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(Bio-)Sensors for skin grafts and skin flaps monitoring

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ABSTRACT

Skin grafting is one of the most frequently performed surgical procedures in dermatology. Nevertheless, the failure rate is still quite high, which can cause a huge burden for patients and the health care system. Early interventions, like salvage surgery, can rescue the grafts that are going to fail. Therefore, real-time and objective monitoring of skin grafts and flaps is crucial to guide clinicians for an evidence-based treatment. This can be achieved by modern sensor applications using advanced techniques in nanotechnology and material science. This review provides an overview on current challenges for the further development of (bio-)sensors for monitoring the uptake of implanted skin grafts and skin flaps. Special interest has been given to invasive/non-invasive as well as wearable/implantable applications. In addition, the adaptation of recent developments in alternative sensing systems with physical, optical and electrochemical transducers for the continuous monitoring (intra- and post-operative) of skin transplants has been discussed.

1. Introduction

As the largest organ in the body, the skin provides a protective barrier against harmful substances such as pathogens, microorganisms and ultraviolet radiation [1]. In addition to these primary roles, other important functions of the skin include regulation of the body temperature, production of vitamin D, and controlling of moisture loss [1,2]. Skin integrity plays a crucial role in maintaining the physiological homeostasis of the body [3]. Large skin wounds caused by skin cancer, severe burns, trauma, or non-healing chronic wounds are common and can lead to severe clinical problems [1,4]. Skin grafting is one of the most common surgical procedures in dermatology, which is often used to cover large wounds, especially in the area of non-healing wounds [5].

Despite advanced surgical techniques, failure in skin grafting implies a huge burden for patients and the health care system. Depending on several factors such as preoperative patient risks, bacterial load of the wound bed, and the location of the recipient area, the failure rate (complete loss of the skin transplant) varies from 0.5% to 5.5% [6–11], and in extreme cases, it can reach up to around 24% [12–14]. A collection of failure rates for different skin grafting surgeries is overviewed in Table 1. The vast majority of these studies showed that early interventions, like salvage surgery or medications, can rescue the grafts that are going to fail. However, the rate of success inversely correlates with the time of re-intervention after the first signs of failure are observed [8]. Therefore, it is crucial to be vigilant in continuously monitoring the uptake of skin grafts and/or flaps.

Biosensor-based diagnostic devices play an important role in timely monitoring of biomarkers and guiding clinicians accordingly for an evidence-based treatment [15]. In parallel, biosensors have rapidly expanded and evolved in many new fields, also triggered due to the Corona virus disease 2019 (COVID-19), thanks to the advances in nanotechnology, material science, and microfluidics [16–20]. Over the past five years, several reviews have highlighted the attractive capabilities of modern wearable and implantable sensors for temperature, impedance and pH monitoring for health care applications [21–27], and especially for wound monitoring [28–32]. At the same time, there is only little information on (bio-)sensing techniques for monitoring the status of transplanted skin. Monitoring of transplanted skin (e.g., skin grafts and flaps) differs from wound monitoring with some characteristics; skin grafting as a closure technique (closed wound bed by skin grafts or flaps) limits (bio-)sensors to directly access the wound fluids in the wound bed; the transplanted skin is vulnerable to mechanical stress as well as

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Table 1
Failure rates after different skin transplant procedures.

Transplant type	Total number of transplants	Failure rate	Reference
Free flap	1195	0.5% (complete failure)	[6]
Free flap	1193	1.2% (complete failure)	[7]
Free flap	1142	1.6% (complete failure)	[8]
Full-thickness skin graft	80	2.5% (complete failure)	[9]
Free flap	149	4% (complete failure)	[10]
Free flap	691	5.5% (complete failure)	[11]
Split-thickness skin graft	72	20.8% (on 14th postoperative day)	[12]
Split- and full-thickness skin grafts	132	23.7% (on 5th postoperative day)	[13]
Free flap	21	23.8% (complete failure)	[14]

usually covered by dressings; depending on the transplanted tissue, the sensors need specific adaptations, for instance, requirement of non-invasive measurements from deep tissue (e.g., microvascular blood flow sensing) or real-time, intraoperative monitoring of particular grafting-related biomarkers.

In this review, we provide an overview on current challenges and requirements for implementing (bio-)sensors in monitoring the status of implanted skin grafts and skin flaps for different applications (e.g., invasive/non-invasive or wearable/implantable). We discuss how recent developments in alternative sensing systems (including physical, optical and electrochemical transducers) can be adapted in their design for continuous monitoring (intra- and post-operative) of skin transplants.

2. Skin transplantation

The rationale of skin grafting is to transfer a section of skin from one portion of the body (donor site) to an area to be repaired (recipient area) such as a large wound. However, various factors that influence the success of the procedure must be taken into account: the size and location of the wound, skin quality, skin thickness, possibility of contractility, convenience, the source of the damage, possible scar formation as well as the limitation regarding the fact that donor sites can only be harvested once. After incorporation and healing, the provided skin is carried out its usual role, like normal skin. Taking into account the anatomical structure, skin grafts are divided into several categories based on their composition. As the most commonly used graft in dermatology, the full-thickness skin grafts are composed of both the full epidermis and dermis, while split-thickness skin grafts contain the epidermis and a variable amount of the dermis (usually only the superficial part of the dermis) [33,34]. In contrast to skin grafts that are completely removed from their blood supply at the donor site, skin flaps —as another type of wound closure— remain attached to a blood supply via a pedicle. Fig. 1 schematically depicts the skin layers and possible application types of skin grafting [35].

Based on their origin the grafts can be further divided into three categories: autografts (donor and recipient of the same subject), allografts (donor and recipient of different subjects of the same species, usually taken from cadavers), and xenografts (donor and recipient subjects of different species, usually harvested from porcine skin). For the treatment of chronic wounds, the use of autografts is the most common approach. However, for skin injuries involving an extended surface area or insufficient amount of donor sites, the use of autologous skin grafts is limited. In this case, either allografts or xenografts are used for transplantation. Nevertheless, clinical applications of allografts/xenografts are less common, due to the higher rejection risk. Another strategy to meet the urgent requirement of large skin grafting is to implement bio-engineered artificial skin substitutes acting as bio-active wound closures. Although numerous skin substitutes and approaches have been demonstrated, an ideal bio-engineered skin substitute has not been achieved yet [36,37]. Hence, the use of split-thickness skin autografts or skin flap transplantation is considered as current "gold standard" as these methods provide the most effective, safest, and economically viable outcome for wound closure and healing [4].

3. Current challenges

While technology and modern micro-surgical closure techniques have improved distinctly, graft failures still occur. As discussed in section "Introduction", worst-case scenarios show failure rates close to ¼ of all skin-grafting procedures. The main reason for flap failure is hemodynamically compromised circulation in the blood vessels (arterial occlusion named ischemia or venous occlusion named congestion) due to thrombosis [38–40]. Surgical-site infections after surgical procedures are another important contributor to graft loss. While the risk of surgical-site infections in dermatological surgery is usually considered to be varied from 5 to 10% [41,42], the risk can be as high as 28.5% depending on the anatomical location and the type of surgery performed [43]. In a study [13], graft loss secondary to infection was found to be 23.5%. The failure in skin graft or skin flap is a devastating complication and a huge burden for both patients and health care systems, which usually happens within **the first 72-hour window** [7].

