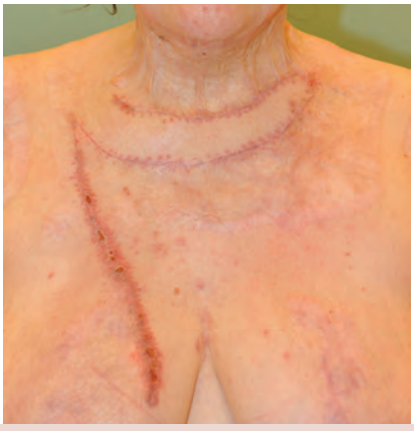

***Figure 5.*** *Example of a non-islanded perforator flap after scar contracture of the neck of a 23-year-old female patient (three weeks postoperative). This flap measured a length-to-width ratio of 5.9:1 and was performed after the inclusion period of this study.*

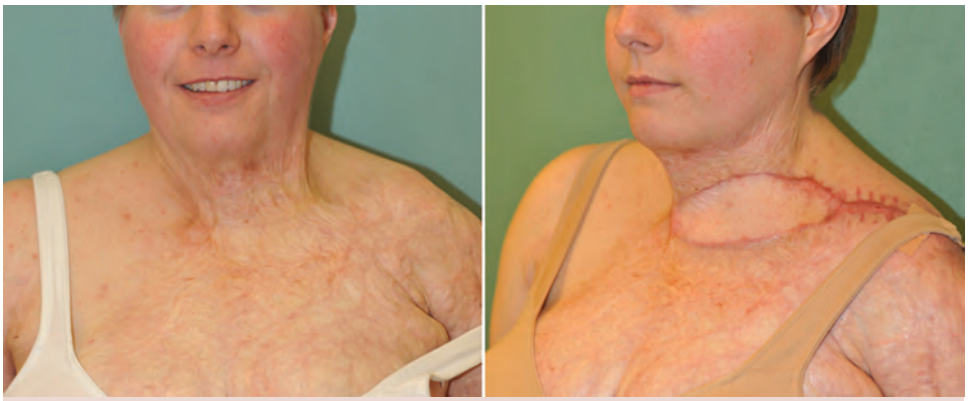

***Figure 6.*** *The left picture shows a scar contracture in a 31 years old female patient, which caused complaints of impaired elevation and rotation in the head-neck region. Contracture release was performed using an islanded perforator flap. The right picture displays the result 2.5 months postoperatively.*

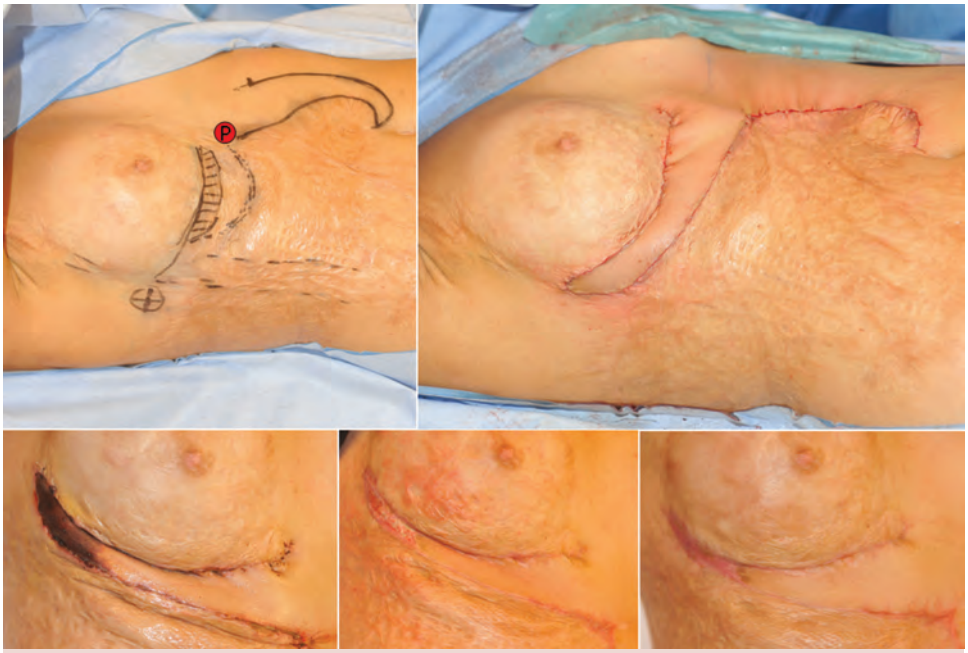


***Figure 7.*** *An example of flap necrosis. (Above, left) Preoperative design of a perforator-based interposition flap for release in the infra-mammary region of a 17 years old female patient. The red dot indicates the perforator. (Above, right) Direct postoperative result: although intraoperative testing of the vascularization of the flap showed a good viability, in this picture a slightly cyanosed apex of the flap can bee seen. (Below, left) Necrosis of the apex 9 days postoperatively (23.1% of the surface area of the flap). (Below, middle) Necrosis of the flap 1 month postoperatively. (Below, right) Scar tissue at the apex, which is partially contracted 2 months postoperatively.*

ranks Test, p= 0.42 and p= 0.59, respectively). *Figure 8* shows an example of an expanded perforator-based flap. The flap that was converted into a FTG measured 48% of the original width and 35% of the original area 2.5 months postoperatively.

## Discussion

So far studies on the application of perforator-based interposition flaps for scar contracture release are lacking in breadth and depth. Mehrotra et al. introduced the "perforator-plus flap"[19]. They presented ten patients, of whom one case concerned a post-burn scar contracture. Even though these perforator-plus flaps were successfully used, no systematic data on flap geometry were collected. Waterston et al. reported on "ad hoc" perforator flaps for burn scar contracture release[18]. These "ad hoc" perforator flaps all concerned island flaps, although probably in some cases a local transposition perforator flap, without islanding, would have been sufficient. They performed a retrospective study and structural data on the flap geometry and follow-up were lacking.

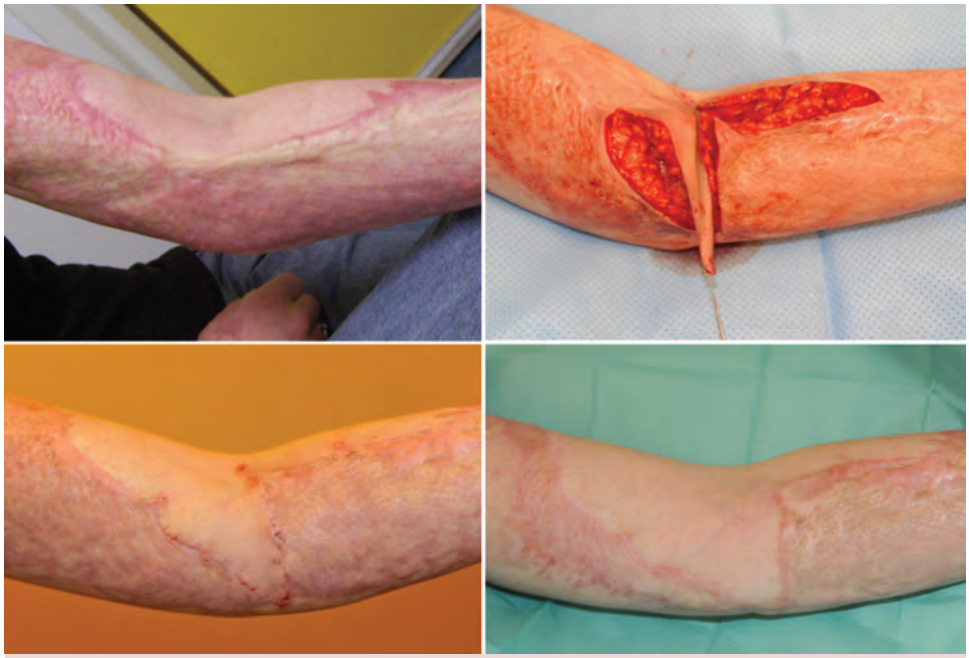

***Figure 8.*** *(Above, left) A burn scar contracture of the elbow in a 27-year-old female patient, leading to functional impairment. (Above, right) A release of the scar contracture was performed and, after identifying the perforator, the flap was designed and raised (width: 3.8 cm, length: 10.2 cm, and surface area: 24.8 cm$^2$). (Below, left) The postoperative result after two weeks already showed expansion of the flap. The width of the flap had expanded from 3.8 to 5.8 cm (+53%) and the surface area from 24.8 to 28.6 cm$^2$ (+15%). (Below, right) After 7 months the flap had further expanded: the width of the flap has increased from 3.8 to 11.8 cm (+211%) and the surface area from 24.8 to 60.8 cm$^2$ (+145%).*

We merged the principles of perforator-plus flaps and ad hoc perforator flaps into a treatment algorithm (*Figure 4*). Initially, flaps were raised with their base intact. However, a flap can be safely and easily islanded intraoperatively, if the need arises, and we consider this flexibility a major advantage of our flap design. Our algorithm for perforator-based flaps provides a safe and versatile tool to ensure sustainable scar contracture release. Firstly, the vascularization of these flaps is secured by the presence of a perforator, which can be found practically everywhere[28-31]. During this study we confirmed that reliable flaps could be raised based on perforators at all anatomical sites. This reliability was confirmed with low flap necrosis of 3.8%. Harvesting a flap adjacent to a scarred area may also have contributed to final flap survival. We propose that following the initial burn injury the subdermal plexus of healthy adjacent skin may have been adapted due to changes in microcirculation. Therefore the vascularization of this adjacent skin is suited to a situation of inferior blood supply. Practically, it may be compared to a "flap delay procedure", which was shown to promote flap survival[32].

Secondly, the best tissue is being used: adjacent healthy skin with subcutaneous tissue, which showed no contraction. In our study we evaluated the changes in flaps geometry using reliable, valid and standardized measurement techniques. We objectively showed that these flaps provide sustainable contracture release. This clinically significant finding demonstrates the adaptation (expansion/stretching) of the perforator-based flaps as opposed to contraction that normally occurs for SSGs and FTGs[1-5]. After a mean follow-up of 7.8 months both the width and surface area of the flaps had expanded with an increase of 123% and 116% of the original size, respectively. This flap expansion could not be contributed to a possible difference between the flap size prior to incision and the size after suturing the flap. This is quantitatively supported by analysis of these flaps at an average of 2.9 months postoperatively: the width and the surface area of these flap when comparing this to flap dimensions before the incision measured 103% and 100% of the original width and flap surface area, respectively (data not shown).

Thirdly, the applied algorithm proved to be versatile and practical. It was shown clinically that supple scar tissue could be included in the flap design, probably because the subdermal plexus appeared to be preserved in this tissue. Supple scar tissue may therefore be considered as a second choice and safe alternative when sufficient healthy skin is lacking, such as in extensively burned patients.

Initially, the flap was designed with the perforator located at the base of the flap. Later, the perforator was placed outwith the local flap design (*Figure 1b* and *1c*). This small but practical modification circumvented the necessity to explore the perforator and therefore reduced the risk of damaging these vessels. This adaptation reduced operation time for the majority of the cases where no kinking of the flap base occurred and no conversion to

an island flap was necessary. Consequently, the operation time required for raising these safe perforator-based flaps is comparable to the operation time for random flaps. On the other hand, no significant differences between non-islanded and islanded flaps regarding the incidence and percentage of necrosis could be demonstrated which means that flaps could be safely islanded when indicated.

Lastly, the perforator-based interposition flap results in a cosmetically superior outcome compared to the standard treatment. All donor sites were closed primarily. The scar of the donor site was situated along the present burn scar and is therefore less notable. These perforator-based flaps can be applied to many other reconstructive scenarios, such as coverage of a trauma wound with exposed bone, chronic wounds or coverage of third or fourth degree acute burn wounds.

## Conclusions

The algorithm for perforator-based interposition flaps was found to be practical, safe and feasible. We demonstrated that perforator-based flaps provide sustainable contracture release. For the first time surface area measurements of (perforator-based) flaps for contracture release were objectified. Interestingly, our data even indicated an expansion of the width and surface area of these flaps in time. In this study we confirmed that reliable flaps could be raised based on perforators on all evaluated sites. We believe this algorithm and flap method is easily reproducible and can be incorporated into clinical practice of any surgeon routinely performing burn contracture release.



## Acknowledgements

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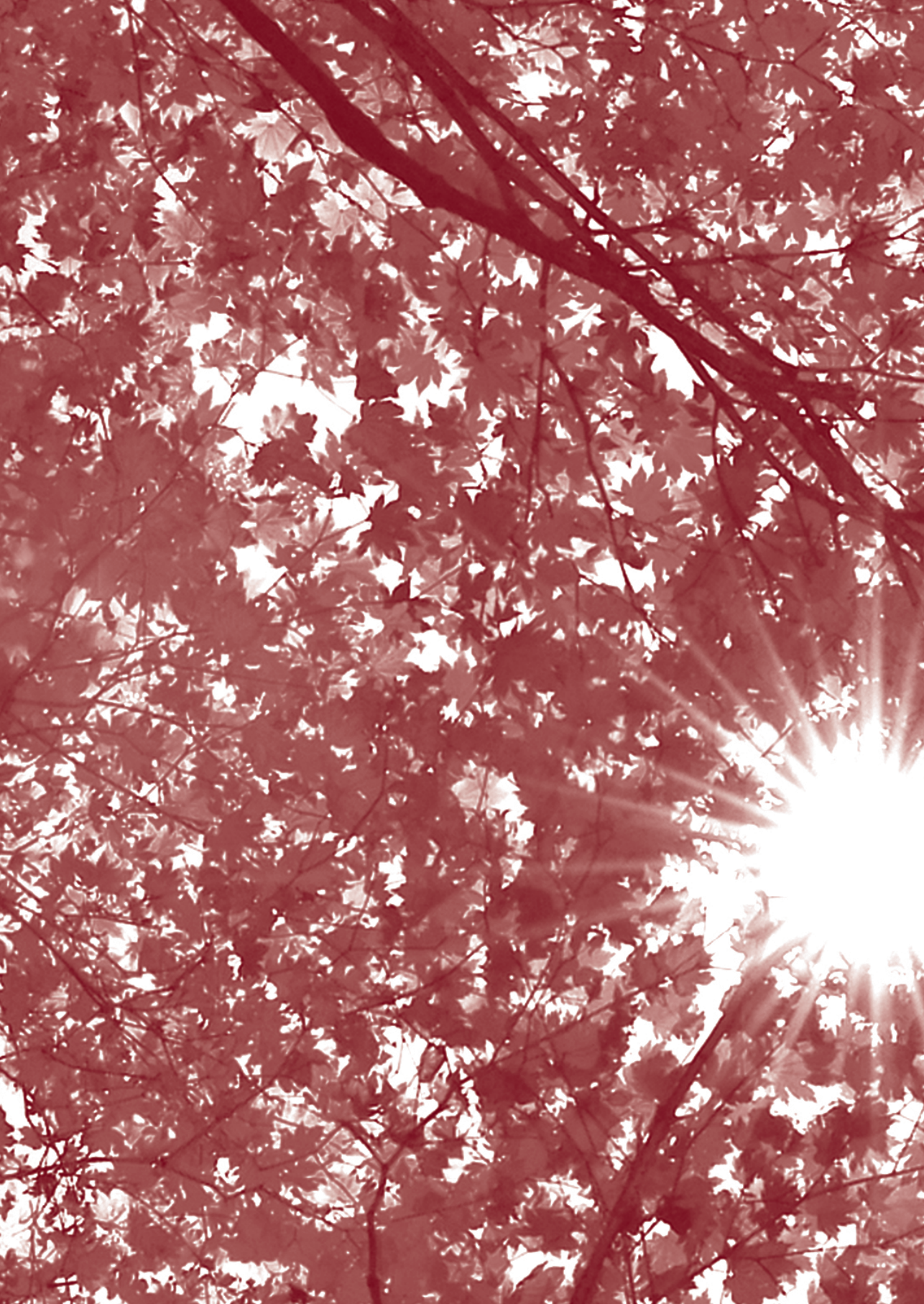

# 7

# Perforator-based interposition flaps perform better than full thickness skin grafts for the release of burn scar contractures: a multicenter randomized controlled trial

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## Abstract

**Background:** Burn scar contractures remain a significant problem for the severely burned patient. Reconstructive surgery is often indicated to improve function and the quality of life. Skin grafts (preferably full thickness grafts) are frequently used to cover the defect that remains after scar release. Local flaps are also used for this purpose and provide, besides healthy skin, subcutaneous tissue. The vascularization and versatility of local flaps can be further improved by enclosing a perforator at the base of the flap. Until now, no randomized controlled trial (RCT) has been performed to determine which technique has the best effectiveness in burn scar contracture releasing procedures.

**Materials and Methods:** A multicenter RCT was performed to compare the effectiveness of perforator-based interposition flaps to full thickness skin grafts (FTSGs) for the treatment of burn scar contractures. The primary outcome parameter was change in the surface area of the flap or FTSG. Secondary outcome parameters were width, elasticity, color, POSAS, and range of motion. Measurements were performed after 3 and 12 months.