Therefore, early interventions are crucial to increase the rescue rate of the transplanted cutaneous tissue. It is necessary to be cautious in monitoring (preferentially real-time monitoring) the uptake of grafts and flaps as the time loss between the occurrence of the event and clinical assessment of the recipient area could reduce the survival rate of

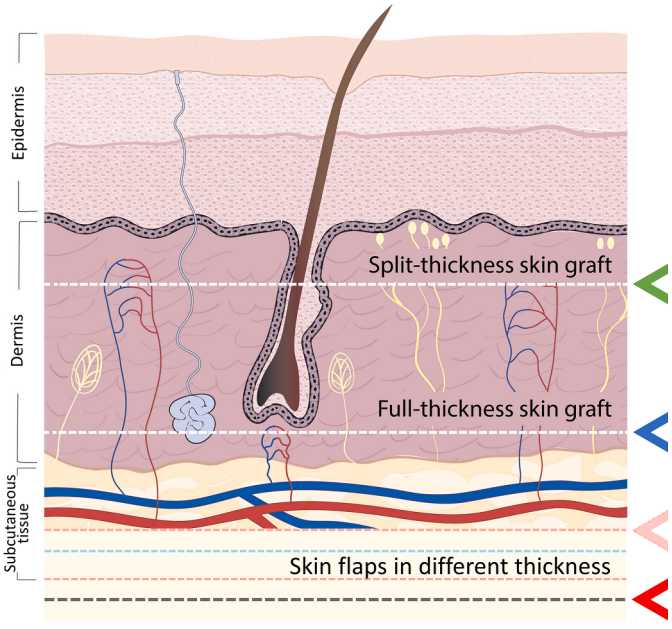

Fig. 1. Graphical representation of skin traditionally classified into three layers: epidermis, dermis, and subcutaneous tissue. Based on these layers, the skin to be transplanted can usually be divided into a split-thickness skin graft, full-thickness skin graft, and skin flaps. The segmental divisions in the figure were shown indiscriminately as the thickness of the sections can vary according to different grafting applications and the location of the recipient area. (Adapted from [35], with permission from Tidsskriftet, Copyright 2022).

the tissue [44,45]. However, it is almost impossible to inspect healing or possible deterioration such as pathogenic infections in detail by todays standard clinical methods, because the implanted tissue can be damaged, due to the examination itself. Typically, as a general practice of grafting, after preparation of the wound bed and homeostasis is achieved, usually, only graft edges are sutured on this place. Thereafter, a tie-over dressing, which is not transparent and covers the whole surgical area, is implemented to secure the entire graft in place. Fig. 2 shows representative photos of the workflow of skin grafting and related tie-over dressing.

Unlike the other wound management practices, the dressing is usually not removed for at least 5 to 7 days after grafting, to avoid any desiccation and negative effects [41,46,47]. It was reported that 23.7% of skin grafts were lost within this dressing period due to infection, which otherwise might be treated after the early diagnosis of the causative microorganisms [13]. More importantly, the first 72-hour window requires regular manual check-ups of the transplanted material such as

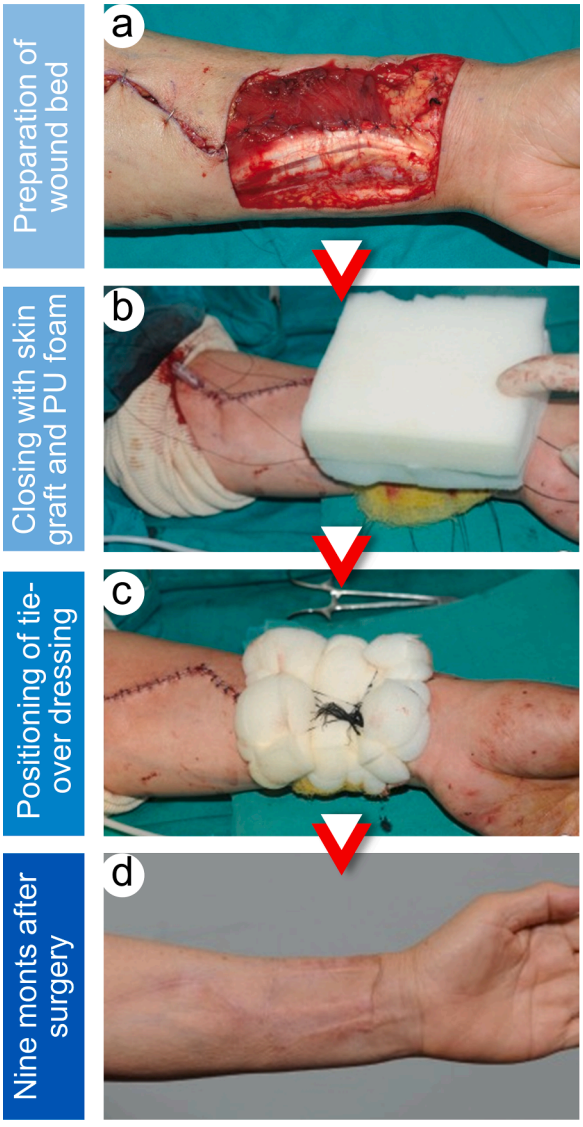

Fig. 2. Representative images for the short workflow of skin grafting and related tie-over dressing. a) Preparation of the wound bed in the forearm. b) Closing the wound bed with a split-thickness skin graft and applying a polyurethane (PU) foam (Reston, 3 M, USA) as bolster material. c) Positioning the tie-over dressing after squeezing the foam to compress the graft. d) Postoperative photography nine months after surgery. (Adapted from [45], with permission from Thieme, Copyright 2015).