**Results:** The mean surface area between flaps (N=16) and FTSGs (N=14) differed statistically significant at 3 months (123% vs. 87%, $p<0.001$) and 12 months (142% vs. 92%, $p<0.001$). In terms of the secondary outcome parameters (specifically the POSAS observer score and color), interposition flaps showed superior results to FTSGs.

**Conclusions:** Perforator-based interposition flaps result in a more effective scar contracture release than FTSGs and should therefore be preferred over FTSGs when possible.

## Introduction

Burn scar contractures remain a significant problem in severely burned patients[1]. Patients suffering from these contractures often experience considerable limitations in daily life. Therefore surgical treatment is often necessary[2]. Many treatment regimens are available for burn scar contracture release. A recently performed systematic review, however, showed that it is still unclear which technique is the most effective treatment[3]. In clinical practice, wide scar contractures are regularly treated with a skin graft, which is preferably full thickness (full thickness skin graft, FTSG)[4]. However, their effectiveness in terms of re-contraction has never been objectified in burn patients. The available studies on the contraction rate in other patient groups show that FTSGs have the tendency to re-contract, which could result in partial or total recurrence of the initial problem in burn patients[5,6].

Ideally, tissue that does not contract and will grow with the patient is used for the release of scar contractures. For this purpose, locally available tissue is preferred because it provides tissue of superior quality and contains healthy adjacent skin and subcutaneous fat. The safety and versatility of local flaps can be improved by incorporating a perforator bundle. This means that the vascular supply (an artery with concomitant veins) is secured, which is illustrated in *Figure 1*. The discovery that perforators are dispersed throughout the body[7-10], has led to the development of many perforator-based flaps in specific regions of the body[11,12]. For example, the thoracodorsal artery flap in the breast-axilla region[13,14], and the cervical artery flap in the neck region[15,16].

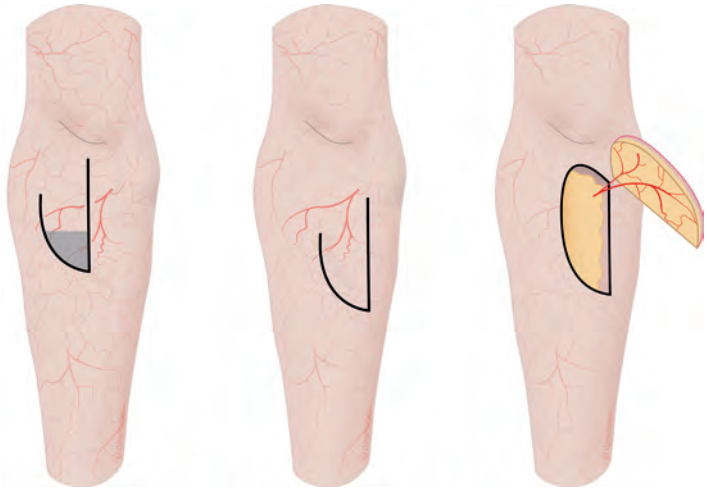

***Figure 1.*** *Illustrates the concept of incorporating a perforator in a local flap. In the left image a local flap is designed disregarding the location of the perforator. The grey area represents subsequent necrosis. In the middle, the perforator is localized and the flap is designed in such a way that it incorporates the perforator bundle. The flap may be non-islanded (middle) or islanded (right).*

Burn scar contractures occur almost on all body sites, also on locations at where well-known perforators are not available for reconstructive purposes. The so-called ad hoc perforator-based flap may provide a solution here[17]. These flaps are based on any perforator adjacent to the contracture that is capable of sufficient blood supply. In a cohort study that was published by our group in 2011, an algorithm was presented describing the use of perforator-based interposition flaps for the treatment of large scar contractures[18]. Follow-up measurements of the surface area of these flaps were performed and showed an expansion of 116% after a mean follow-up period of 7.8 months[18]. Moreover, two other studies showed that no revision surgery is required with the use of this type of flaps for the reconstruction of scar contractures[17,19]. Hence, the use of perforator-based interposition flaps for the treatment of scar contractures points towards favorable results. The implications by means of a randomized controlled trial (RCT) however, have yet to be determined. For this reason we performed an RCT in which the effectiveness of perforator-based interposition flaps was compared to FTSGs for the release of scar contractures.

## Materials and Methods

### Study design and randomization

An open randomized controlled trial was conducted to evaluate the effectiveness of perforator-based interposition flaps compared to FTSGs for scar contracture release. Recruitment took place in two burn centers in the Netherlands (the Red Cross Hospital in Beverwijk and the Martini Hospital in Groningen). All patients gave written informed consent. The study protocol was approved by the national medical ethics committee (M010-070) and registered at clinical trials (no. NCT01409759). This study could not be blinded because the treatment allocation was clearly recognizable by both the patient and the observer.

Patients were randomly assigned to receive either treatment with a perforator-based interposition flap, which will be referred to as flap from now on, or a FTSG. Block randomization, stratified per center, was applied with a randomization ratio of one-to-one to ensure balance of the numbers in each treatment group. To prevent anticipation on the randomization sequence, block sizes of 6 and 4 were used. The order of the blocks was determined with a random numbers table[20]. To ensure allocation concealment, sequentially numbered opaque sealed envelopes were used. To avoid differences in preoperative work up (including wound bed preparation), the randomization took place during the operation procedure (before releasing the contracture).

## Patients

We enrolled patients of 18 years and older with an indication for release of a wide scar contracture. Only patients that had sufficient tissue for a flap were eligible. In addition, patients had to be able to give informed consent. Scars on the face and scalp were excluded.

## Surgical procedures

In both groups, the location of suitable perforators was assessed preoperatively using Doppler (Huntleigh Dopplex D900, Cardiff, UK) or Duplex (iU22 Duplex with a L17-5 transducer, Philips, Eindhoven, The Netherlands). Using this approach, we assured that both groups received a uniform preoperative work up, thereby limiting expectancy bias. Presence of scar tissue in the flap or graft was documented.

Once a flap was allocated, we applied the algorithm that was previously published by Verhaegen *et al*[18]. In this algorithm, the flap is preferably pedicled resulting in a non-islanded flap, meaning that the skin base is left intact. If the vascularization of the flap appeared to be compromised in the intended position, the flap was converted to an islanded flap. This was primarily a clinical decision that allowed for greater angles of rotation where necessary. The predesigned flap was incised and consisted of cutis and subcutis, hereby preserving the dermal vascular plexus. The flap was mobilized and the viability of the flap was assured in the intended position. If the flap remained viable, it was sutured using subcutaneous and intracutaneous absorbable polyglactin sutures respectively (Vicryl™ 2-0 and Vicryl™ 4-0, Ethicon Johnson and Johnson, USA). The donor site was closed primarily. *Figure 2* and *Figure 3* show two examples of flaps (non-islanded and islanded, respectively).



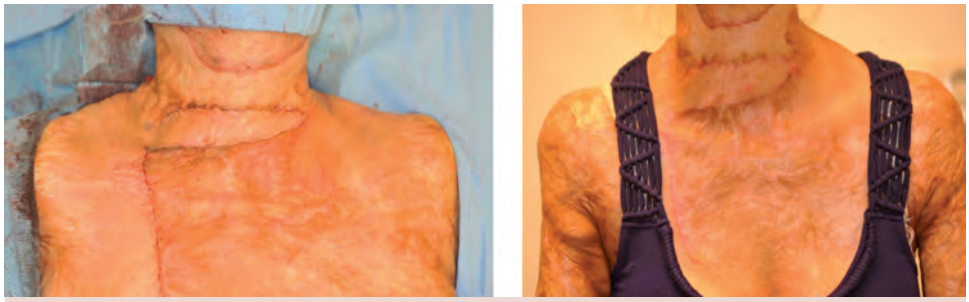

***Figure 2.*** *Example of a 23-year-old patient with a contracture of the head-neck region. A non-islanded perforator flap was performed (left). The photograph on the right represents the flap at a follow-up period of 3 months.*

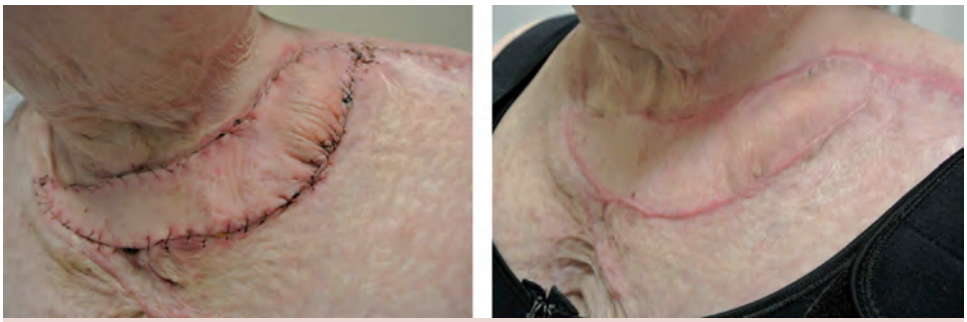

***Figure 3.*** *Example of an islanded perforator flap in the neck region of a 56-year-old patient. The photograph on the left shows the flap at 1 week postoperative, the photograph on the right at 3 months postoperative.*

In case a FTSG was allocated, the incisions were made following the design. The donor site was chosen at the same location as where the flap would have been sited. Subsequently, the skin - together with a thin layer of subcutaneous fat - was harvested. Defatting of the subcutaneous tissue was performed to facilitate survival of the graft. The graft was fixated using resorbable sutures (Vicryl Rapide™ 3-0, Ethicon Johnson and Johnson, USA) and a tie-over was applied that was removed after seven days.

## Primary outcome parameter

The primary outcome parameter was the surface area of the flap or graft after a follow-up period of 3 months and 12 months. This is the most genuine and accurate parameter because it is the least influenced by external factors (such as joint stiffness). To measure the surface area, planimetry was performed by tracing the boundaries of the flap or graft on a transparent, pliable sheet that was subsequently digitized. Planimetric measurements were performed digitally (NIS-elements AR 2.6, Nikon, Amstelveen, the Netherlands). This is a reliable and valid measurement method[21].

## Secondary outcome parameters

### *Necrosis*

Necrosis was defined as a disorder in wound healing resulting in an unhealed wound after 3 weeks. The surface area of necrosis was measured according to the digital tracing method described above.

### *Width of the flaps*

The width of the flaps was measured on a transparent sheet as described previously[18]. In short, the width of the non-islanded flaps was measured by drawing a line between both arms of the flap: from the end of the short arm, perpendicular on the long arm. The width of the islanded flaps was assessed by measuring the distance between the long arms at the center of rotation[18]. The width of the FTSGs was measured in the center of the graft.

*Elasticity and Color*

Elasticity measurements were performed using the Cutometer® (Courage & Khazaka GmbH, Cologne, Germany), which is a reliable and valid instrument for the evaluation of skin elasticity[22]. The Cutometer® provides several elasticity parameters, of which the parameter *elasticity (Ue)* was used. This single parameter was shown to sufficiently represent the elasticity of the tissue[22]. Color measurements were performed by the DermaSpectrometer, a validated assessment tool for skin erythema (Cortex Technology, Hadsund, Denmark)[14]. The results of the DermaSpectrometer represent the extent of color deviation from normal skin. Three to five measurements of the flap or graft were taken, depending on the size of the flap or graft, according to a predefined measurement protocol (*Figure 4*). The mean of these measurements was used for further analysis.

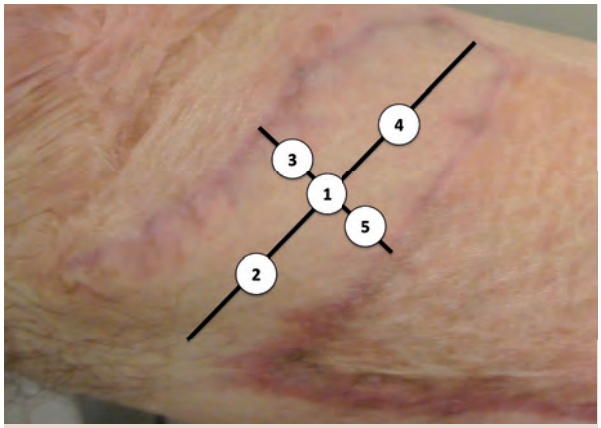


***Figure 4.*** *Example of a flap on the left upper arm. According to the standardized measurement protocol, the measured surface area is divided by drawing a line through the horizontal and vertical axis of the surface area. Point 1 was measured at the intersection of these lines. Points 2, 3, 4 and 5 were measured halfway from the intersection to the borders of the surface area.*



*POSAS*

Subjective scar assessment was performed by means of the POSAS[23], a reliable and valid scar assessment tool that consists of two parts; the patient and the observer scale, that numerically scores 6 items on a 10-point rating scale, in which a score of 10 reflects the worst imaginable scar[24]. A mean score of the observer and the patient was calculated by averaging the 6 separate item scores.

*Range of motion*

Range of motion was measured in degrees using goniometry according to a standard measurement protocol[3]. In case motion was limited in more directions, the mean of the measured range of motions was used for further analysis.

## Measurement points

Preoperatively, we performed scar elasticity, scar color, POSAS and range of motion measurements, to retrieve baseline data of the contractures. The surface area, width, and percentage of scar tissue included in the flap or graft were measured immediately after surgery. Postoperative complications were also registered. After 3 weeks, an experienced plastic surgeon evaluated the presence of necrosis and performed surface area measurements. After 3 and 12 months, an independent researcher assessed the following outcome parameters: surface area, width, elasticity, color, POSAS and range of motion.

## Power analysis and statistics

We performed an *a priori* power analysis (G*Power 3 version 3.0.3.) to estimate the required sample size. For the power analysis, the results of Stephenson *et al.* and Verhaegen *et al.* were used[5,18]. Stephenson *et al.* documented a decrease in mean surface area of full thickness grafts to 62%[5]. Verhaegen *et al.* demonstrated an increased surface area of 116% for perforator-based interposition flaps[18]. In the current study, we considered a remaining surface area of 100% (no contraction) as a clinically significant outcome for the interposition flaps. Therefore, 100% was selected in the power-analysis. The power was set at 0.80 and alpha at 0.05. A sample size of 13 patients per group was calculated. However, in anticipation of a dropout rate, a sample size of 15 patients per group was chosen.

Statistical analysis was performed using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Normal distribution was tested by calculating the skewness and kurtosis, evaluating frequency histograms, and performing the Shapiro-Wilk test. This was done for each parameter at each measurement point. Significant differences between independent data were tested using the independent t-test (in case of a normal distribution) or the Mann-Whitney U (MWU) test (in case of a non-normal distribution). To compare categories (POSAS outcomes) for independent data, the Chi-Square test was used. For paired data, the paired t-test was used (normal distribution) or the Wilcoxon signed ranks test (non-normal distribution). The two-tailed significance criterion was set at 0.05.

# Results

## Baseline characteristics

Patients were recruited from July 2011 until January 2014. *Figure 5* represents a flow diagram that shows the progress through the phases of the trial. Baseline characteristics are presented in *Table 1*. No statistically significant differences were found between the two groups. All patients suffered from post burn scar contractures. One patient had a history of diabetes mellitus. In 9 out of 16 flaps and 3 out of 13 FTSGs, supple scar tissue was included with a mean surface of 29% and 20%, respectively (p=0.141, MWU test). No correlation between the inclusion of scar tissue and the incidence of necrosis (p=0.351, MWU test) or area of necrosis (p=0.681, MWU test) could be demonstrated. In 14 out of 16 flaps the base was left intact.