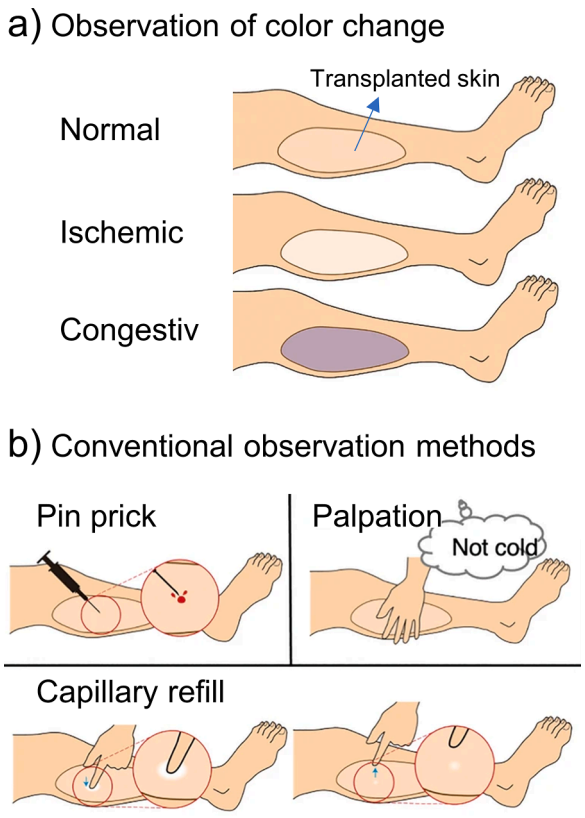

Fig. 3. Traditional routine examinations of the transplanted skin after grafting. a) Color change observation for simple prediction of the health status of transplanted skin (e.g., skin flaps underwent ischemia or congestion). b) Other physical observation methods: pin prick method (tissue is pricked by a needle, and observation of the color of blood and the speed of bleeding), palpation (observation of temperature), capillary refill (estimation of blood flow of the tissue by compressing on it until the tissue turns white, then, observing the time taken for the color to return). (Adapted from [40], with permission from Springer Nature, Copyright 2022).

color observation, pin prick tests, palpation, and inspection of capillary refill (Fig. 3), which is based on a rather subjective perception of the clinical staff involved [38–40,42,44]. Detailed discussions of the conventional observation methods can be found in Section 6.

Only a few diagnostic parameters have yet been revealed about the assessment of the course of implanted skin grafts [41,47]: objective profiling of these diagnostic parameters is mainly limited to downstream laboratory testing, such as ELISA (enzyme-linked immunosorbent assay) as well as long-lasting bacterial culturing in case of an infection.

4. An ideal monitoring system for the most effective surveillance

To address the above-mentioned challenges, researchers have been working on developing (handheld) point-of-care (POC) devices to guide clinicians for timely and evidence-based treatment. In general, as expected from all diagnostic devices, such as miniaturized sensors, the ideal monitoring device should meet the following requirements (ASSURED criteria): Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free, and Deliverable to the end-user. However, when it comes to sensors for monitoring implanted tissue (e.g., skin flap) a multi-parameter sensing strategy is highly advantageous involving multiple diagnostic markers (e.g., temperature, oxygen saturation, bacteria, and blood flow) detected at the same time [40]. In addition, to monitor further (bio-)markers in-situ might be helpful, with regard to checking the viability and possible inflammation reactions. These further (bio-)markers to check viability and inflammation reactions, like

pH value, matrix metalloproteinases, and interleukin-1 beta, are discussed in detail in Section 6.1.

Such sensor systems should also provide some specific features, such as being non- or minimally invasive, wearable (but soft, comfortable, ideally cableless, and easy-to-integrate), as the implanted tissue and its wound bed are enough vulnerable to external influences. As the wound area can be considered as "closed box" after grafting/dressing, implantable sensors would provide an early warning tool for failure. This could also help to eliminate the need for higher levels of immunosuppression or antibiotics, in particular. More importantly, even if a grafting failure occurs during surgery, its signs might only become clinically apparent several hours later in the early postoperative period [48]. Therefore, an ideal sensing system should also be able to perform "intraoperative" readings and to predict the future outcome based on this intraoperative data [49,50].

One additional aspect to achieve the most ideal monitoring system for the most effective surveillance is being able to fulfill the requirements for accurate and real-time data transmission. The sensor system designed for skin grafting should facilitate the transmission of data wirelessly and in real-time to the clinician's device or a monitoring system to enable prompt decision-making and intervention. The reliability and accuracy of the data transmission should also be ensured to prevent false alarms or missed complications.

5. Invasive or non-invasive?, wearable or implantable?

Currently, the majority of developed sensors for implanted skin monitoring consists of optical sensors, usually targeting non-invasive monitoring of the target tissue. For instance, non-invasive near-infrared (NIR) spectroscopy-based systems, such as the ViOptix tissue oximeter, enable to detect vascular compromise [51,52]. In addition, fluorophore (e.g., methylene blue or indocyanine green)-based optic systems in combination with NIR spectroscopy as fluorescence angiography have been studied [49,50,53]. Other non-invasive monitoring approaches include camera-based imaging devices, where, for example, Li et al. explored rapid-drying liquid bandages monitored with a camera set-up, while Marks et al. demonstrated the use of a paintable phosphorescent bandage and the use of a digital single-lens reflex (DSLR) camera for postoperative tissue oxygen assessment [38,54].

Although non-invasive monitoring of both microsurgical skin flaps and skin grafts is always a profound demand, existing sensing approaches cannot always provide an ideal probing ability. For example, the use of non-invasive NIR spectroscopy systems for monitoring the graft oxygenation level is limited, especially in deep tissues, due to the penetration depth of near-infrared light [55]. In addition, when it comes to the postoperative stage, where the implanted tissue is tightly covered by bandages and dressing materials, monitoring with NIR- or camera-based systems cannot be performed continuously. From this perspective, wearable sensors play an important role for the continuous monitoring of transplanted skin, as they can be attached directly to the tissue. In this case, the monitoring device that is attached to the target tissue should operate with customized (e.g., soft and elastic) power/data transmission cables from the sensor to a base station (if the base station is located in another place on the body) not to cause any discomfort and mechanical stress on the tissue [39,40]. Ideally, the device should be coupled with all necessary instruments, such as power delivery and management, data acquisition and wireless transmission modules, as an "all-in-one" concept without the need for an external cable connection [56].

On the other hand, wearable devices as skin-mounted systems still lack from deep tissue recordings, due to the limited penetration depth. Until now, as an advanced application, only a few studies have demonstrated the use of implantable sensors for real-time monitoring of microvascular blood flow [57] or oxygen saturation in flaps [58]. For a detailed discussion of microvascular blood flow and oxygen saturation monitoring in flaps, see Section 6.3 and Section 6.2, respectively. Moreover, a millimeter-scale ultrasonic implant has been proposed for monitoring deep-tissue oxygenation [55]. This sensor had several advantages: there is no need for tethering it to an external hardware with electrical wires that restricts the movement of the patient as well as creating the potential for mechanical damage and the risk of additional complications. While taking place in clinical situations, the task of monitoring tissues with implantable sensors shares many challenges with in-vivo applications, such as biocompatibility, corrosion resistance against body fluids, and biofouling. Ideally, after some desired operational period, the implanted sensor should degrade and ultimately disappear from the physiological environments of the body, in other words, being bioresorbable. Current techniques, however, rely on a biodegradable/bioresorbable encapsulation of the sensing components, a minimally invasive implantation, and removing the internal sensing elements after resorption of the encapsulation layer [58].

To our knowledge, there is no report demonstrating the use of implantable (bio-)sensors for skin graft monitoring, where the sensor can be implanted between the wound bed and the graft. One reason is that the implanted sensor could obstruct the diffusion of nutrients from the wound bed to the graft. As skin grafts do not have their own blood supply and only rely on a well-vascularized wound bed for growth and neovascularization [59], such obstructs could decrease the graft survival rate. Recently, Saleh et al. have demonstrated the continuous secretion of wound fluids from full-thickness skin grafts to tie-over dressings [41]. Similarly, Daulton et al. reported the secretion of biomarkers to dressings [60]. By extracting the wound fluid from the dressing, they showed the possibility of analyzing specific (bio-)markers, such as matrix metalloproteinases (MMPs), interleukin-1 beta (IL-1β) and volatile organic compounds (VOCs). In future, a wearable, wireless, multi-sensor device, which can be designed to monitor, for instance, infection and early rejection markers (such as MMP-3), might directly be integrated into those disposable dressings (e.g., tie-over bolster). In addition, the integration of such sensors into smart skin graft/wound dressings in combination with potential future developments in this field, such as artificial intelligence for data analysis, would be an ideal route.

6. (Bio-)sensors for skin transplants

6.1. Electrochemical (bio-)sensors

As powerful analytical devices, electrochemical biosensors can detect biochemical events such as concentration changes of pH, ions, metabolites (e.g., induced by enzymatic catalysis), antibody-antigen reactions, DNA (deoxyribonucleic acid) hybridization events, or even cellular metabolisms [61–64]. Furthermore, they transduce this information to electrically readable signals. At the same time, studies involving electrochemical (bio-)sensors for transplanted skin monitoring are scarce. Based on the target molecule of interest and transducer, various measurement principles are discussed, such as potentiometry, conductometry, impedimetry, amperometry and field-effect sensors with analysis in biomedical applications, like blood, plasma, sweat, saliva, interstitial fluids, etc. The possibility of real-time and rapid monitoring of target molecules with high sensitivity and selectivity makes electrochemical biosensors highly desirable [15,65].

As a first attempt, a conventional glass pH electrode has been used for continuous monitoring of the subcutaneous tissue pH. In this study, a pH change to acidic direction has been found as an indicator to evaluate occlusion in the blood flow of skin flaps, which could cause anaerobic glycolysis, leading to lactic acidosis, due to tissue hypoxia [66]. In a recent study, Lee et al. demonstrated the use of a conformable microneedle-based pH sensor integrated with two different siloxane polymers for pH mapping of skin tissue [67]. The authors perform measurements on the skin of a peripheral vascular disease rat model by compromised blood flow and hypoxic insult; the reported pH sensor could also be used for monitoring skin grafts (Fig. 4) and skin flaps, in particular, because both scenarios share the same path, increased

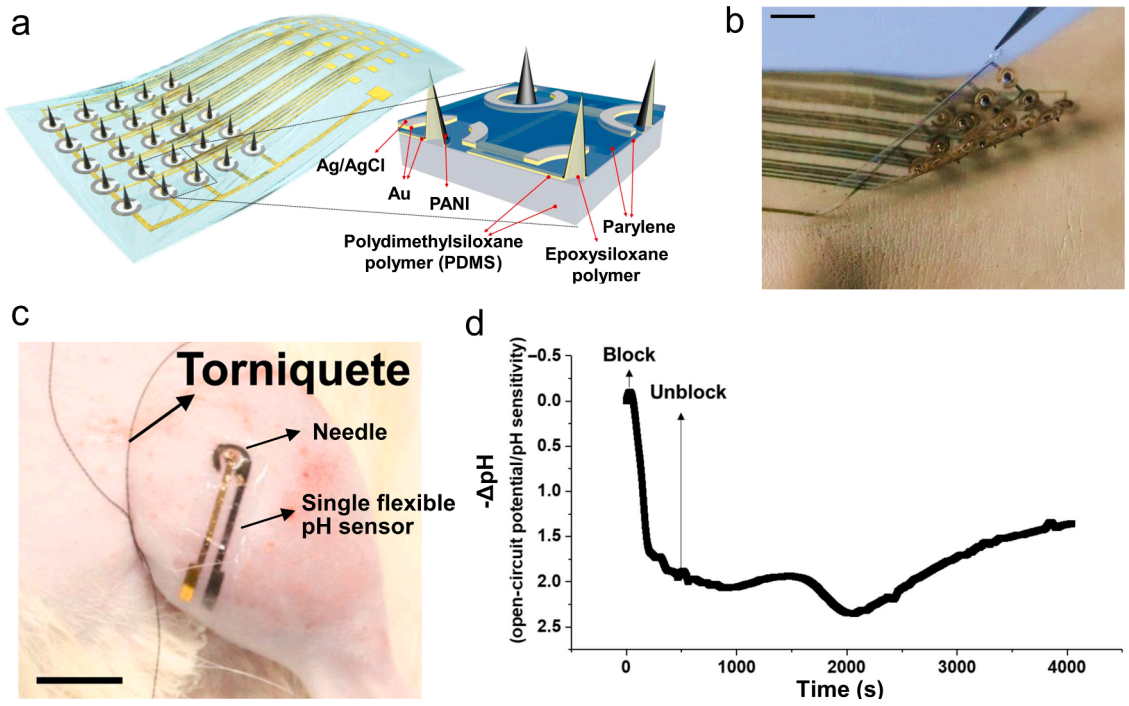

Fig. 4. Microneedle-based sensor for dermal pH monitoring in a rat model with compromised blood flow and hypoxic insult. a) Schematics of flexible pH sensor array with microneedles and its cross-sectional representation. b) The sensor array with microneedles on the skin (scale bar, 5 mm). c) Single sensor inserted on the leg of the rat and application of vascular blockage with a tourniquet (scale bar, 10 mm). d) Recorded pH change corresponding to compromised blood flow. (Adapted from [67], with permission from American Association for the Advancement of Science, Copyright 2021).

acidosis ($\Delta pH = -2$) indicating the damage in the ischemic tissue.

Furthermore, monitoring the pH of the wound bed before grafting plays also an important role in predicting of the grafting success. It was demonstrated that a wound bed with a pH value below 7.3 has associated with unsuccessful skin grafting (low take-rate) [68]. pH sensing addressing wound monitoring, in general, can also be employed to evaluate the wound pH for skin grafting: for example, a microfluidic-based multiplexed multi-parameter sensor platform has been suggested in [69].