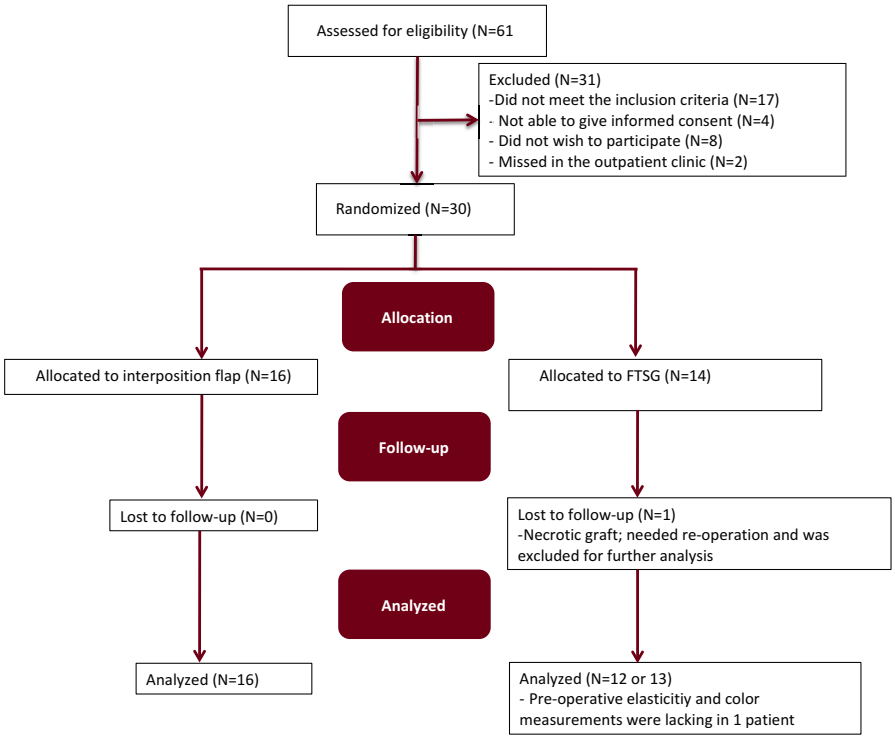


***Figure 5.*** *Flow chart of the numbers of patients that were included and measured throughout the course of the study.*

## Differences between flaps and FTSGs

*Figure 6* shows the primary outcome parameters and corresponding p-values. After a mean follow-up period of 3.1 months (SD: 0.7 months), the surface area of the perforator-based interposition flaps increased to 123%, whereas the surface area of the FTSGs decreased to 87% (95% confidence interval of the difference -53 to -19, p<0.001, independent t-test). After a mean follow-up period of 12.5 months (SD: 0.9 months), the surface area of the perforator-based interposition flaps increased to 142%, whereas the surface area of the FTSGs decreased to 92% (95% confidence interval of the difference -76 to -23, p<0.001, independent t-test).

| Characteristics | | Flaps N=16 | FTSGs N=14 | p-value |
|---|---|---|---|---|
| Male/Female | | 8/8 | 7/7 | - |
| Age patient, mean (SD) | | 49 (19) | 39 (21) | 0.183[1] |
| Smoker | | 2 | 3 | 0.464[2] |
| Location | Head/neck | 4 | 5 | - |
| | Arms | 5 | 4 | - |
| | Legs | 0 | 1 | - |
| | Back/Thorax | 5 | 3 | - |
| | Abdomen | 2 | 1 | - |
| Color, mean (SD) | | 8.9 (4.3) | 6.3 (2.9)* | 0.071[1] |
| Elasticity, mean (SD) | | 0.7 (0.3) | 0.6 (0.4)* | 0.775[3] |
| POSAS observer score, mean (SD) | | 3.6 (0.8) | 4.0 (1.1) | 0.254[1] |
| POSAS patient score, mean (SD) | | 5.1 (1.5) | 5.9 (1.3)* | 0.151[1] |
| Range of Motion in degrees (SD) | | 84 (56)** | 92 (75)* | 0.976[3] |

***Table 1.*** *Baseline demographic and clinical characteristics of both treatment groups.*
** refers to N=13; preoperative elasticity, color, range of motion measurements and subjective patient score of one patient are lacking. ** refers to N=15; one perforator-based interposition flap was located at the abdomen and did not involve any motion, nor restriction of motion. [1]=Chi-square test [2]=Independent t-test, [3]= Mann-Whitney U test.*

The results of the secondary outcome parameters are shown in *Table 2*. The width of the flaps was significantly larger than the width of the FTSGs after both 3 and 12 months. Furthermore, the mean POSAS score by the observers was significantly lower (i.e. better in terms of scar quality) for the flaps compared to the FTSGs after both 3 and 12 months. Also, the POSAS score by the patients was better at 3 and 12 months in the flap group, although not statistically significant. The color difference between flaps and normal skin was lower than for FTSGs. No statistically significant differences were found in terms of elasticity, measured with the Cutometer® between the two interventions at both follow-up points.

| | Flaps N=16 | FTSGs N=12* | 95% confidence interval of the difference | p-value |
|---|---|---|---|---|
| **Secondary outcome parameters** | | | | |
| Difference width flap/graft in percentage after 3 months, mean (SD) | 124% (19) | 95% (11) | -41 to -18 | <0.001 |
| Difference width flap/graft in percentage after 12 months, mean (SD) | 120% (20) | 90% (19) | -76 to -23 | 0.001 |
| POSAS observer score after 3 months, mean (SD) | 1.9 (0.6) | 2.4 (0.6) | 0.0 to 1.0 | 0.040 |
| POSAS observer score after 12 months, mean (SD) | 1.8 (0.5) | 2.8 (1.4) | 0.2 to 1.8 | 0.019 |
| POSAS patient scar score after 3 months, mean (SD) | 3.0 (2.1) | 3.7 (1.6) | -0.7 to 2.2 | 0.319 |
| POSAS patient scar score after 12 months, mean (SD) | 2.8 (2.0) | 3.5 (1.6) | -0.9 to 2.1 | 0.409 |
| Color after 3 months, mean (SD) | 3.7 (3.0) | 8.3 (2.8) | 2.3 to 6.9 | <0.001 |
| Color after 12 months, mean (SD) | 2.9 (2.7) | 8.1 (4.6) | 2.2 to 8.2 | 0.001 |
| Elasticity after 3 months, mean (SD) | 1.2 (0.4) | 0.9 (0.7) | -0.8 to 0.1 | 0.134 |
| Elasticity after 12 months, mean (SD) | 0.8 (0.3) | 0.8 (0.4) | -0.3 to 0.3 | 0.969 |

***Table 2.*** *Results of the secondary outcome parameters, measured 3 and 12 months postoperative. The independent t-test was used to calculate the differences. * N=12 because one FTSG was subject to complete necrosis and in one subject secondary outcome measurements are lacking.*

## Range of motion

In the flap group, the range of motion increased from 84 degrees to 95 degrees (p=0.012, Wilcoxon signed ranks test) after 3 months and to 96 degrees (p=0.041, Wilcoxon signed ranks test) after 12 months. In the FTSG group the range of motion increased from 92 to 98 degrees (p=0.074, Wilcoxon signed ranks test) after 3 months and to 104 degrees (p=0.114, Wilcoxon signed ranks test) after 12 months.

## Complications

All flaps survived. However, in the FTSG group one graft was subject to complete necrosis. This FTSG required revision surgery. Because the primary outcome as well as the majority of the secondary outcomes could not be measured to any further extent, this patient was subsequently excluded from further analysis. A mean percentage of necrosis of 6% was found for the flap group and 17% for the FTSG group (p= 0.208, MWU test). In the patient that suffered from diabetes mellitus, the flap was vascularly compromised 5 days after the operation. The tip became necrotic and the flap was surgically trimmed 9 days after the initial procedure. The initial surface area measurement and consecutive follow-up measurements were performed from that moment on.

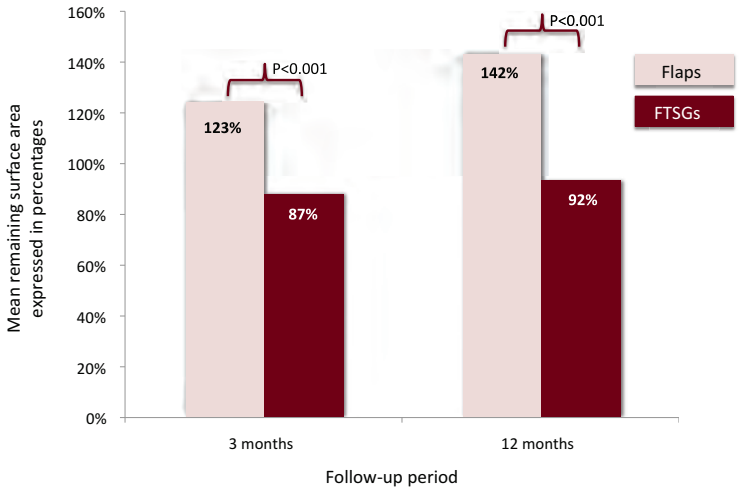


***Figure 6.*** *Bar chart representing the change in surface area (%) of the flaps and FTSGs after 3 and 12 months. Accompanying p-values are shown behind the braces.*

## Discussion

This is the first RCT that investigated the efficacy of perforator-based interposition flaps for the treatment of burn scar contractures. The long-term results showed convincingly that flaps perform better than FTSGs in providing a safe and effective tool to sustainably release burn scar contractures. We observed an increase in surface area of the flaps to 123% after 3 months and a further increase to 142% after 12 months. On the other hand, FTSGs showed a significant contraction; the remaining surface area decreased to 87% after 3 months. After 12 months, the surface area of the FTSGs slightly increased to 92% but was still contracted. The mean surface area differences between the two interventions were statistically significant at 3 and 12 months ($p<0.001$ at both follow-up moments). The results of this RCT strengthen the conclusions from our pilot study that was previously published[18]. In that study, which described the safety and versatility of perforator-based flaps for the reconstruction of scar contractures, an increase in surface area was found[18]. Again, we found that the size of the flaps increased with time. This finding merits to be highlighted and shows the sustainability of the technique for scar contracture releasing.

In the present study, the range of motion improved significantly in the flap group after both 3 and 12 months. Additionally, the FTSG group showed improvement in the range of motion, however without being statistically significant. Although both 'range of motion' and 'surface area' are important outcome parameters, we considered surface area to be more appropriate as primary outcome parameter because the range of motion is influenced and

confounded by factors such as stiffness of the joints or contractures in other directions. For this reason, and because range of motion was measured on different locations with diverse ranges (for example neck vs. shoulder), it is in our opinion not appropriate to perform an analysis between the two intervention groups. Nevertheless, the results concerning the range of motion support the results of the primary outcome parameter.

Other studies on the effectiveness of perforator-based interposition flaps for burn scar contracture release demonstrated favorable results. However, in those studies both objective outcome measures and control treatment groups were lacking[17,19]. The difference in contraction rate between the two interventions can be explained by the following hypothesis: after a release of a burn scar contracture, a considerable defect is generated because of the substantial forces that are exerted in the contracture by the contractile properties of the scar. The created wound bed has the tendency to contract again and the interpositioned tissue (the FTSG or flap) is subject to this contraction process. In contrast to FTSGs, flaps contain subcutaneous fat tissue. It may be hypothesized that the subcutaneous fat acts as a functional sliding layer to prevent the flap from adhering to the underlying wound bed, thereby making it less susceptible to contraction. The presence of subcutaneous fat tissue may also explain the fact that the flaps were found to be more similar to normal skin, as was shown by the secondary outcome parameters.
The treatment algorithm that was used in the present study provides a step-wise approach for the surgical treatment of scar contractures[18]. It implies that the base of the interposition flap is left intact, requiring that the flap is not vascularly compromised. The intact skin pedicle supports the blood supply and the venous outflow and, in addition, no unnecessary scar is created. However, when the angle of rotation is too large, the flap should be islanded to prevent an unalterable dog ear and/or a compromised vascularization caused by torsion of the perforator bundle. In this study, conversion to an islanded flap was often not necessary (in only 2 out of 16 interposition flaps), so 14 flaps benefitted from an intact skin base. The option to convert the peninsular flap into an insular flap makes this algorithm extremely versatile. The safety of the perforator-based interposition flaps was particularly underlined by the lower rate of necrosis compared to FTSGs: 6% compared to 17%. Moreover, one FTSG was subject to complete necrosis and needed a re-operation. Although we presume that incorporating the perforator bundle in the interposition flap enhances its safety, we did not prove that the perforator we detected preoperatively, is responsible for the perfusion of the flap. For that purpose we should have dissected the perforator bundle from its surrounding fat tissue. In flaps where the skin base is left intact this is unnecessary and should be discouraged because it may cause unwarranted damage to the perforator bundle.

Since local interposition flaps are more effective, safe and versatile, they should be preferred over FTSGs for the treatment of scar contractures. One limitation of perforator-

based interposition flaps is that sufficient adjacent healthy skin has to be available. However, inclusion of a certain amount of supple scar tissue is possible. In this study, the majority of the flaps (9/16) contained some scar tissue, with a mean surface area of 30%. We did not observe differences in the rate of necrosis and the surface area between flaps that contained scar tissue and flaps that consisted completely of healthy tissue. For the future we anticipate that interposition flaps based on a perforator will become a keystone in reconstructive burn surgery. Because this intervention is relatively easy to perform and has proven to be safe and effective, these flaps may provide a sustainable solution to other challenges such as acute burns in functional areas or large defects that are preferably not closed with a skin graft.

## Conclusions

This RCT demonstrated that perforator-based interposition flaps result in a more effective scar contracture release than FTSGs. Therefore, in scar contracture releases where both techniques are interchangeable, we advocate the use of a perforator-based interposition flap over a FTSG.

## Acknowledgements

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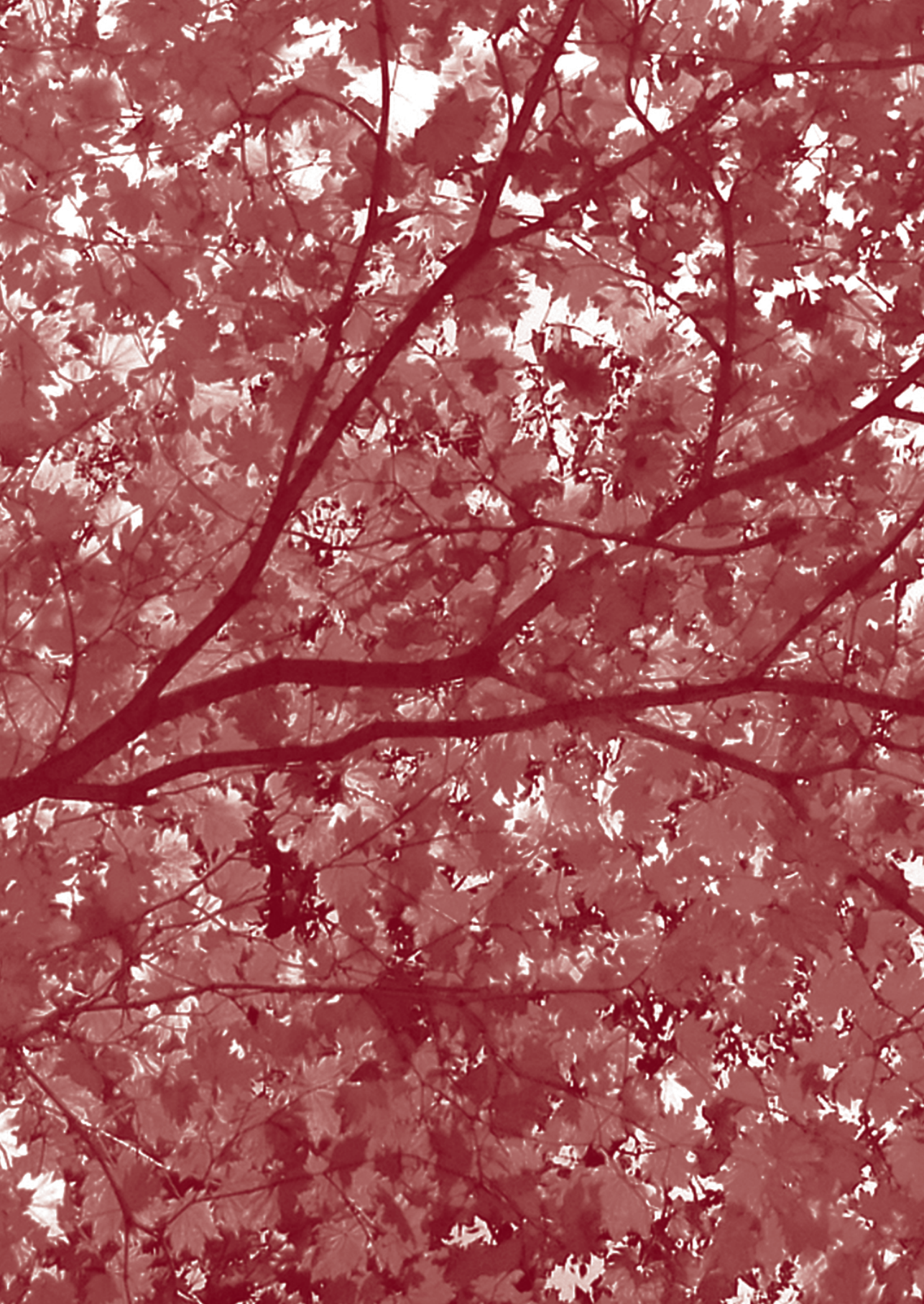

# 8

# The hand held Doppler device for the detection of perforators in reconstructive surgery: What you hear is not always what you get

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## Abstract

**Introduction:** Perforator-based flaps have become indispensable in the treatment of burn scars. Preoperative perforator mapping is often performed by use of the hand held Doppler device, partly due to its convenience and the low costs. We expected to find sufficient evidence in literature to support the use of the device, however available literature showed a distinct lack of clinimetric studies that adequately tested the reliability.

**Materials and Methods:** To assess reliability, perforator locations were mapped independently by two clinicians using an 8MHz Doppler device. In healthy volunteers the elbow region or the peri-umbilical region were randomly chosen to be the measurement areas of predefined squares (7x7 cm). Subsequently, the perforators within the area were mapped with Duplex to establish the validity by means of the positive predictive value.

**Results:** 20 volunteers were included. The hand held Doppler technique showed moderate reliability with a mean Dice coefficient of 0.56. Also, poor validity was found expressed by a mean positive predictive value of 55%.

**Conclusions:** Surprisingly, this study has shown that the performances of the hand held Doppler device were moderate. The Doppler should not be used solitary for the detection of perforators.

## Introduction

Scar contractures are frequently observed following extensive burn wounds. The use of perforator-based flaps in reconstructive (burn) surgery has increased significantly and has been established as a safe procedure[1-6]. Because perforators are distributed throughout the body, viable flaps can be raised from a great variety of anatomical locations[7]. The exact locations of perforators however, vary significantly between individuals. Preoperative perforator mapping facilitates flap harvesting and saves operating time.