The sensor was also designed to measure multiple biophysiochemical parameters of wound fluid based on one Au counter electrode at the periphery and petal-shaped working electrodes sharing one Ag/AgCl reference electrode at the center. For pH sensor fabrication, a PANI (polyaniline) layer was formed on the electrode surface by electropolymerization of the solution of 0.1 M aniline/0.1 M HCl using cyclic voltammetry (CV). For bacteria sensing, a thin layer of an

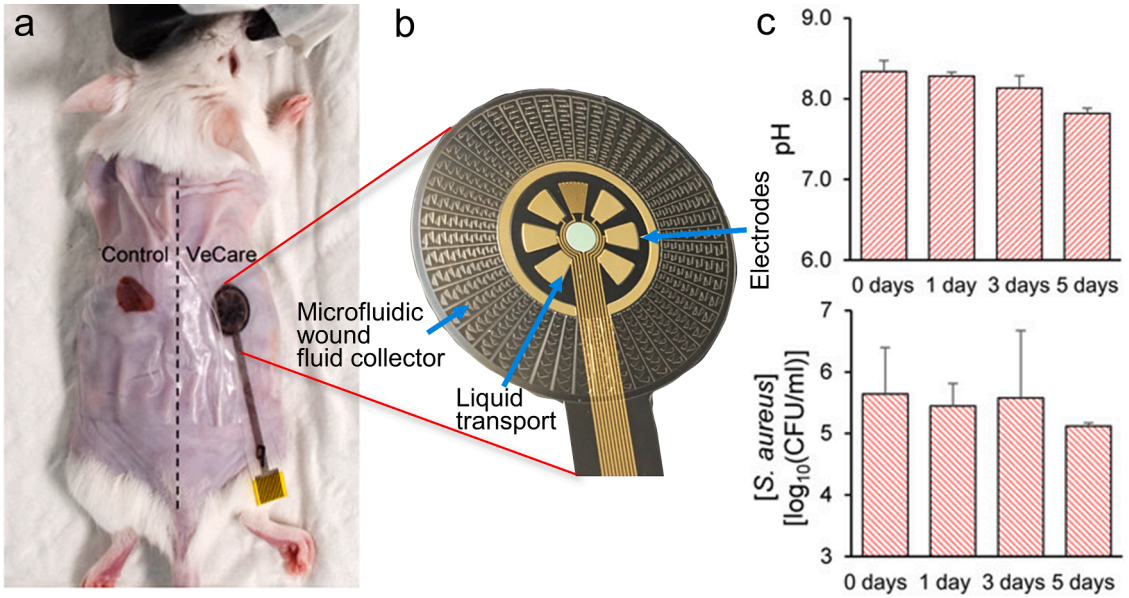

Fig. 5. Wound monitoring in an animal model. a) Photography of a mouse with two bilateral full-thickness excisional wounds and the sensor platform in direct contact with the right wound. b) A closer look at the sensor platform showing electrodes for multiplexed sensing and a microfluidic-based wound fluid collector. c) In-situ monitoring of pH and *Staphylococcus aureus* by the sensor platform. (Adapted from [69], with permission from American Association for the Advancement of Science, Copyright 2021).

electrochemically exfoliated graphene–gold nanoparticle (AuNPs-GP) nanocomposite was coated on the electrodes and aptamer sequences modified with methylene blue were further covalently bound to AuNPs. This sensor provides a simultaneous quantitative assessment of wound pH together with the detection of bacteria (*S. aureus*) thanks to its aptamer-based detection principle (Fig. 5).

Guinovart et al. developed a potentiometric pH sensor integrated into a wound bandage [70]. The authors implemented a screen-printing fabrication method to structure silver/silver chloride electrodes on the bandage. Further modification of the electrodes was carried out using polyvinyl butyral polymer (PVB) as a reference electrode material and electropolymerized PANI for a pH-sensitive working electrode. The performance characteristics of the sensor were evaluated by using buffer solutions emulating the composition of a wound. This solid-state, wearable potentiometric sensor showed attractive analytical features in terms of sensitivity, linearity, selectivity, and stability. Similar work has been reported by Rahimi et al., in which they developed a pH sensor array (3 × 3) on paper integrated into a wound dressing [71]. Further research is needed to show the full potential of these wearable sensors, especially by addressing challenges, like biocompatibility, a higher degree of uncertainty in intercept, long-term stability, and drift behavior. Moreover, the incorporation of wireless communication and multiplexed sensing features (e.g., detection of other analytes such as ammonium and sodium) would be an ideal route to achieve smart sensor-assisted dressing materials for skin grafting.

Huang et al. reported on a bioelectrical impedance measurement system, which can record impedance changes by applying different frequencies after a vascular compromise in the flap between two stainless-steel electrodes [72]. The vascular compromise has been created in rats by transecting the femoral vessels in the groin. A significant increase in the impedance signal could be observed (three hours after the vascular compromise). Furthermore, Natta et al. reported a soft, thin, and flexible patch for vascular graft monitoring [73]. This sensor patch relies on a piezoelectric aluminum nitride thin film on a polyimide substrate, which can be wrapped around the external surface of a prosthetic vascular graft. It was demonstrated that the sensor can record real-time variations in the hemodynamics parameters (such as pulse wave signal and pressure) by measuring the motion of the graft wall due to the blood pulse wave in the vessel. This sensing method could also be adapted for real-time monitoring of pathological variations such as vascular compromise in transplanted flaps.

As discussed in detail in the next subsection (optical sensors), real-time monitoring of graft oxygenation is essential. However, to our best knowledge, an electrochemical oxygen sensor for this purpose has not yet been reported so far. Marland et al. developed an implantable, miniaturized oxygen sensor for real-time measurement of tissue (tumor in this case); the sensor consists of a three-electrode setup (Pt working electrode, Ag/AgCl reference electrode, Pt counter electrode) [74]. After being implanted in a lung tumor (naturally occurring pre-clinical ovine pulmonary adenocarcinoma) in a sheep, the sensor gave a linear response to oxygen; however, it showed some susceptibility to biofouling. Such sensors might find applications for oxygenation monitoring for cutaneous tissue after further miniaturization as well as coupling with a bioresorbable coating being “easy-to-remove”. In another study [75], a functionalized hydrogel (based on poly(acrylamide) (PAAm)) film-based wearable electrochemical sensor has been developed for monitoring of transcutaneous oxygen pressure ($tcPO_2$), which indicates the graft vascularization status (Fig. 6). The sensor system was also combined with a temperature sensor, a tissue impedance sensor, and a heating element. This element was used for extracting oxygen molecules from blood vessels under the skin to the platinum electrode, where they will be reduced. The temperature sensor avoided overheating. In future, such sensing setups might also play an important role in the monitoring of implanted skin tissues.

Recently, different biomarkers indicating the rejection or inflammation of transplanted skin tissue have been discussed in literature. For example, Saleh et al. found that concentrations of matrix metalloproteinases (especially MMP-2 and MMP-9) and interleukin-1 beta (IL-1β) correlate with the wound status of transplanted full-thickness skin grafts, where the authors have analyzed the wound fluids extracted from

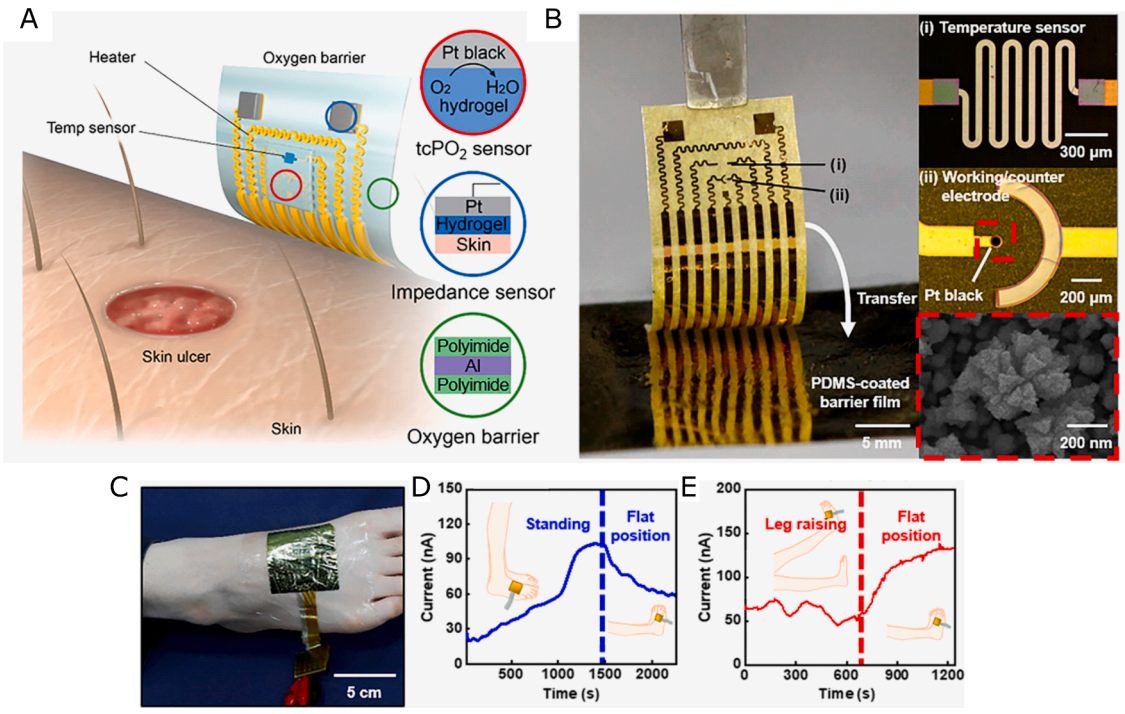

Fig. 6. Schematic illustration (a) and corresponding photograph (b) of the wearable $tcPO_2$ and impedance sensor. The device consists of a temperature sensor, poly (dimethylsiloxane) hydrogel for an enhanced oxygen transport and a platinum electrode for impedance measurements. c) Image of the sensor device fixed onto a right foot and d), e) in-vivo $tcPO_2$ measurements for various leg positions: standing subject or leg in a flat position; leg raised or leg in a flat position. (Adapted from [75], with permission from American Association for the Advancement of Science, Copyright 2021).

tie-over dressings which were kept on the transplanted grafts for a week [41]. For analyzing the possible markers, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), an azocasein assay, and commercial bioassay-type ELISA kits (i.e., not biosensors) have been used. Moreover, Kollar et al. reported that the increased level of MMP3 correlates with a severe rejection in face transplantation [76]. For the monitoring of these biomarkers from venous blood samples of the transplant receivers before and after transplantation, the authors implemented an aptamer-based proteomics platform (SOMAscan) as well as an ELISA bioassay platform. Interestingly, the biomarker concentration is directly related to the presence of microorganisms in the wound area (e.g., the contribution of possible microorganisms, even microbiota).

The advances reported in these studies demonstrate the potential of biomarkers (e.g., MMPs, IL-1β, bacteria) for monitoring transplanted skin tissue, however, their detection requires sample preparation or phlebotomy, which is not compatible with continuous monitoring. Recent studies in wearable biosensors can help to also develop novel biosensors for continuous monitoring of these biomarkers from transplanted cutaneous tissues. For example, Jang et al. suggested a wearable, soft electronic device that can carry out real-time measurement of the MMP-9 concentration in tear fluids using a graphene field-effect transistor (FET) integrated into a contact lens [77]. The contact lens mainly consists of a polydimethylsiloxane substrate modified with silver nanofibers-silver nanowires encapsulated in parylene. In this study, the graphene surface was functionalized with immunoglobulin G (IgG) and changes in the drain current were recorded as a function of the concentration of MMP-9 based on the antigen-antibody reactions with the graphene FET. The biosensor also enables real-time wireless transmission of the data to an external reader, such as a portable device (e.g., a smartphone). In-vivo experiments using animals and human subjects confirm biocompatibility and reliability. Similarly, Gao et al. developed a flexible, microfluidic-based multiplexed biosensor platform (named VeCare) that can be attached on a wound (venous leg ulcers) area [69]. The transduction mechanism of this aptamer-based biosensing platform relies on microelectrodes that consist of a thin layer of electrochemically exfoliated graphene-gold nanoparticles. In this study, aptamer sequences were modified with methylene blue (MB) as a redox probe and the variation of peak current height associated with the MB redox tag distance to the electrode, as sensor signal change, was monitored by square wave voltammetry (SWV). The presented biosensor approach provided a simultaneous quantitative assessment of *Staphylococcus aureus* bacteria, which was shown to be associated with skin graft loss in another study [13]. When properly adapted and implemented, such non-invasive, mobile point-of-care systems could also provide new opportunities for monitoring the wound status of transplanted skin grafts and flaps. In parallel to the abovementioned markers, an electrochemical monitoring of other indirectly related markers such as glucose might also be very helpful to managing the conditions such as diabetes and hypoglycemia; both of which can affect the healing of the transplanted skin and could increase the risk of complications. Here, a strong demand developing those sensors is still existing.

6.2. Optical sensors

To optically observe the status of a skin graft, different methods can be applied. These methods can be divided into methods, which directly observe optical effects, while in other case, an optical read out of probes is used. As described before, in clinical routine a pin prick test is performed to check for circulating blood in the skin graft (see Fig. 3): the examiner uses a small needle, which is pushed into the patient's skin graft, and observes if and how blood is collecting on the skin surface as an indicator for blood circulation, which also can be verified by observing the capillary refill [40]. Therefore, pressure is applied to the place of examination, leading to a color change of this spot. After removing the pressure, the normal skin tone returns to its initial state. The time needed for and the behavior of this –more qualitative rather than quantitative– color change is then observed by trained professionals to check the capillary refill of this area.

Another non-invasive method in clinical routine that is typically used observes the discoloration of the skin graft over time. This can be done manually by the medical staff [40], however, it can be also assisted with photographies to get a better impression of the change over time (e.g., see experiments for skin flaps in rabbits [78]). This concept is further extended to color sensors, as it is challenging for conventional cameras to observe a discoloration due to different lighting conditions, as well as for measurements of a moving patient. Commercially available color sensors have been placed together with temperature and pulse wave sensors on a flexible printed circuit board which can be attached to the skin (see also Section 6.3, Fig. 10) [39,40]. Such a color sensor usually consists of LEDs (light-emitting diode) of different wavelengths (red, blue and green) to illuminate the measurement spot with a specific color, and a photodiode to detect the reflected light of the specific wavelength. Gu et al. used their system to measure compromised circulation in groin flap models using ischemia and congestion rat models [39]. The skin color can have an effect on some optical detection methods as visible and infrared light is absorbed by melanin. The sensor system has been refined by wireless transmission and mobile power source as a wearable device for continuous multi-point tissue circulation monitoring and tested on patients following tissue grafting surgery [40]. Bringing such electric devices in direct contact with a patient requires a good sealing of the sensor (no water intake), and a current limit must be implemented. In a clinical trial with data from 45 patients, a good agreement between calculated risk (determined by the device) and classical observation by clinical staff was found.