In the past many years, several advanced diagnostic tools have become available, such as Magnetic Resonance Imaging (MRI), Computed Tomography Angiography (CTA), Digital Substraction Angiography and Color Doppler Sonography (Duplex)[8]. These techniques have proven to accurately detect perforator locations. They are however time consuming, cannot be performed during operation and most of these techniques are invasive and expensive. Furthermore, they have difficulty marking the exact location of identified perforators on the skin. A less modern device, the hand held Doppler, is on the other hand portable, inexpensive, easy to perform and interpret, and can be used during surgery by the surgeon. Furthermore, it has gained an important place as diagnostic tool in the upcoming field of perforator flaps because of its flexibility and readily available character[1,2,4-6,9].

The hand held Doppler device should be reliable and valid for application in clinical practice. When two clinicians use the same Doppler device they should be able to trace the same perforators. We expected to find sufficient evidence to support the use of the hand held Doppler device, however, available literature showed a distinct lack of clinimetric studies that adequately tested reliability. So far the Doppler device has only been studied for its validity, which means that a positive signal indicates the presence of a perforator[10-17]. The presented validity properties of the Doppler device differ considerably across studies[10-17]. Therefore, the aim of this study was to 1) test the reliability of the Doppler device for locating perforators 2) assess the validity of Doppler as a diagnostic tool for detecting perforators.

# Materials and Methods

## Subjects

Healthy volunteers participated in the study. The general principles outlined in the Declaration of Helsinki were followed. Participants were randomly assigned to two different groups based on the location in which perforators were mapped: elbow crease or the periumbilical region. Allocation concealment was carried out using sequentially numbered, opaque sealed envelopes. The sequence was determined by shuffling the envelopes by a researcher. The elbow crease was chosen because it is one of the areas prone to burn scar contractures, which are commonly released by means of perforator-based flaps[4]. The periumbilical region was chosen because this is a well-established location for perforator-based flaps, such as the deep inferior epigastric perforator (DIEP) flap. Each participant was positioned supine, with both arms resting alongside the body and the palms facing down. An area of 7x7 cm was marked using a plastic mould and a black permanent marker. To standardize the locations on the elbow or the abdomen, anatomical landmarks (the belly button and midline of the elbow crease, respectively) were used.

## Hand held Doppler device

A Huntleigh Dopplex D900 (Cardiff, UK) with an EZ8 8MHz probe and Parker Aquasonic 100 ultrasound transmission gel was used. The hand held Doppler device will be referred

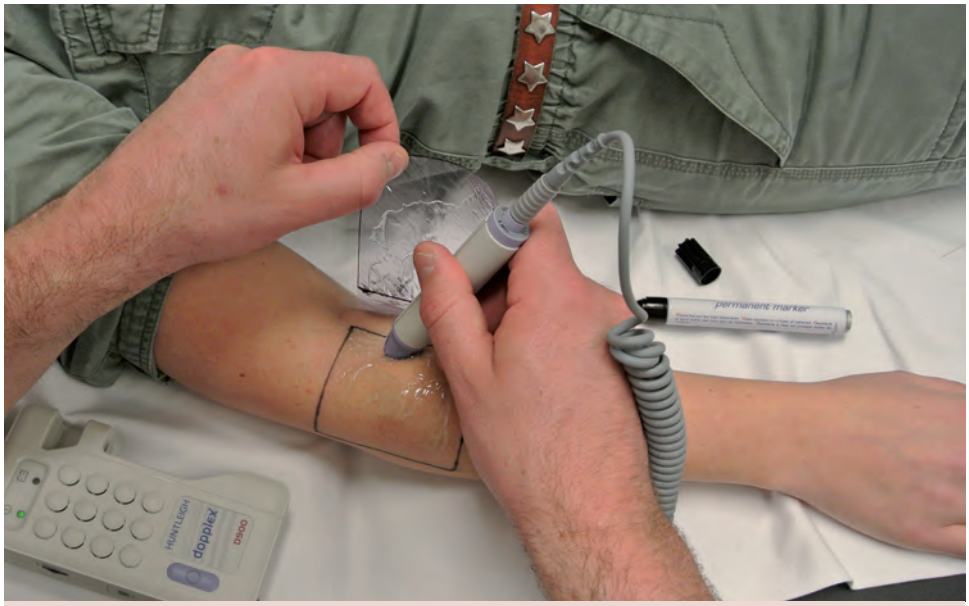


***Figure 1.*** *Example of the performance of Doppler mapping. The transparent sheet is lifted when mapping is performed and replaced on the skin to mark the locations with a permanent marker.*

to as Doppler in this study. When a positive signal was located, the probe was moved in all directions to ensure that the signal did not continue in any direction; indicating an axial vessel instead of a perforator. Each perforator location was marked with a permanent marker, on a transparent sheet that was laid on top of the previously marked area on the skin (*Figure 1*). This procedure ensured blinding of the observers.

## Color Doppler sonography (Duplex)

To assess the validity, Color Doppler sonography (iU22 Duplex with a L17-5 transducer, Philips, Eindhoven, The Netherlands) was used as standard for comparison, which has been successfully used to preoperatively assess flaps for reconstructions in the head and neck, trunk and extremities[8]. The same vascular laboratory technician mapped the perforators within the same squares described. These perforator locations were traced onto another transparent sheet using the permanent marker.

## Measurement procedure

Two clinicians mapped the perforator locations within the squares on the participants. Both clinicians were plastic surgeons with extensive experience using the Doppler device for the detection of perforators. The locations were marked on transparent sheets and compared to assess the reliability through the agreement between the detected locations. Markings within 1 cm radius were considered to correspond to the same perforator location[16,18]. Duplex was performed directly following the Doppler procedure (with a maximum of 1 hour in between) by a vascular laboratory technician to check if a perforator was present at a location that was found by Doppler. During all repetitive measurements the participants remained in the same position and room temperature was kept constant.

## Statistical analysis

### *Reliability*

The interobserver reliability was calculated based on the two measurements of two clinicians. The positive agreement was quantified (both clinicians detected a perforator on a specific location), by use of the Dice coefficient (DC)[19,20]: $\frac{Dice=2*n_{AB}}{n_A+n}$, where $n_A$ and $n_B$ are the number of locations found by the two observers (A and B) and $n_{AB}$ is the number of perforator locations shared by the two observers. The Dice coefficient (DC) is also known as the proportion specific positive agreement[19-21]. This coefficient is the best parameter to express the agreement in this study, because it equals 1 if A and B find exclusively shared locations. When A and B find perforator locations that are not found by the other observer it is smaller than 1 and the coefficient equals zero if none of the locations found by A and B correspond. For each volunteer the DC was calculated based on the number

of corresponding perforator locations per volunteer. These DC's were bootstrapped with replacement of 10,000 times. The average of the 10,000 mean DC's was calculated and from this, the bias corrected accelerated (BCa) 95% confidence interval was calculated.

*Validity*

To analyze the validity of the Doppler as a diagnostic device, the locations of the perforators found by Doppler were compared with the locations found with Duplex using the positive predictive value. Of the positive Doppler perforator locations that were not confirmed with Duplex (false positives), it was registered if it concerned the presence of an axial or intramuscular vessel or not. These features are important in clinical practice because both vessels are not suitable to base a perforator-based flap upon.

# Results

## Participant characteristics

A total of 20 participants (1 male and 19 female) were enrolled in this study. The mean age was 44.2 (SD 14.1) years and the mean Body Mass Index (BMI) was 25.7 kg/m$^2$ (SD 4.1). Four participants were smokers. Eleven participants were randomly assigned to the 'elbow crease group' and 9 to the 'periumbilical region group'.

## Reliability

Clinician A detected a total of 133 perforators, clinician B a total of 122. Seventy-six of these were found on similar locations. A mean of 6.4 perforators were detected per square of which a mean of 3.8 were matching. More perforators were found in the umbilical region (a mean of 7.0 perforators) compared to the elbow region (a mean of 6.0 perforators). An overview of the amount of detected perforators per clinician in each group is given in *Table 1*. The mean DC was 0.56 (BCa 95% confidence interval of 0.47-0.65).

| First/second clinician | Clinician A | Clinician B |
|---|---|---|
| **Total detected perforators** | 133 | 122 |
| elbow region (number of volunteers) | 70 (N=11) | 60 (N=11) |
| umbilical region (number of volunteers) | 63 (N=9) | 62 (N=9) |
| **Mean detected perforators (SD)** | 6.7 (1.7) | 6.1 (2.0) |
| elbow region | 6.4 (1.5) | 5.5 (1.8) |
| umbilical region | 7.0 (1.9) | 6.9 (2.0) |
| **Total overlapping** | 76 | |
| elbow region | 34 | |
| umbilical region | 42 | |
| **Mean overlapping perforators per square (SD)** | 3.8 (1.8) | |
| elbow region | 3.1 (1.7) | |
| umbilical region | 4.7 (1.6) | |

***Table 1.*** *The sum and mean of detected perforators per clinician and per region.*

## Validity

A mean positive predictive value rate was found to be 52.6% for clinician A and 57.4% for clinician B. Of the perforator locations that were found positive with Doppler but negative with Duplex, a mean of 32.4% were axial vessels and a mean of 45.1% were intramuscular situated vessels. The majority (70.6%) of these intramuscular situated perforators were found in the elbow region. See *Table 2* for the detailed information.

| | Duplex positive | Duplex negative | Doppler positive Total | Positive predictive value |
|---|---|---|---|---|
| **Clinician A Doppler positive** | **70** | **63**<br><br>**19 axial situated:**<br>9 elbow region<br>10 umbilical region<br><br>**29 intramuscular situated:**<br>22 elbow region<br>7 umbilical region | **133** | 70/133=**52.6**% |
| **Clinician B Doppler positive** | **70** | **52**<br><br>**18 axial situated:**<br>7 elbow region<br>11 umbilical region<br><br>**23 intramuscular situated:**<br>15 elbow region<br>8 umbilical region | **122** | 70/122=**57.4**% |

***Table 2.*** *The positive predictive value rates per clinician. The number of intramuscular detected perforators and axial vessels per region are also presented.*

# Discussion



For the first time the reliability was assessed of the hand held Doppler as tool for the detection of perforators. The interobserver reliability of the Doppler device was remarkably poor, expressed by a Dice coefficient of 0.56. Also, 55% of the perforator locations found by Doppler were true perforators confirmed by Duplex, 45% of the locations detected with the Doppler were not confirmed by Duplex. These results implicate that the Doppler as a single device does not suffice in identifying perforator locations.

Surprisingly, so far no studies were performed on the reliability of the Doppler device, which is a basic requirement of a diagnostic device. Literature on the validity of the Doppler for detecting perforators has shown variable results. Giunta et al. and Ensat et al. found positive

predictive value rates of 52% and 69%, respectively[12,13]. Two other studies reported higher positive predictive value rates varying from 82 to 94%[14,16]. Also, high sensitivity rates were presented in previous studies (varying from 81 to 100%)[11,12,16]. The higher positive predictive value and sensitivity rates in previous studies compared to the present study may be explained by the difference in study design; these studies investigated the validity of Doppler for the detection of established perforators, such as the DIEP[10,11,13], the superior gluteal artery perforator[11,13] and thoracodorsal artery perforator[11]. On the contrary, we focused on the Doppler as a diagnostic tool to detect all perforators within a square of 7x7 cm, so also smaller perforators. These perforators are located more dispersed and may differ in diameter, which most likely results in a lower positive predictive value. Taylor et al already demonstrated that the body contains a few hundred perforators with a diameter larger than 0.5 mm[7]. The total number is expected to be much larger since also smaller perforators (<0.5 mm) can be detected with the hand held Doppler. This study was the first to assess the validity of the Hand held Doppler for the detection of these smaller perforators. This is particularly relevant now that not only larger perforators, but also smaller perforators are used for local ad hoc flaps.
In this study Duplex was chosen as standard of comparison because this technology has been shown to validly identify the position of perforators preoperatively in the setting of all types of flaps[8]. Nonetheless, comparisons with more modern technologies such as CTA and MRA showed that color duplex was less accurate and provides less information on the intramuscular course of vessels. However, considering the purpose of our study -detection of smaller perforators- and the radiation hazards for the volunteers, we deemed Duplex as most appropriate standard of comparison for this study. Most studies compared the locations found using Doppler with locations found during operation[11-16]. A disadvantage of this method of comparison is that when the skin is incised the location changes, which makes it difficult to evaluate if the location found intraoperatively actually corresponds to the location that was marked on the skin preoperatively.

A limitation of the present study, which also accounts for many of the previously mentioned studies[11,13-16], is that the validity was not tested independently. The intentional set up of this study was to assess the validity independently: perform a Duplex without knowing the locations found with Doppler. This strategy however, appeared unattainable in clinical practice because of the time it took for the laboratory technician to perform the Duplex. A consequence of dependently assessing the validity is that the measurements become subject to expectation bias, which occurs when the interpretation of the outcome is subconsciously influenced by the knowledge of previously measured outcomes[22]. This may lead to higher positive predictive values.

We found that 45% of the positive signals assessed by the Doppler were not confirmed by Duplex and therefore assessed as false positives. Of these false positives 32% were

axial vessels and 45% were intramuscular vessels. Both types are inappropriate for the use for ad hoc perforator flaps. The amount of false positives caused by intramuscular vessels was larger in the elbow region than in the umbilical region, probably because the subcutaneous fat layer is usually thinner in the elbow region. A considerable amount of false positives were found in the umbilical region, which is striking since this region is frequently used for reconstructions. These findings illustrate that the Doppler does not provide enough information to sufficiently distinguish these different types of vessels from perforators.

The Doppler, however, remains a popular tool in the determination of perforator locations in clinical practice. Especially in the upcoming field of ad hoc perforator flaps, the Doppler device is commonly used for perforator detection[1-6]. There are several practical advantages, like easy handling and the possibility for peroperative use, which enables direct monitoring during operation. Until now, the more advanced techniques are incapable of peroperative localization. This study does not aim to banish the Doppler as a diagnostic tool for the detection of perforators, as its beneficial properties might perform well when the device is used complementary to a more advanced technique such as Duplex. The complementary use of Doppler to Duplex may be carried out as follows: the perforator is located and assessed for suitability (e.g., not situated intramuscular or axial) with Duplex. Subsequently, Doppler is used peroperatively to confirm the location and to monitor the viability of the perforator during the operation procedure. In this way the Doppler is used as a monitoring tool instead of a single diagnostic tool thereby optimally utilizing the valuable properties of both techniques. An interesting line of research would be to carry out validity analysis for the Doppler used as a monitoring tool.

## Conclusions

In conclusion, this study reveals novel and essential clinimetric properties of the hand held Doppler device. We have shown that Doppler is not suitable as a single diagnostic tool for the detection of perforators. This is an important finding in the field of reconstructive surgery where Doppler is frequently used for the detection of perforators for the use of ad hoc perforator flaps.



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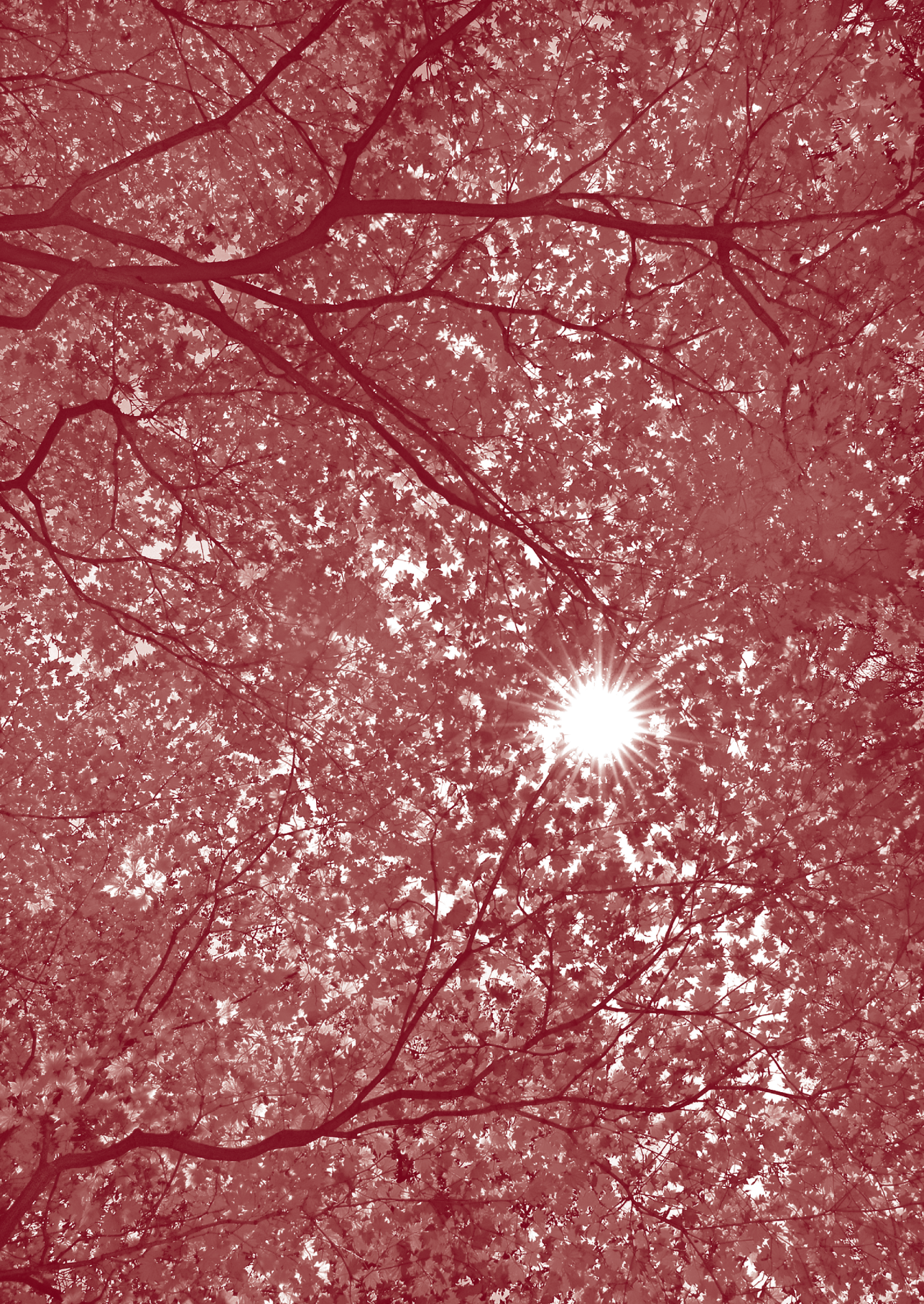

# 9

# General discussion

# General discussion

In this thesis, we focused on the improvement of the surgical treatment of burn scar contractures and on measurement tools. Firstly, clinimetric studies on 3D stereophotogrammetry for surface area and volume measurements of scars are described. In the following chapters, the current literature on the surgical treatment of burn scar contractures is reviewed and the effectiveness of the full thickness skin graft to treat burn scar contractures is evaluated. In the last part we assessed the suitability of the Doppler device for locating perforators and we performed two clinical trials that investigated the effect of the use of perforator-based interposition flaps for the treatment of burn scar contractures.