To study non-invasively the blood flow dynamics of an area can be accessed by video recording of the skin with a thermal camera together with spectral filtering as temperature reading [79]. These thermal cameras detect the temperature by recording longwave IR (infrared) signals from the body. This way, transplanted skin flaps in a pig model were observed [47,80]. A dependency between temperature decrease and skin flap failure was shown, a sudden temperature drops of more than 3 °C within a short time occurred in failed skin flaps [80]. Oda et al. followed the healing process of 14 transplanted skin grafts of patients at the Nagoya City University Hospital using an infrared thermometer. Here, they observed a general increased surface temperature of the skin graft transplant, i.e. all skin grafts healed successfully [47]. These contactless methods to determine the surface temperature can assist the surgeons with additional information [81,82]. Results from contact-based temperature measurements are discussed in detail in Section 6.3. Next to the mean temperature information (e.g., to prevent a possible flap failure), especially infrared cameras can point to areas that need special attention (due to locally colder areas). However, these devices are not implantable and often still need regular visits by trained medical staff to be operated. Beside of spatial-resolved measurements, time-resolved measurements of the temperature can be used. In the work of Sagaidachnyi et al. the behavior of the blood flow dynamics in endothelial (0.005–0.02 Hz), myogenic (0.02–0.05 Hz) and neurogenic (0.05–0.1 Hz) frequency bands could be observed [79]. Experiments were performed on a right hand and for skin blood flow on feet, however, for a good image acquisition, the subject's extremities were fixated during recording of the thermal image sequences. In future, the same might be used during engraftment of skin flaps and burns healing.

As light spectra of deoxyhemoglobin (Hb) and oxyhemoglobin (HbO_2) are quite different, they can be used to determine the current oxygenation state of the patient's hemoglobin. Typically, in these setups two distinct light sources with wavelengths in the red and near-infrared (NIR) region (e.g., 612 nm and 725 nm) are utilized [83]. In a finger clip pulsoxymeter, this is usually done in transmission but the same principle can also be applied for the reflectance. Berthelot et al. [56] have utilized such an optical sensor to measure the oxygenation state of patients after free tissue transfer in a clinical study. By applying this technique

perfusion changes can be correctly detected and feedback about the viability of the free tissue transfer can be given. Using this technique in reflectance mode with multiple units on a single flexible substrate, a reflectance oximeter array was constructed, allowing to record 2D oxygenation maps [83]. NIR sensing offers the potential of postoperative monitoring after a free flap surgery [84]. A sensor system based on the absorption of Hb and HbO_2 was implanted to measure the oxygenation in deeper layers [58,85–87]. Exemplary, a wire-bound implantable probe was presented to measure the blood oxygenation in muscle flaps and kidneys in live porcine models, see Fig. 7. The probe is held in place with the help of bioresorbable barbs and is connected by wires to an external electronic for wireless communication [58]. Oxygen saturation is measured during multiple experimental cycles, representing ischemia and congestion, by implantable NIR probes.

An alternative option to monitor the tissue's partial pressure of oxygen (pO_2) is given by oxygen-sensitive dyes which were implemented to liquid bandages [38,54]. The oxygen-sensitive dye used by Marks et al. [38] had a red emission increasing for lower pO_2 concentrations; with the help of a reference dye (green) the current pO_2 value was calibrated. In this work, the measurement was conducted on top of the wound enabling an easier recording of a wide area of interest. The same principle of oxygen-sensitive dyes or films was applied for implanted sensors [55,88].

In [55], an implanted LED-based sensor system produces excitation light, which is then passing an O_2-sensing film and after filtering, only the emitted light of the ruthenium dyes (which undergo collisional quenching with O_2 molecules) is recorded by an integrated circuit with a photodiode.

Instead of implanting the whole sensor setup, also experiments have been conducted where only the phosphorescence sensor part was implanted [88]. The sensor (Pd-porphyrin for O_2 detection embedded in a porous poly(2-hydroxyethyl metacrylate) hydrogel with a size of 5 mm x 0.5 mm) was injected by an 18 gauge needle into the subcutaneous fat of rats over the gastrocnemius muscle (Fig. 8). With an external