## Part I Clinimetric studies on scar surface area and volume

### Outcomes

In **Chapters 2 and 3** we presented the clinimetric studies on 3D stereophotogrammetry for measuring scar surface area and volume. 3D stereophotogrammetry showed to have a very high reliability, expressed by a high ICC (intraclass correlation coefficient), and a very high validity, expressed by a high CCC (concordance correlation coefficient). The ICC and CCC are both relative correlation parameters. They relate the measurement error to the variability between patients, using the ratio of variances[1,2]. Relative correlation parameters tell us something about how well patients can be distinguished from each other, despite the presence of measurement errors. If the variation between patients is high (in a heterogeneous population), the reliability parameter will be larger than in a homogenous population (little variation in the characteristic to be measured)[2,3]. However, in clinical practice we are interested in the absolute measurement error of an individual measurement because that determines the change that can be detected beyond the measurement error. Therefore, in **Chapters 2 and 3** we also used absolute parameters: the SEM (standard error of measurement), the CV (coefficient of variation) and the limits of agreement based on Bland and Altman plots. This additional analysis showed a moderate agreement between observers. This means that the high reliability was achieved because of the large variation in the area and volumes of the scars that we evaluated. So, in this study population 3D stereophotogrammetry can be used to distinguish scars despite the large measurement error.

By using Bland and Altman plots **in Chapter 2 and 3**, it became clearly visible that the measurement error was larger when larger objects were assessed. This is a rather uncommon phenomenon in clinimetrics, but for example also observed in measuring skin folds[4]. The dependency of the measurement error on the size of the scar was observed

when measuring surfaces, and to an even greater extent when measuring volumes and can be explained by the dimensions in which surface areas and volumes are assessed. When measuring the surface area, a measurement error can be made in the length and width of the scar; the measurement error is then multiplied instead of summed up. For scar volumes, cubic units are used which means that the measurement error is cubed. As the data on scar surfaces and volumes were not normally distributed and the measurement error increased by an increasing size of the scar, we used a log transformation and cube root transformation respectively to overcome this problem[4]. Unfortunately, transforming the data hinders an easy interpretation of the Bland and Altman plots. Therefore, after calculating the SEM (and ICC), we transformed them back to the original Bland and Altman plots to allow for a better understanding of the data. The limits of agreement now form a funnel instead of horizontal lines. As the limits of agreement correspond to the smallest detectable change this also means that with increasing scar sizes, larger changes in surface or volume are needed to be able to observe changes beyond the measurement error.

## Comparison with other studies

Relative parameters, such as ICC and Pearson's correlation coefficient, are widely accepted and are to date the most common parameters used in clinical research to assess the reliability and validity[1,5]. In many clinical studies high correlation parameters are found on the basis of which is concluded that the measurement error is small. However, to assess measurement errors, relative correlation parameters are misleading and inappropriate[3,6]. Information on the measurement error is especially important when a measurement tool is tested for its use in the clinical follow-up of scar sizes in time[1,2]. We should therefore take extreme caution when assessing the value of reliability and validity studies that only use relative correlation parameters[7-10]. Bland and Altman suggested, already in 1986, an alternative method to analyze the agreement between methods: the Bland and Altman plot[3]. Therefore, it is surprising that since then so little has changed with regard to using absolute measures of agreement instead of relative correlation coefficients to assess the agreement.

## Implications

We have shown that 3D stereophotogrammetry is a reliable and valid tool to assess scar surface area and volume for research purposes. For research purposes, measurement errors are much smaller as they are leveled out in groups because the error is divided by the square root of the number of patients included in the study[1]. For the clinical follow-up of patients though, where we are interested in the absolute measurement error of an individual measurement, the measurement error was found to be rather large for both surface area and volume measurements. We expect that other measurement tools currently in use most certainly are not superior in terms of the measurement error[7-10]. This means that still no ideal tool is available to register the surface area and volume of scars used for the clinical follow-up of patients.

## Future perspectives

Future research could focus on optimizing 3D stereophotogrammetry to quantify scar surface area and volume. Besides that, other three dimensional imaging techniques are rapidly developing. A recent advancement is laser technology in combination with digital photography of which the Artec MHT™ 3D Scanner (The Artec Group, San Diego, USA) is an example. An advantage of this device is that it is able to measure larger surface areas. We have initiated a study to assess the clinimetric properties of this device for measuring the wound surface area of burns. Furthermore, 3D technology is becoming more and more available for consumers in the form of application on smartphones and portable devices. An example of such a tool is the structured 3D-scanner™ which was recently developed by Occipital and can be easily attached to Apple hardware (Occipital and Lynx laboratories, Boulder, Colorado, USA). For clinicians it is important to keep up with these developments and to be able to judge whether these devices are a valuable addition to clinical practice. Clinimetric analysis of new devices is therefore warranted. The first part of this thesis illustrated once more that relative parameters do not provide an answer to the question how precise a measurement is and to what extent it is free from measurement error. We therefore recommend for future clinimetric studies to report parameters of absolute measurement error. As was illustrated by the studies that were performed in **Chapters 2 and 3**, solid clinimetric research can be challenging. To aid future research initiatives that investigate the clinimetric properties of a device we have included detailed statistical descriptions in **Chapters 2 and 3**. These analyses can be difficult to perform by clinicians. For that reason, we strongly recommend collaborations between epidemiologic departments and clinical research departments.

# Part II Burn scar contracture treatment: the current state of the art

## Outcomes

For the treatment of burn scar contractures, many techniques are available and new techniques are developing rapidly. It is important to shed light on the available knowledge on the effectiveness of different treatment regimens. Therefore, we performed a systematic review that is presented in **Chapter 4**. By performing this review, we hoped to be able to develop an algorithm for the treatment of burn scar contractures. Although we did not expect to find many high quality studies, the result of studies concerning the effectiveness of different treatment therapies was extremely disappointing. Using an extensive search strategy, over 1600 articles were found and analyzed of which only 17 articles described a surgical treatment regimen in a sample of ≥ 15 procedures[11-26]. The included studies were found to be of low overall quality. First, the low quality was caused by a poor study design (pre-postoperative design). Second, the outcomes were often poorly described, using a great variety of (not always relevant) outcome parameters. Finally, the majority

of the studies did not succeed in an adequate data presentation and statistical analysis (e.g. standard deviations were lacking or statistical analysis not performed). Therefore, we were not able to provide sufficient evidence to draw conclusions on the effectiveness of reconstructive techniques after burn scar contracture release. Moreover, developing a standardized treatment algorithm remains a challenge on which we aimed to contribute in the later chapters in this thesis (part III).

In **Chapter 5** the effectiveness of full thickness skin grafts (FTSGs) is described. In clinical practice FTSGs are an important tool of the reconstructive surgeon. Although in the past decades a shift has been observed to more advanced techniques such as perforator flaps and dermal substitution, FTSGs are still frequently used for reconstruction of burn scar contractures. The reason is that they are relatively easy to perform and useful in many facets of reconstructive surgery. Especially in the treatment of burn scar contractures it is of paramount importance that the added tissue retains its original surface area. FTSGs are often preferred over split thickness skin grafts (STSGs) because they are supposed to result in less contraction[15,27-29]. In **Chapter 5** however, it was demonstrated that the surface area of FTSGs contracts considerably on the long term. Even though we were able to demonstrate the contraction pattern of FTSGs over time, the underlying mechanism of contraction remains unclear. We assume an important role for the underlying wound bed in this contraction process. When a contracture release is performed a considerable wound is created. The subsequent wound healing process aims at accelerated wound closure and reducing the size of the wound in order to minimize the chance of infection. This contraction process involves a wide array of processes that is not fully understood yet[30]. The myofibroblast has a potential important role in this process, because of its contractile structure and its strong retractile activity[31]. It is conceivable that the FTSG that is placed on top of a contracting wound bed is subject to this contraction process. This hypothesis is supported by the fact that a significant difference in contraction rate was observed between grafts harvested from the trunk, compared to grafts harvested from the extremities. Skin originating from the trunk is generally considered to contain a thicker dermis than skin from the extremities[32] and it may be suggested that a graft with a thicker dermis will provide better results with reduced contraction compared to a graft with a thinner dermis. Also, a thicker dermis likely contains a more extensive collagen network, which is more capable of stretching[33,34].

## Comparison with other studies

As holds true for the surgical techniques that were described in the included studies in the systematic review, the effectiveness of FTSGs to release scar contractures has been studied insufficiently. The general thought is that FTSGs do not contract, a belief that is probably held intact because of the fact that FTSGs are mostly compared to STSGs, which tend to contract to a greater extent[15,27,35-37]. Also, in most studies the contraction

rate is expressed in the recurrence rate (i.e. recurrence of contracture), which is to our opinion a suboptimal outcome parameter, as it is influenced by many other factors[15,37]. Only one study used surface area reduction, measured by digital photography, to express the contraction rate in FTSGs and demonstrated a considerable contraction (to 62%) of the original surface area[38]. In **Chapter 5** we observed a reduction of surface area to 85.9% of the original surface area after a comparable follow-up period of 13 weeks.

## Implications

As disappointing as the evidence from the abovementioned review may be, it uncovers the flaws in the current available scientific literature and thereby provides important lessons for future studies investigating the effectiveness of burn scar contracture release surgery. First, a sufficient sample size should be chosen. A realistic power calculation is needed to determine the number of patients that should be acquired in a trial, depending on the effect of an intervention in a specific patient population. Second, the study should be designed in such a way that a comparison is made with another intervention. Only then can the effect of the treatment be distinguished from the clinical course and from the treatment with other surgical techniques. Third, we would like to stress the importance of the outcome assessment; it should be carefully linked to a relevant clinically expected outcome. Reliable and valid measurement techniques should be used to assess the outcome, which allows for comparison between study results[1]. The introduction of new measurement tools, without validating them, is not recommended[1]. Finally, an adequate data presentation and statistical analysis are a necessity. Although randomized controlled trials are promoted as the holy grail for establishing how well an intervention works, they have some shortcomings in terms of recruitment, ethics, patient preferences, and treatment comparisons[39]. Due to these shortcomings, the duration of RCTs is often long, which may hinder an adequate response to new developments. The ability to scientifically anticipate to new developments is essential for a more evidence-based medicine in reconstructive surgery. When performing the randomized controlled trial that is described in Part III, we experienced a lengthy research process of five years from concept to results. The long duration was mainly caused by extensive ethical procedures, patient preferences and rigidity of the inclusion criteria that were according to the predefined protocol. Recently, a new design to overcome these shortcomings has been introduced: the cohort multiple randomized controlled trial (cmRCT)[39,40]. The basis of the cmRCT is a large observational cohort of patients that is recruited for multiple trials in which a random selection of some participants is used for comparison between (new developed) interventions. This study design could allow for multiple, comparisons simultaneously and a lower drop off due to patients' preferences. We believe this could be a valuable study design in the field of reconstructive surgery where new techniques or adaptions to yet existing techniques are rapidly developing.

In line with previous findings[38], it was demonstrated in **Chapter 5** that FTSGs contract. Although the study does not satisfy to all the above-mentioned requirements: it was an observational cohort study and no power analysis was performed, it provides a unique insight in the contraction process of FTSGs over time. This increased knowledge on the contraction pattern allows to take into account the expected contraction and to use another reconstruction technique in cases where a re-contraction is least desired, as is the case in scar contracture release. Furthermore, it should be recommended to harvest a FTSG with a larger surface area than expected to be needed on the recipient location, taking future contraction into consideration. Furthermore, regarding our finding that grafts excised from the trunk endure significantly less contraction on the long term than grafts excised from the extremities, we advise to, whenever possible, use the trunk as the donorsite location of preference.

### Future perspectives

Inspired by the revolutionary developments that characterized the reconstructive surgery during the First and Second World Wars, it is now time to make steps forward to a more evidence-based medicine approach in reconstructive surgery. Implementation of the lessons that were addressed above should be pursued in future studies. We suggest repeating a systematic review of literature with respect to this subject within a five-year period to detect a shift towards better studies that enable a more evidence-based clinical practice within the burn field.

## Part III Progress in burn scar contracture reconstruction by perforator-based interposition flaps

### Outcomes of perforator-based interposition flaps

Since the survival of patients with extensive burns has improved significantly, burn scar reconstruction becomes increasingly important. As is highlighted in **Chapters 4 and 5** of this thesis, many surgical techniques are available. In our opinion the best technique should be simple and easy to perform, create as little as possible donor site morbidity and be safe and effective. We therefore advocate the use of local tissue. Local flaps have been used for a long time, are safe and are technically simple to perform. The disadvantage of local flaps is that they are subject to a restricted length-to-width ratio and exceeding this ratio increases the risk of vascular problems[27,35,41,42]. Incorporating a perforator bundle in the flap overcomes this restriction. This way a safe and versatile interposition flap can be used, without a restriction of the length-to-width ratio. The flaps that were described in **Chapters 6 and 7** had a mean length-to-width ratio of 3.0:1 and 2.9:1 (data not published) respectively. Flaps can be created much larger without compromising on the vascularization. The maximum length-to-width ratio's in the studies in **Chapters 6 and**

**7** were 4.5:1 in and 5.9:1 (data not shown), respectively, and showed successful results. Moreover, no correlation between length-to-width ratio and incidence or percentage of necrosis was demonstrated. By creating longer flaps (higher length-to-width ratio) we probably could have demonstrated more challenging possibilities of perforator-based interposition flaps. However, it was not our purpose to create as long as possible length-to-width ratios but to provide a safe and effective treatment that is tailored to individual needs.

Because the current literature could not provide an algorithm for the treatment of burn scar contractures (**Chapter 4**), we developed an algorithm based on clinical experience. The treatment algorithm was presented and tested in **Chapter 6** and provides a step-wise approach for surgical treatment of scar contractures. In short, the algorithm implies the following. A non-islanded flap should be preferred in case of small angles of rotation because an intact flap base provides extra venous outflow and prevents the necessity for additional scar tissue. However, when the perfusion of the flap is at risk because of a too large angle of rotation, the flap can be islanded quite easily. The flap can be converted to a FTSG as an escape in cases where the flap remains vascular compromised. This provides surgeons with a versatile tool to adequately take on burn scar contractures. The algorithm was found to be effective and safe.
With regard to the effectiveness, favorable results were found in of both our studies. In the pilot study (**Chapter 6**) an increase in surface area of the flaps was observed to 116% measured after a mean follow-up of 7.8 months. In the randomized controlled trial (**Chapter 7**) we were able to demonstrate an even larger increase in surface area after 3 and 12 months follow-up. The flaps showed an increase of the original surface area to 123% after 3 months and to 142% after one year, which was in contrast to the substantial decrease in surface area of FTSGs after 3 months and after one year. From our point of view, this could be completely attributed to the properties of adjacent healthy tissue (and in some cases subtle scar tissue) that is inserted into the defect created by the contracture release. First of all, interposition flaps contain, in contrast to FTSGs, the subdermal fat tissue. An important property of the subdermal fat tissue is to provide a functional sliding layer. In Part II of this thesis, we already assumed an important role of the underlying wound bed in the contraction process after contracture release. The additional subcutaneous sliding layer of a flap prevents the skin from being attached to the underlying wound bed. The skin of the flap has the possibility to stretch in time. Second, in perforator-based interposition flaps the subdermal plexus is preserved. This rich network of cutaneous arteries and veins, which is spread out between the subcutis and dermis, provides blood supply to the skin and its adnexes. By preserving the perforator and the subdermal plexus, the blood supply to the skin is secured from the moment the tissue is transferred. For the transplantation of FTSGs, the graft is thinned to the dermis and ingrowth of the grafts initially succeeds by diffusion of nutrients. Skin grafts can tolerate

an ischemic period without being subject to necrosis, however this is not favorable for graft take and subsequently for the quality of the grafted skin[28]. Based on our findings and the interpretations of our findings we conclude that local flaps possess a better tissue quality and thereby are more capable of stretching which is probably caused by the fact that they remain in their original surrounding tissue and are provided with an uninterrupted blood supply.

With regard to the safety of the perforator-based interposition flaps we found a relatively low percentage of necrosis compared to FTSGs (6% versus 17%). In all cases we were able to detect a suitable perforator adjacent to the contracture. The calibers of the perforators were measured incidentally and ranged between 0.3 mm and 0.8 mm (unpublished data). This advocates that flaps can be based on smaller perforators (<0.5 mm). We could however not prove that the perforator that was located preoperatively is responsible for an adequate perfusion of the flaps, since we did not standard dissect the perforator bundle.

## Comparison with other studies on perforator-based interposition flaps

Studies on the use of perforator-based interposition flaps mainly focus on the use in specific regions such as the thoracodorsal artery flap for the breast or axilla region[43,44] and the cervical artery flap for the neck[45,46]. The results from these studies are useful in cases where contractures appear in that specific region. Burn scar contractures though, will occur almost on all body sites. Moreover, healthy tissue is not always available for flap preparation. The concept of the ad hoc perforator-based flaps overcomes these problems, and was introduced and described to be safe and sustainable in small cohort studies[47,48]. Nevertheless, the concept is not routinely applied for burn scar reconstructions.

## Implications and future perspectives on perforator-based interposition flaps

The long-term results as demonstrated in our study described in **Chapter 7** show that local flaps, based on a perforator, are a safe, effective and sustainable technique for the surgical treatment of burn scar contractures. We provided convincing evidence that these flaps lead to better long-term results compared to the current standard of skin grafting. We hypothesize that the subcutis has an important role in this difference in outcome between the two techniques. Therefore, we strongly suggest future research into the precise role of the subcutis and its possibilities in reconstructive surgery.

In clinical practice perforator-based interposition flaps should be added to the armamentarium of the reconstructive surgeon and be considered as preferred treatment of wide burn scar contractures. Besides the treatment of burn scar contractures, there is a role for perforator-based interposition flaps in other fields of reconstructive surgery. Since they are easy to perform and provide a safe and effective treatment option, they may become an important tool in the surgical treatment of other reconstructive defects,

such as deep burns in functional areas or large defects as a result of decubitus. They might extend the repertoire of the reconstructive surgeon considerably. In our burn center we have already been successfully treating several acute burns with perforator-based interposition flaps (*Figure 1*). Future research should further clarify the role, possibilities and limitations, and outcomes of perforator-based interposition flaps in the treatment of other defects.

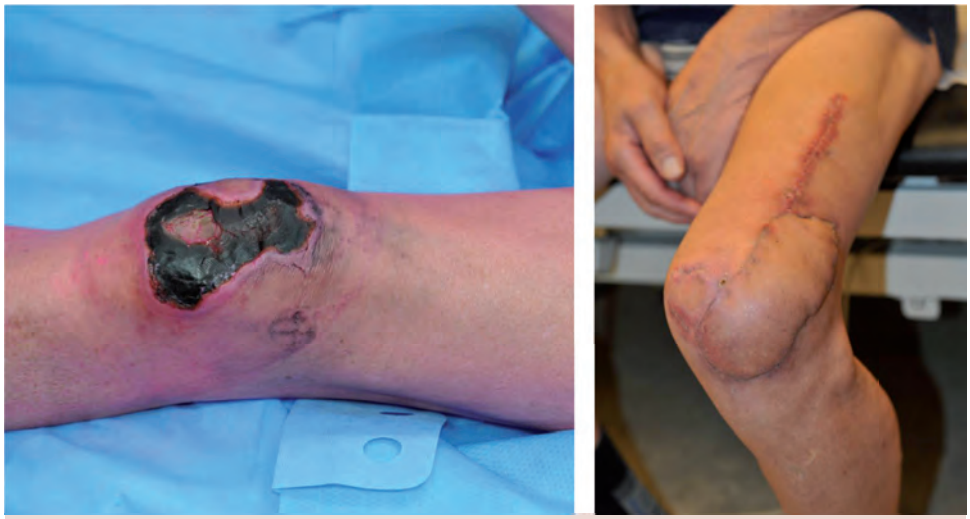

*Figure 1. A 70-year-old male with a flame burn to the left knee, penetrating to the patella (left). The burn was surgically treated after 28 days with an islanded perforator-based flap. The photograph on the right represents the perforator-based flap after 5 weeks. Maximum range of motion was already achieved at that time.*

Further recommendations concern the design of perforator-based interposition flaps. First, as described in the algorithm, interposition flaps do not necessarily have to be islanded. Leaving the skin base intact provides extra arterial inflow and venous outflow. Furthermore, no additional scar tissue is created. Islanding or 'propelloring' the flap is only required in case the flap is vascular compromised by exceeding the maximal angle of rotation. Second, it is preferable to design the flap in such a way that the perforator bundle is located outside, but close to the flap base, which was illustrated in **Chapter 6** ***Figure 1***. This reduces the risk of accidentally damaging the perforator artery and vein. In islanded flaps, where it may be necessary to dissect the perforator bundle to a certain extent, we advise to leave a cuff of fat tissue. This tissue offers extra protection to the delicate structure of the bundle. Finally, the design of the flap itself and the maximum angle of rotation are often dependent on local situations. It would be interesting for future research to experimentally investigate the influence of flap design and angle of rotation on the outcome of interposition flaps.

## Outcomes on vascularization

In this thesis the clinimetric properties of the hand held Doppler for the detection of perforator locations were studied. The use of Doppler to locate the origin of perforators is not new and has been used by many reconstructive surgeons since the early nineties[49-54]. In **Chapter 8** we discovered that the agreement between the observers was poor. In clinical practice this means that when one plastic surgeon locates a certain perforator, another plastic surgeon is not capable of finding the same location. Furthermore, we demonstrated a very low validity of the device, which may be explained by the moderate reliability since a high validity is not attainable without reliability.

## Comparison with other studies on vascularization

Before the start of the study that is described in **Chapter 8**, there were conflicting reports on the suitability of the Doppler device as diagnostic tool for the detection of perforator locations. Several studies had shown that the device was only moderately capable of validly detect perforators[50,53], while other studies reported a high validity of the device[54,55]. At the same time the device is increasingly being used in the upcoming field of ad hoc perforator flaps. It was therefore striking that we could not find any papers that studied the reliability of the device. But how can we explain the difference in validity results between our study and other studies? First, the higher validity rates in previous studies compared to our study may be explained by the difference in study design; these studies investigated the validity of Doppler for the detection of established perforators, such as the deep inferior epigastric perforator (DIEP)[51,56], the superior gluteal artery perforator[51,56] and the thoracodorsal artery perforator[51]. In contrast, we focused on the Doppler as a diagnostic tool to detect all perforators within a square of 7 by 7 cm, including smaller perforators. These perforators are located more dispersed and may differ in diameter, which most likely results in a lower positive predictive value. We propose that the Doppler device is a suitable measurement tool to confirm the exact location of a known perforator as mentioned above, but not to detect an unknown (smaller) perforator. Second, this can be attributed to the use of another gold standard; in most of these studies the validity was tested by comparing the Doppler locations with the locations that were found intraoperatively. Usually perforator locations that are detected with Doppler are marked on the skin, but the location changes per definition once the skin has been incised. With the knowledge that many perforators are present in a certain area, it could be that perforators that were detected with Doppler were mistaken for nearby located perforators. It is difficult to evaluate if the 'match' that is described in these studies is real or that it concerns another perforator[51,53-55]. It was for that reason we chose Duplex as the standard of comparison. Also, the volunteers were kept in the same position so locations could not change based on changing position of the volunteer. This could have led to a lower positive predictive value than the values presented in the majority of previous validity studies.

Still, in the upcoming field of ad hoc perforator-based interposition flaps, the Doppler is a very popular tool for the detection of perforators. Studies that assessed the outcome of these type of flaps commonly use the Doppler device to preoperatively locate the perforators. Also many good results with minimal flap necrosis have been presented[47,57-60]. This leaves us with the question, how it is possible that a diagnostic tool with very low clinimetric properties is able to perform that well in clinical practice. To solve this problem, we have to understand the anatomy of the human integument. Extensive basic research on the vascularization of the human integument has brought us the knowledge that the body contains a few hundred perforators with a diameter larger than 0.5 mm[61]. The total number is expected to be much larger as smaller perforators (<0.5 mm) can also be detected with the hand held Doppler. The perforator detected preoperatively is almost certainly surrounded by many other (possibly smaller) perforators. It is plausible that the perforator that is detected preoperatively is not the perforator that is supplying the flap postoperatively.

## Implications on vascularization

The popularity of the Doppler in clinical practice has most certainly to do with its ease in use, the possibility to use it intraoperatively and the relatively low costs of the device. Until the development of more advanced and yet feasible techniques we therefore propose a unique application of the Doppler: complementary to Duplex (which was described in **Chapter 8**). The perforator is located and assessed for suitability (e.g., not situated intramuscular or axial) with Duplex. Subsequently, Doppler is used preoperatively to confirm the location and to monitor the viability of the perforator during the operation procedure. In this way the Doppler is used as a monitoring tool instead of a single diagnostic tool, thereby optimally utilizing the valuable properties of both techniques. Future research could investigate the validity for the Doppler used as a monitoring tool.

## Future perspectives on vascularization

The success of perforator-based flaps is established on an improvement of local flaps by incorporating a perforator. Besides the perforator, also the subdermal plexus supposedly plays an important role, which was highlighted above. Further research into techniques that visualize the vascularization is needed to enhance our knowledge on the vascularization of the skin. In the past decades many advanced visualization techniques have become available. These techniques will play a key role in improving the outcome of burn and reconstructive surgery. Noninvasive optical techniques that measure vascularisation (and/or perfusion) such as optical coherence tomography (OCT), photoacoustic imaging and thermography are still under development but have great potential for improving noninvasive imaging of the vascularization of the human integument, even at a microscopic level. Others are already in use in clinical practice but are not explored yet to their full potential in terms of application for different purposes, such as Laser Doppler imaging

(LDI), Duplex and thermography. In our opinion future research regarding vascularization should focus on the visualization of the subdermal plexus and perforators. Clinical studies have already been initiated to further explore the value of OCT, thermography, LDI and Duplex. Advanced vascularization techniques could be of value for different purposes in clinical practice. First, they could aid in a better preoperative localization of perforators and provide additional information on the flap perfusion peri and postoperatively. This may improve flap survival and thereby result in an enhanced safety of perforator flaps and a better outcome of burn scar reconstruction. In line with this improvement it would be interesting to investigate the diameters of perforators and their course through the subcutis. A better knowledge on the course of perforators would probably lead to a lower risk of damaging the perforator bundle peroperative. Second, advanced techniques may provide further insight in the role of vascularization in hypertrophic scar formation. An increased vascularization is thought to play a role in the derailing process of hypertophic scars, but its exact role remains unclear[30]. At present a clinical trial is in progress to test whether LDI is capable of detecting an increased blood flow in hypertrophic scars.

Summarizing, in this dissertation we focused on the improvement of the treatment of burn scar contractures. We reviewed the available literature and brought to light that the current literature on the effectiveness of reconstructive techniques for burn scar contracture release is below par in both quantity as in quality of the studies performed. Due to the lack of evidence we were not able to provide definitive conclusions on the effectiveness of different techniques or make specific recommendations. In order to attain improvement, trials should be performed that make use of sensible outcome parameters, using reliable, valid and feasible measurement tools. Because such tools were not available to assess the scar characteristics surface area and volume, we assessed the clinimetric properties of 3D stereophotogrammetry. It was revealed that for research purposes, 3D stereophotogrammetry was a reliable and valid technique. For use in clinical practice however, the measurement error appeared to be too large. Until now, burn scar contractures are often treated by use of FTSGs. We found that FTSGs contract considerably over time, with the extremities as donorsite being a predisposing factor for increased contraction. Instead of skin grafting we therefore advocate the use of local flaps and developed an algorithm accordingly. The clinical studies in this thesis showed that the algorithm using local flaps based on a perforator provides a versatile, effective and safe treatment option for burn scar contractures. Moreover, the RCT showed that these local flaps perform considerably better than FTSGs in the treatment of burn scar contractures on the long term. Detection of the location perforators is often done by use of a Doppler device. Research into the clinimetric properties of the Doppler however showed that as a single diagnostic tool it is not suitable for the detection of perforators. This leaves an opportunity for more advanced techniques to become standardized in daily clinical practice.

By providing an overview of the current literature, by thoroughly assessing the suitability of scar measurement tools, and by investigating the true effectiveness of perforator-based interposition flaps, we have made progress in improving the current state of the art of treatment of burn scar contractures.

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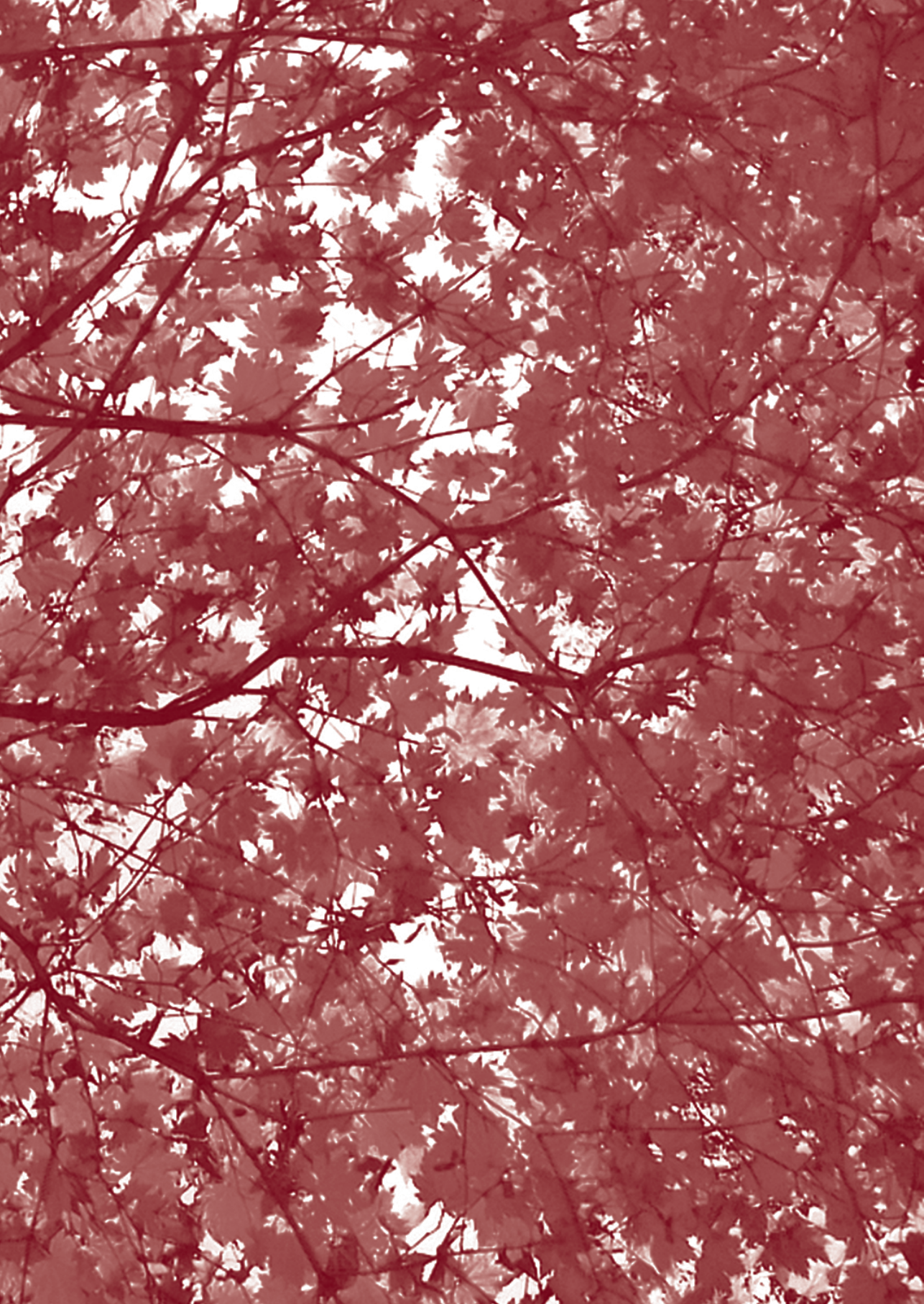
# 9



# Appendices

# Summary

During the last decades, advances in burn care have led to an increased survival of patients with extensive burns. As a consequence, new challenges arise to improve the treatment of scars. Although scar treatment has already improved, scars resulting from deep burns still result in considerable functional problems in daily life. These functional problems are often represented by contraction of scar tissue resulting in disabling contractures. This dissertation focuses on the improvement of the treatment of burn scar contractures and on measurement tools.

## Part I Clinimetric studies on scar surface area and volume

Different scar features may be distinguished that are clinically relevant and contribute to the overall quality of a scar, including color, elasticity, volume and surface area. For some of these scar characteristics (such as color and elasticity), suitable measurement tools are readily available. For the scar characteristics *surface area* and *volume* however, reliable and valid measurement tools are lacking. In **Chapter 2** and **Chapter 3** the reliability of 3D stereophotogrammetry for measuring scar surface area and volume was examined. We showed that 3D stereophotogrammetry is a reliable and valid tool to assess scar surface area and volume for research purposes. For research purposes, measurement errors are much smaller as they are leveled out in groups because the error is divided by the square root of the number of patients included in the study. For the clinical follow-up of patients though, where we are interested in the absolute measurement error of measurements in a single patient, the measurement error was found to be unacceptably large for both surface area and volume measurements. In **Chapter 2 and 3** it was furthermore illustrated that relative parameters do not provide an answer to the question how precise a measurement is and to what extent it is free from measurement error. As most previously performed studies only use relative measurement parameters, it is expected that other measurement tools currently in use most certainly are not superior in terms of the measurement error. This means that still no ideal tool is available to register the surface area and volume of scars used for the follow-up of patients in clinical practice.

## Part II Burn scar contracture treatment: the current state of the art

Treating burn scar contractures remains challenging for reconstructive surgeons. Because no consensus existed on when to use what kind of technique, a systematic review was performed on the effectiveness of the different surgical techniques after burn scar contracture release (**Chapter 4**). It was brought to light that the available literature on the

effectiveness of reconstructive techniques for burn scar contracture release is below par in both quantity and quality of the studies performed. Due to the lack of evidence we were not able to provide definitive conclusions on the effectiveness of different techniques or make specific recommendations. This review however did uncover the flaws in the current available scientific literature and thereby provided important lessons for future studies investigating the effectiveness of burn scar contracture release surgery. These lessons include the importance of 1) a comparison intervention, 2) a solid outcome assessment, using reliable and valid measurement techniques, 3) a sufficient sample size and 4) an adequate data presentation and statistical analysis. Only when future studies apply these lessons, evidence on the effectiveness of treatments for burn scar contractures becomes available.

In **Chapter 5** we explored the effectiveness of full thickness skin grafts (FTSGs) for treating burn scar contractures. In clinical practice FTSGs are an important tool of the reconstructive surgeon. Although in the past decades a shift has been observed to more advanced techniques such as perforator flaps and dermal substitution, FTSGs are still frequently used for reconstruction of burn scar contractures. The reason is that they are relatively easy to perform and useful in many facets of reconstructive surgery. Especially in the treatment of burn scar contractures it is of paramount importance that the added tissue retains its original surface area. In **Chapter 5** however, it was demonstrated that the surface area of FTSGs contracts considerably on the long term. Moreover, the vast majority of the FTSGs showed contraction at final follow-up. Furthermore, we observed that grafts excised from the trunk endure significantly less contraction on the long term than grafts excised from the extremities. This increased knowledge on the contraction pattern allows to take into account the expected contraction and to use another reconstruction technique in cases where re-contraction is least desired, as is the case in scar contracture release. When, however, FTSGs are preferred, it should be recommended to harvest FTSGs with a larger surface area than expected to be needed on the recipient location, taking future contraction into consideration. Furthermore, regarding our finding that grafts excised from the trunk endure significantly less contraction on the long term than grafts excised from the extremities, we advise to, whenever possible, use the trunk as the donor site location of preference.

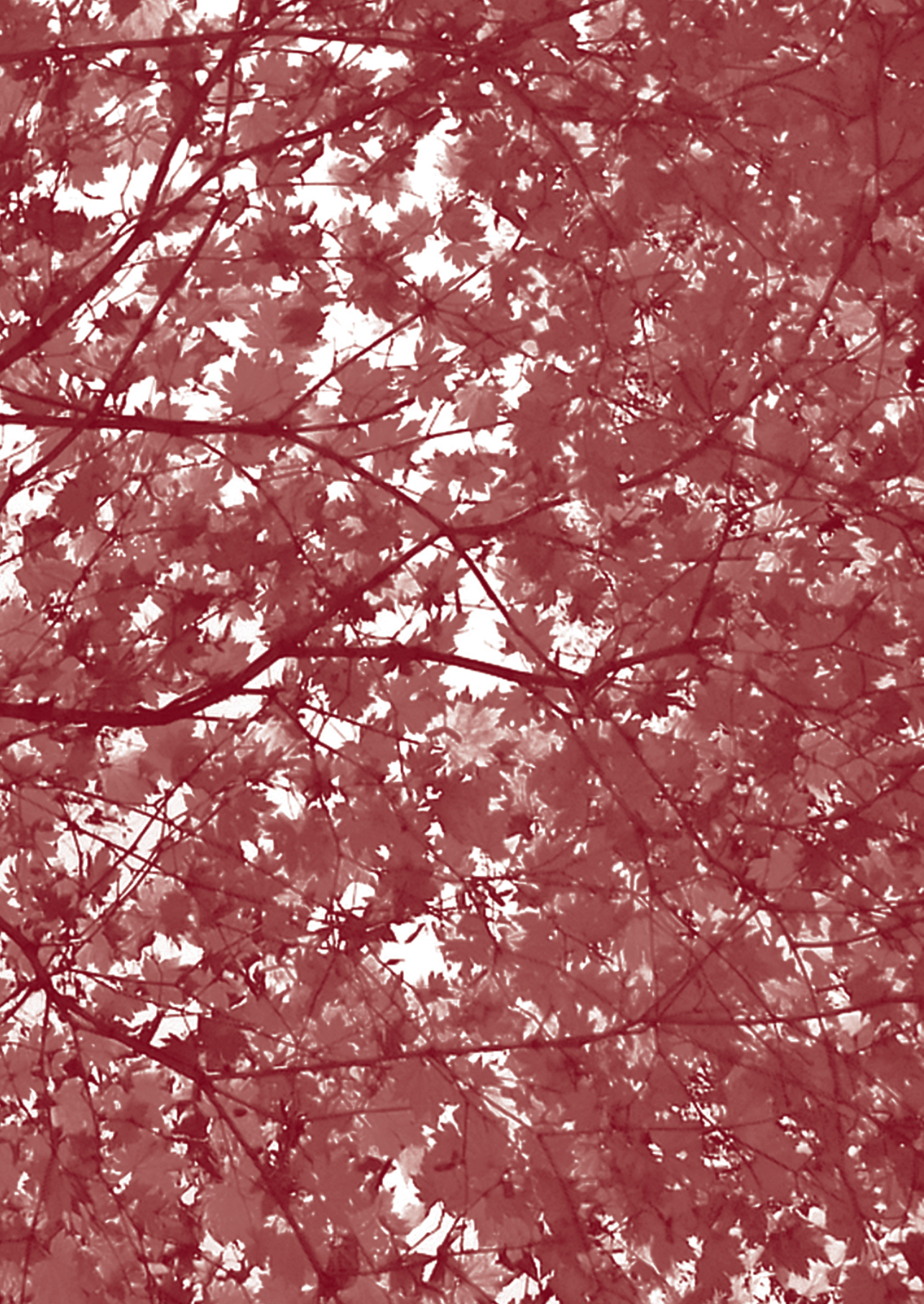
## Part III Progress in burn scar contracture reconstruction by perforator-based interposition flaps

The clinical studies in the last part of this thesis describe the use of local tissue for the treatment of burn scar contractures. In **Chapter 6** an algorithm was described that provides a step-wise approach for the surgical treatment of scar contractures. In short, patients with burn scar contractures underwent a release using a perforator-based

interposition flap. A non-islanded flap was preferred in case of small angles of rotation because an intact flap base provides extra venous outflow and prevents the necessity for additional scar tissue. However, when the perfusion of the flap was at risk because of a too large angle of rotation, the flap was islanded. By assessing the short-term results, it was found that this concept of perforator-based interposition flaps was a safe and versatile technique for treating burn scar contractures. Furthermore, the long-term results showed its effectiveness: the surface area increased after a mean follow-up period of 7.8 months. The effectiveness of perforator-based interposition flaps was further investigated in **Chapter 7** by performing a randomized controlled trial that compared the use of flaps to the conventional treatment of skin grafting. The flaps showed an increase of the original surface area to 123% after 3 months and to 142% after one year, which was in contrast to the substantial decrease in surface area of FTSGs after 3 months and after one year. With regard to the safety of the perforator-based interposition flaps we found a lower percentage of necrosis compared to FTSGs (6% versus 17%). With these clinical studies we provided convincing evidence that interposition flaps lead to better long-term results compared to the current standard of skin grafting. Therefore, we strongly recommend using flaps instead of FTGSGs whenever possible in the treatment of burn scar contractures.

For an optimal use of perforator-based interposition flaps, it is essential to locate the origin of perforators precisely. For this purpose the hand held Doppler is often used in clinical practice. In **Chapter 8** the clinimetric properties of Doppler for the detection of perforator locations were studied. To assess reliability, perforator locations were mapped independently by two clinicians using Doppler in healthy volunteers. Subsequently, the perforators within the area were mapped with Duplex to establish the validity by means of the positive predictive value. We discovered however, that the agreement between the observers was poor. In clinical practice this means that when one plastic surgeon locates a certain perforator, another plastic surgeon is not capable of finding the same location. Furthermore, we demonstrated a very low validity of the device. The results in our study showed that Doppler is not suitable as a single diagnostic tool for the detection of perforators.

In **Chapter 9,** the findings described in this thesis are summarized and discussed in the context of the current practice in burn scar contracture treatments. Conclusions are presented and suggestions for further research are proposed.



# Appendices

# Verbetering van de behandeling van brandwondenlitteken-contracturen
## Een klinimetrische en klinische evaluatie

Dit proefschrift gaat over de behandeling van littekencontracturen. Contracturen ontstaan doordat littekenweefsel de neiging heeft samen te trekken, waardoor er als het ware een tekort aan huid optreedt. Hierdoor kunnen patiënten moeite krijgen om bepaalde bewegingen te maken, zoals bijvoorbeeld het strekken van een arm. *Figuur 1* in de inleiding van dit proefschrift laat twee voorbeelden zien van littekencontracturen.

Littekencontracturen komen veelvuldig voor als gevolg van brandwonden, omdat het vaak uitgebreide en diepe littekens betreft. Doordat tegenwoordig de overleving van patiënten met grote brandwonden aanzienlijk verbeterd is, zien we ook in toenemende mate uitgebreide littekens en littekencontracturen. Onderzoek naar verbetering van de behandeling is dus van essentieel belang. Dit proefschrift richt zich op de verbetering van de behandeling van littekencontracturen als gevolg van brandwonden. In de eerste hoofdstukken hebben we een instrument onderzocht voor het meten van de oppervlakte en het volume van littekens. In het tweede deel hebben we de huidige literatuur over de behandeling van littekencontracturen onder de loep genomen en een veel voorkomende behandelingstechniek bestudeerd. In het laatste deel hebben we, in klinische onderzoeken, het gebruik van lokale huid en onderliggend vetweefsel, dat een bloedvat (perforator) bevat, getest. Met dit proefschrift hopen we een bijdrage te leveren aan een betere zorg voor patiënten met littekencontracturen.

## Deel I Klinimetrische studies naar de oppervlakte en volume van littekens

Om de behandeling van littekens en littekencontracturen te verbeteren moeten we beschikken over meetinstrumenten die in staat zijn littekeneigenschappen op een betrouwbare en valide manier te meten. Alleen dan kunnen we ook daadwerkelijk meten of een behandeling leidt tot verbetering. Voor bepaalde litteken eigenschappen, zoals kleur en elasticiteit, zijn dergelijke meetinstrumenten reeds beschikbaar. Voor het meten van de oppervlakte en het volume van littekens echter nog niet. In **Hoofdstuk 2** van dit proefschrift onderzochten we of 3D-stereofotogrammetrie geschikt is voor het meten van de oppervlakte van littekens. De oppervlakte is een belangrijke uitkomstmaat bij de behandeling van littekencontracturen. Zoals gezegd is er vaak een tekort aan huid waardoor het doel van de behandeling is om extra huid toe te voegen. Door het meten van de oppervlakte van deze toegevoegde huid, zijn we in staat de effectiviteit van de behandeling te meten. In **Hoofdstuk 3** onderzochten we dezelfde techniek voor het

meten van het volume van littekens. Het volume is met name van belang bij littekens die gekenmerkt worden door toegenomen dikte (hypertrofie). Uit de onderzoeken gepresenteerd in **Hoofdstuk 2 en 3** bleek 3D-stereofotogrammetrie een geschikt meetinstrument voor het meten van de oppervlakte en het volume van littekens in klinisch onderzoek. Echter, voor het meten van littekens bij individuele patiënten en het monitoren van verandering van de oppervlakte of het volume gedurende de tijd, bleek het instrument niet precies genoeg. De meetfout van een apparaat moet namelijk kleiner zijn dan de klinisch relevante verandering in oppervlakte of volume. In een onderzoekssetting kan een grotere meetfout geaccepteerd worden omdat dan (meestal) groepen patiënten vergeleken worden. De meetfout wordt dan uitgemiddeld (gedeeld door de wortel uit het aantal patiënten/littekens). De meetfout wordt daardoor veel kleiner, waardoor het apparaat wel in staat is om klinisch relevante veranderingen aan te tonen.

## Deel II De behandeling van littekencontracturen: de huidige stand van zaken

Er zijn veel chirurgische behandelmethoden beschikbaar voor het behandelen van littekencontracturen. Om erachter te komen welke behandeling het meest effectief is, verrichtten we een systematisch review (**Hoofdstuk 4**). De systematische zoektocht resulteerde in 1649 artikelen, waarvan slechts 17 artikelen aan de inclusiecriteria, die overigens niet streng waren, voldeden. Deze overgebleven artikelen beschreven de uitkomsten van verschillende technieken (huidtransplantaten, huidlappen en huidvervangers) voor de behandeling van littekencontracturen. De geïncludeerde studies hadden echter ernstige methodologische tekortkomingen waardoor een antwoord op de onderzoeksvraag niet verkregen kon worden. Een analyse van de beperkingen van de geïncludeerde studies leidde tot een aantal aanbevelingen: 1) vergelijking met een andere interventie, 2) gebruik maken van betrouwbare en valide uitkomstmaten/ meetinstrumenten, 3) gebruik maken van een toereikende onderzoekspopulatie en 4) een adequate datapresentatie en statistische analyse. Het is belangrijk dat bij de opzet van toekomstige studies rekening wordt gehouden met deze aanbevelingen, zodat de kwaliteit van de studies naar de effectiviteit van de behandeling van littekencontracturen zal verbeteren.

In **Hoofdstuk 5** onderzochten we de effectiviteit van huidtransplantaten van volledige dikte voor de behandeling van littekencontracturen. Ondanks de ontwikkeling van geavanceerde operatie technieken, worden huidtransplantaten in de huidige behandeling van littekencontracturen nog vaak toegepast. Waarschijnlijk omdat het een redelijk eenvoudige procedure is die in veel doelgebieden van de reconstructieve chirurgie kan worden gebruikt. Bij de behandeling van littekencontracturen is het van essentieel belang

dat de toegevoegde huid niet gaat krimpen. In **Hoofdstuk 5** werd de oppervlakte van transplantaten van volledige huiddikte gemeten direct postoperatief en na een follow-up periode van ten minste 5 maanden. We ontdekten dat de transplantaten significant afnamen in oppervlakte. Bovendien zagen we een significant grotere afname in oppervlakte bij transplantaten afkomstig van de extremiteiten in vergelijking met transplantaten afkomstig van de romp. Ten aanzien van deze resultaten kunnen een aantal aanbevelingen worden gedaan met betrekking tot het gebruik van huidtransplantaten van volledige dikte. Ten eerste is het belangrijk te beseffen dat er een afname in oppervlakte optreedt waardoor er voor een andere behandelingstechniek gekozen kan worden in gevallen waarin dit absoluut ongewenst is, zoals bij de behandeling van littekencontracturen. Als een transplantaat toch de behandeling van keuze is, kan er door het afnemen van een groter transplantaat dan nodig, geanticipeerd worden op de verwachte afname in oppervlakte. Ten slotte is het beter om de romp als donorsite te kiezen dan de extremiteiten.

## Deel III Klinische toepassing van op perforatorgebaseerde interpositieplastieken in de behandeling van brandwondenlitteken-contracturen

De klinische studies in het laatste deel van dit proefschrift beschrijven de toepassing van aangrenzende gezonde huid in de behandeling van contracturen. In **Hoofdstuk 6** wordt een algoritme gepresenteerd dat een stapsgewijze aanpak met behulp van perforatorgebaseerde interpositieplastieken beschrijft. Kort gezegd zijn dit huidlappen met onderliggend vetweefsel die van bloed worden voorzien door een perforator. Het algoritme houdt onder andere in dat de lap gedeeltelijk vast blijft zitten en als het ware naar de plek gedraaid wordt waar extra huid nodig is. Het ontwerp van de lap kan aangepast worden aan het defect en de beschikbare doorbloeding door de lap te ‘eilanden’. De kortetermijn resultaten toonden aan dat het een veelzijdige en bovendien veilige techniek was. De resultaten op de lange termijn lieten zien dat de oppervlakte van de lappen na een gemiddeld follow-up periode van 7,8 maanden toegenomen was. Hiermee toonden we aan dat de perforator interpositieplastiek effectief is in de behandeling van littekencontracturen. Het was echter nog geen bewijs dat de techniek superieur is aan de meest gebruikte techniek: het huidtransplantaat. Daarom werd er een multicenter gerandomiseerde gecontroleerde studie verricht om deze techniek te vergelijken met het huidtransplantaat van volledige dikte. In **Hoofdstuk 7** wordt de studie beschreven waarin patiënten met contracturen als gevolg van brandwonden werden behandeld met een huidtransplantaat of een op een perforatorgebaseerde interpositieplastiek. Na 3 maanden werden significante verschillen aangetroffen tussen beide technieken: de oppervlakte van de interpositieplastieken was toegenomen en de oppervlakte van de huidtransplantaten afgenomen. Dit verschil was na 1 jaar nog groter.

Ondersteund door de resultaten uit **Hoofdstuk 6 en 7** kunnen we concluderen dat de perforator interpositieplastiek in de toekomst veilig en effectief gebruikt kan worden in de behandeling van littekencontracturen en bovendien de voorkeur verdient boven het huidtransplantaat. Dit geldt voor alle gevallen waar beide technieken mogelijk zijn.

Voor het gebruik van op een perforatorgebaseerde interpositieplastieken is het van belang dat de perforatoren nauwkeurig kunnen worden gelokaliseerd. In de kliniek wordt Doppler hiervoor vaak gebruikt, met name omdat het een simpele techniek is die tevens tijdens de operatie gebruikt kan worden. De Doppler techniek maakt gebruik van geluidsgolven die het weefsel in worden gebracht. Bloed dat in beweging is, wordt anders teruggekaatst dan het omliggende weefsel, waardoor het mogelijk is onderscheid te maken. In **Hoofdstuk 8** onderzochten we of Doppler geschikt is voor het aantonen van perforatoren. Ten eerste lokaliseerden twee clinici met behulp van Doppler, onafhankelijk van elkaar, perforatoren in een bepaald gebied. Vervolgens werd er een Duplex verricht om te verifiëren wat de precieze locaties van de perforatoren waren. Duplex is tevens gebaseerd op geluidsgolven maar zet de terugkomende geluidsgolven ook om in beeld. De resultaten van dit onderzoek lieten zien dat de locaties, gevonden door de twee clinici, onvoldoende overeenkwamen. Daarnaast bleek er ook een slechte overeenstemming tussen locaties gevonden met Doppler en de locaties gevonden met Duplex. Daarom is enkel het gebruik van Doppler niet geschikt voor het detecteren van perforator locaties.

In het laatste hoofdstuk (**hoofdstuk 9**) van dit proefschrift worden de bevindingen uit alle hoofdstukken besproken en geplaatst in de context van de huidige behandeling van littekencontracturen. Daarnaast worden er aanbevelingen gedaan voor toekomstig onderzoek. De belangrijkste bevindingen en aanbevelingen zijn reeds hierboven genoemd.

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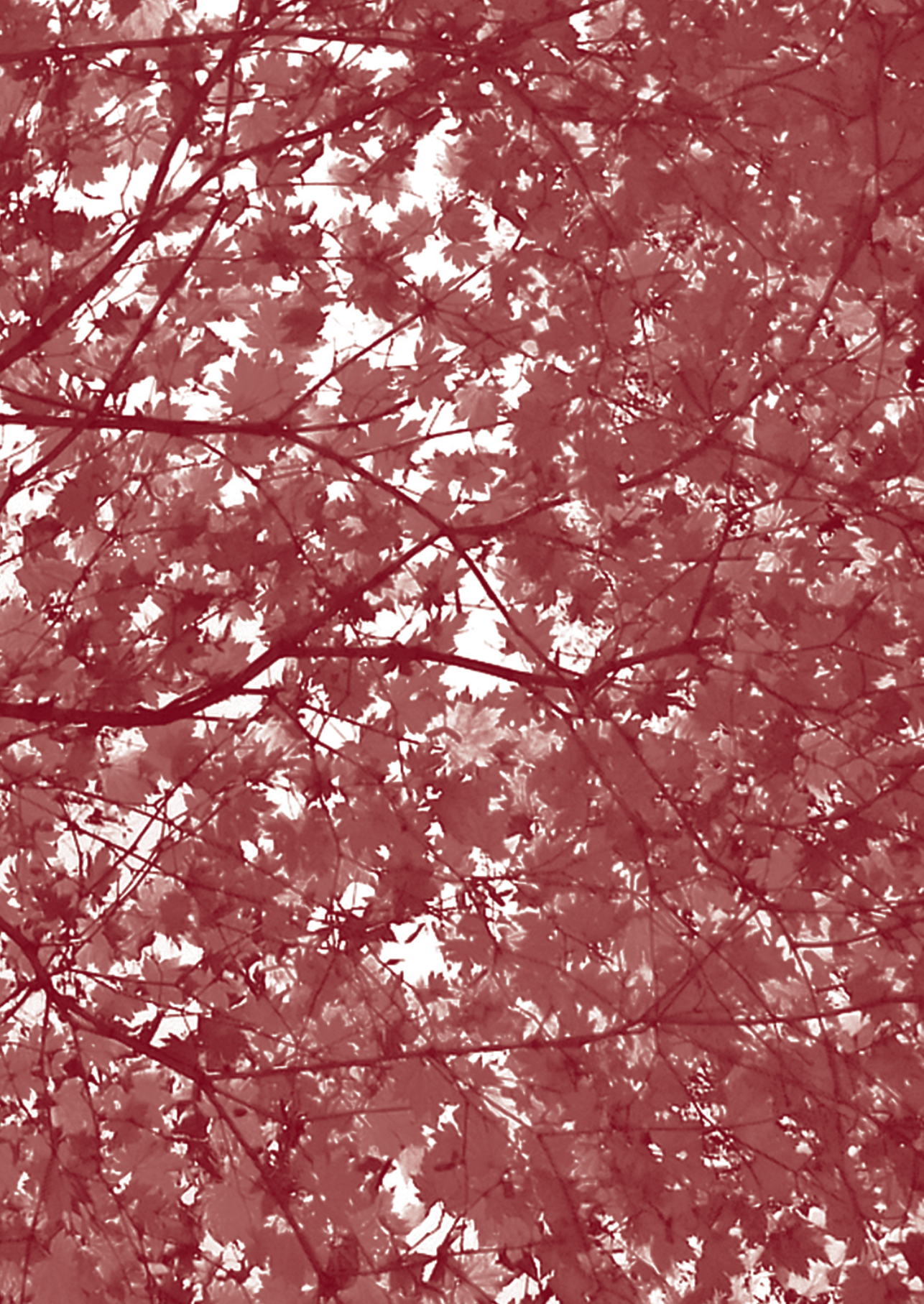

# Appendices

# Dankwoord

In de zomer van 2009 begon ik als co-assistent op de afdeling plastische- en reconstructieve chirurgie in het Rode Kruis Ziekenhuis in Beverwijk, waar ik al snel werd geïntroduceerd op het brandwonden centrum. Hier ging mijn hart sneller kloppen, hier wilde ik verder. Een eerste onderzoek leidde tot een promotietraject en wat ik nooit had durven dromen is gelukt: er is een proefschrift. Het eindresultaat van het werk waar ik met veel energie en passie aan heb gewerkt. Maar dat nooit tot stand was gekomen zonder de hulp van velen.

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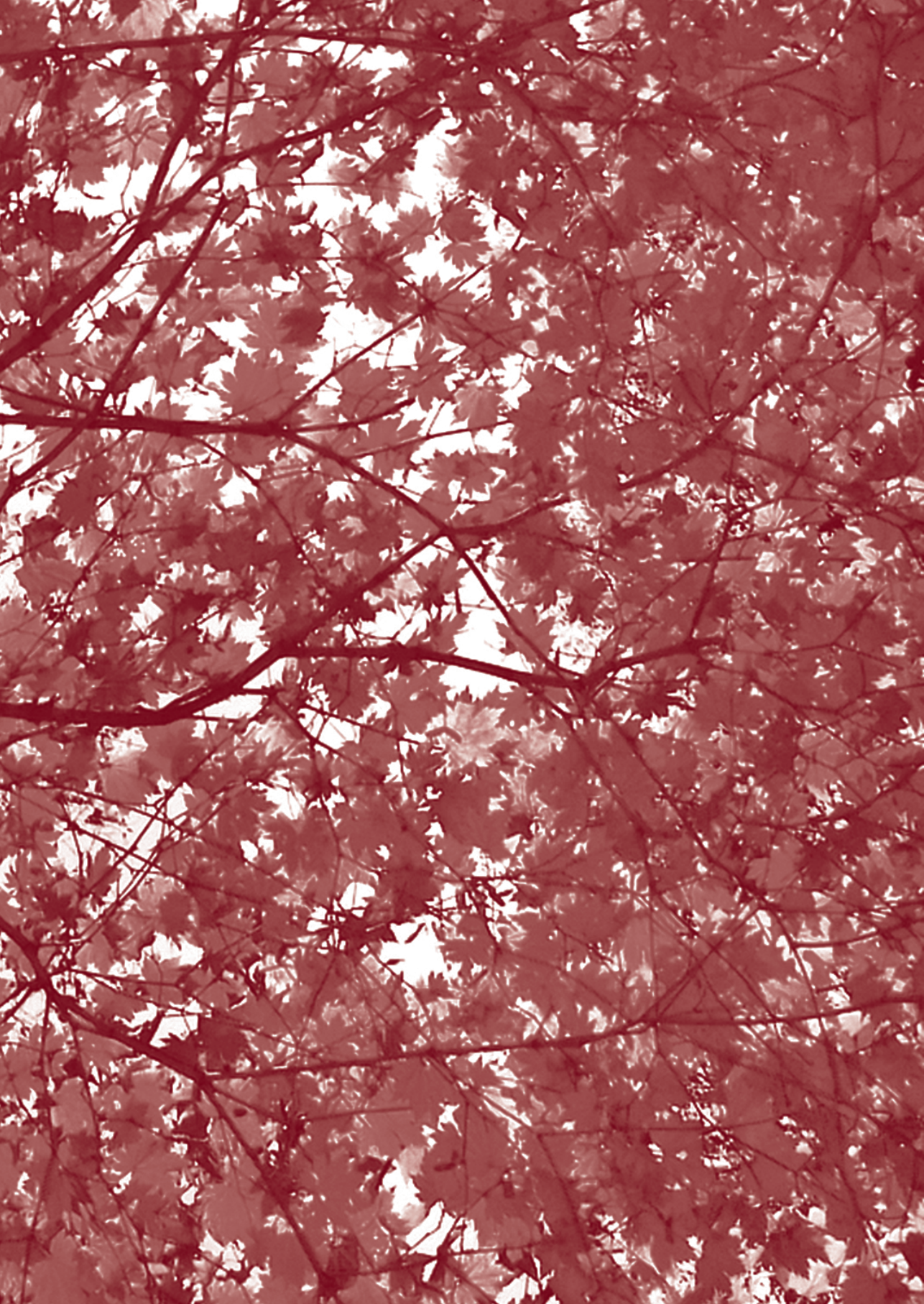


# Appendices

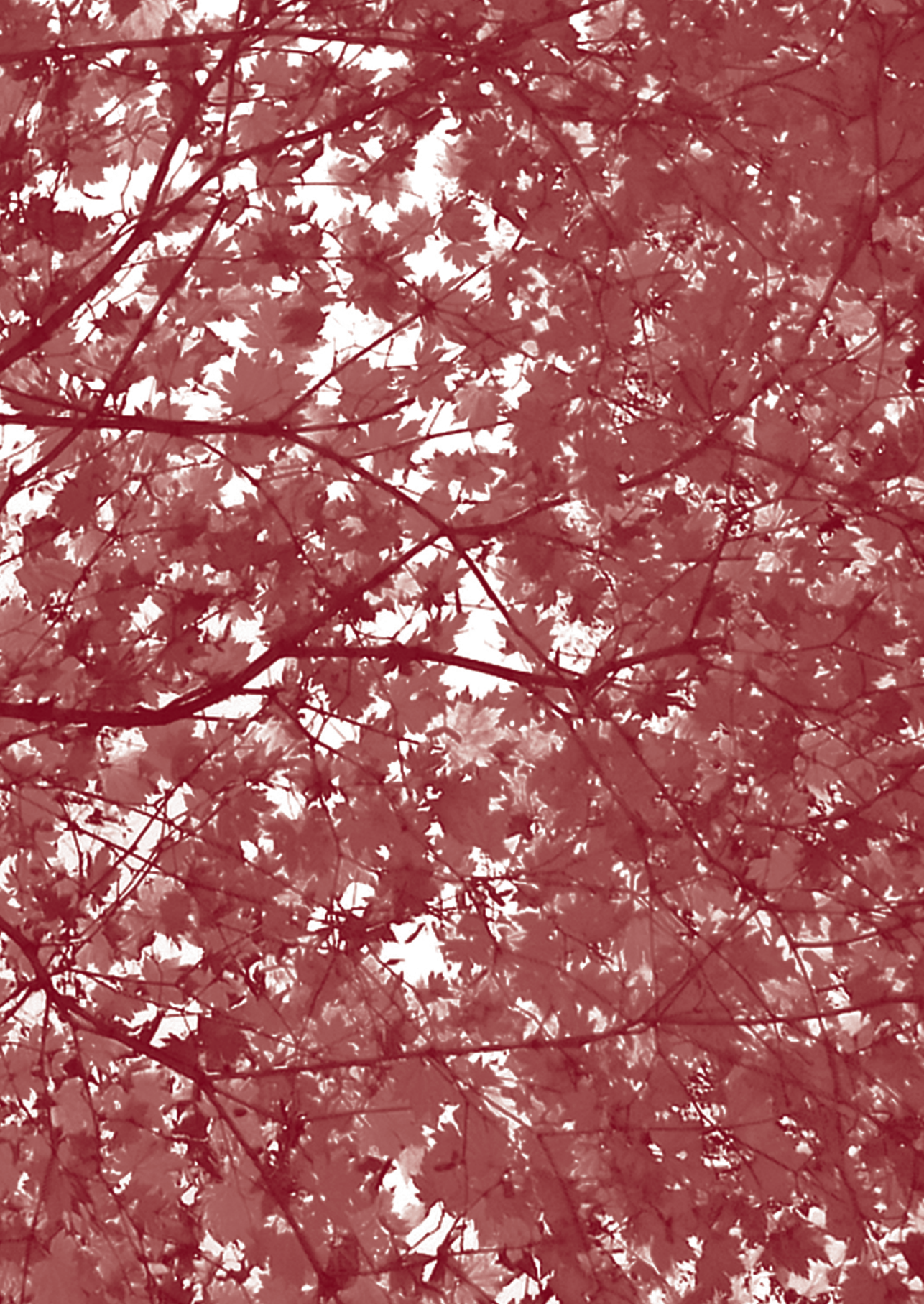
## About the author

Carlijn (Caroline) Monique Stekelenburg was born in Utrecht on October 16th 1984. She graduated from the Gymnasium at the Kees Boeke School in Bilthoven in 2002 after which she left the Netherlands for 6 months to study the Italian language in Perugia, Italy.

In 2003 she started medical school at Maastricht University. During her study she became interested to learn more about Plastic and Reconstructive surgery. This resulted in a scientific internship at the Plastic and Reconstructive department of the Academic Medical Center in Amsterdam (under supervision of dr. S.D. Strackee) and clinical rotations at the Plastic and Reconstructive departments of the Elkerliek Hospital in Helmond (R.N. Fresow) and the Red Cross Hospital in Beverwijk (prof.dr. P.P.M. van Zuijlen). At this point she became involved in the treatment of burn scars and was determined to pursue a scientific career in this field. After receiving her medical degree in 2009, she worked for one year as a surgical resident not in training (ANIOS) at the Jeroen Bosch Hospital in Den Bosch (dr. K. Boscha). In 2010 she returned to the Red Cross Hospital where she was trained as a burn physician for 6 months. After this period she started as a PhD candidate on a project on burn scar contracture reconstruction. Under supervision of prof. dr. P.P.M. van Zuijlen and prof. dr.ir. H.C.W. de Vet, she performed multiple clinimetrical studies and clinical trials that led to the conception of this thesis.

In July 2014 she has started her postgraduate training in Plastic and Reconstructive surgery at the Utrecht University Medical Center under supervision of dr. A.H. Schuurman. As part of this training she is currently working at the surgery department of the Diakonessenhuis in Utrecht (supervisor dr. T. van Dalen).

Carlijn is living in Groenekan, a small village near Utrecht, with Tim Jansen and their two daughters Juline and Clara.



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