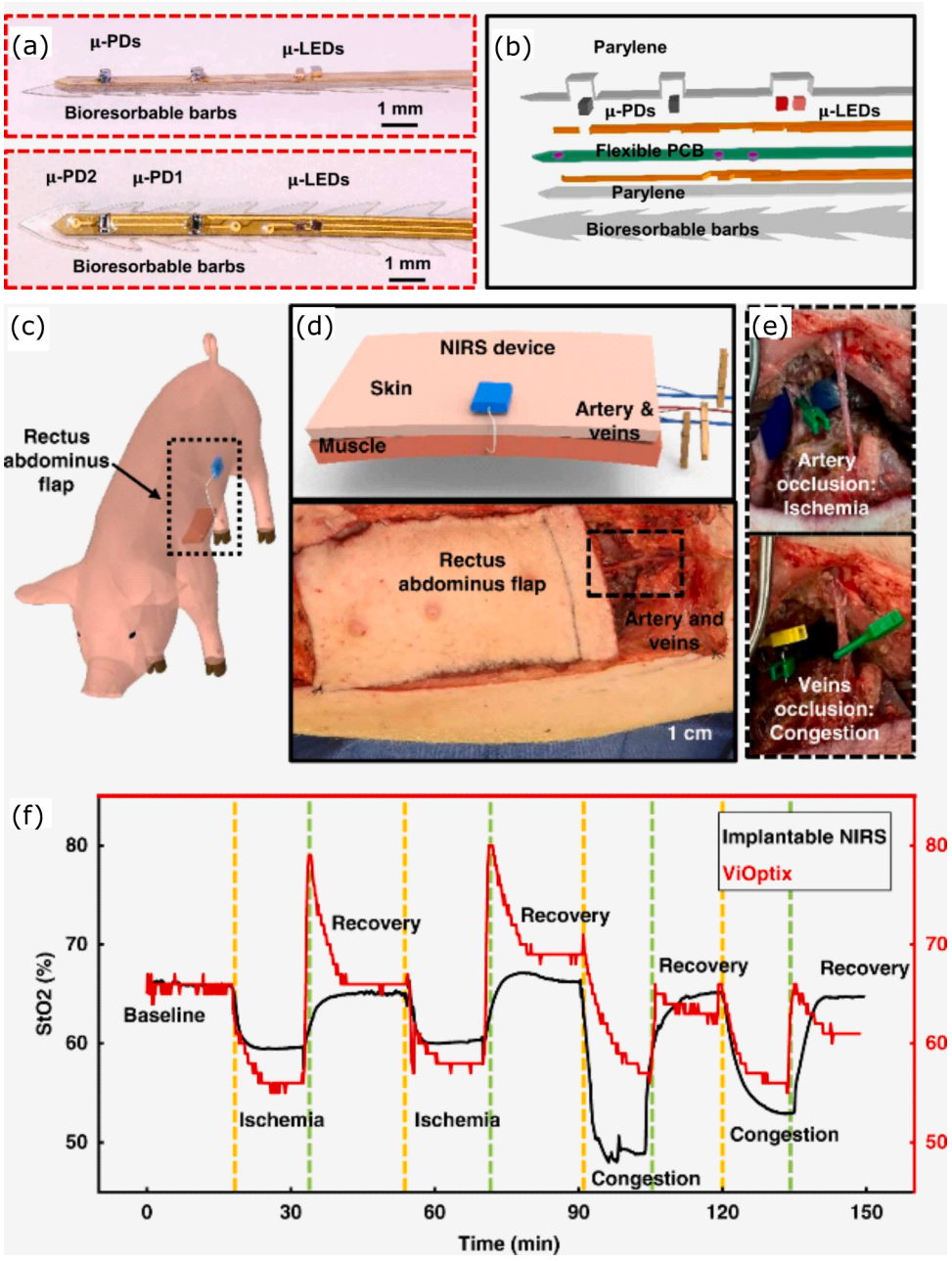

Fig. 7. (a) Images of the implantable NIR sensing probe for blood oxygenation measurement, top: side view, bottom: top-down view and (b) exploded view of the sensing probe. (c), (d) Schematic illustration and image of the sensor placement in a porcine model (left abdominus flap). (e) Images of the experimental setup to trigger events of ischemia and congestion. (f) Measured oxygen saturation during multiple experimental cycles (with simulated events of ischemia and congestion) from the implantable NIR probes in comparison to a skin-mounted device (ViOptix). (Adapted from [58], with permission from Springer Nature, Copyright 2022).

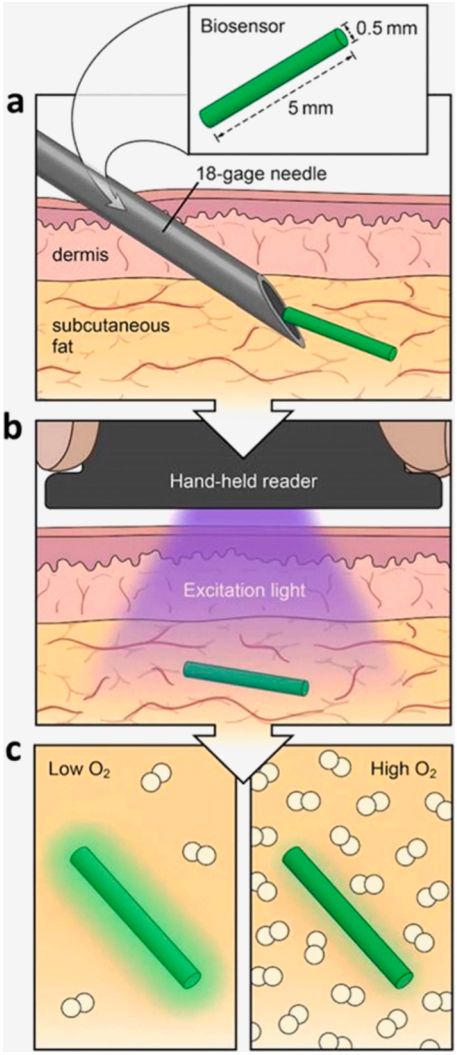

Fig. 8. Schematic of (a) a phosphorescence biosensor (5 mm x 0.5 mm) implanted in the subcutaneous fat layer of a rat and (b) irritated by an external hand-held reader. (c) The phosphorescence of the implanted biosensor depends on the surrounding oxygen concentration. (Adapted from [88], with permission from Springer Nature, Copyright 2017).

hand-held reader, the sensor still worked after 84 days being implanted in a rat. Further research is needed to show the full potential of these sensors, especially by addressing challenges, like being invasive as well as issues regarding biocompatibility, drift behavior and surgery routines for removal of the implanted sensors after healing is achieved. Moreover, the incorporation of multiplexed sensing features would be an ideal approach to achieve a smart sensor for skin grafting.

As mentioned before, the pH level of a wound is an important factor during wound healing. Corsi et al. 2022 [89] suggested a bioresorbable nanostructured pH sensor, implanted subcutaneously on the back of mice to measure the local pH level through the skin. The receptor of the sensor contains fluorophores (Rhodamine-B) fixed to a polymer stack and showing pH-depending photoluminescence, which can be explained by the shrinking/swelling of the polymer stack (self-quenching of the Rhodamine-B photoluminescence). Here, a higher pH value leads to a shrinking of the multilayer stack which results in lower photoluminescence and vice versa for lower pH values.

Several further optical methods, rather than (miniaturized) optical sensors, are employed to monitor skin graft und burn wound healing. As an example, spatial frequency domain imaging (SFDI) analyzes the optical properties of skin in porcine models [90]. A light source followed by a spatial light modulator and cross-polarizers creates a structured illumination of the sample, which is then recorded with a camera with an additional cross-polarizer. Out of these results, the absorption coefficients as well as the reduced scattering can be calculated to follow the healing process over time. Moreover, diffuse reflectance spectroscopy (DRS) has been applied in clinical trials to detect vascularization of skin substitutes expressing the vascular endothelial growth factor (VEGF) protein compared to normal grafts in mice [36]. Here, the spectroscopic data from four light sources with different wavelengths were analyzed using principal component analysis (PCA) and independent component analysis (ICA).

With the help of optical coherence tomography (OCT), the integration of a skin graft was non-invasively observed [91]. OCT is a technique that uses infrared light, the blood vessels (which are important for the skin graft) can be differentiated from the surrounding tissue by performing multiple scans of the same spot within a short time frame. Their signal difference due to the blood flow enables to observe the blood vessels over time. This particular configuration is called optical coherence tomography angiography (OCTA). The OCT/OCTA technique can monitor numerous features of human skin graft health as well as its integration after a split-thickness surgery.

6.3. *Non-optical physical and gas sensors*

Wound healing is a complex multi-stage process: each stage consists of its own specific environment with its specific parameter variations (e.g., temperature, pH, VOCs (volatile organic compounds) and metabolites) [68,92–94]. Depending on the stage of wound healing process, a higher temperature can enhance the transport of nutrients and oxygen to the damaged area or can be used by the body to clean the wound area from invading microbes. At the same time, a sudden increase in temperature is a sign of infection, as a sudden drop of temperature can indicate blood inclusion [95,96]. Therefore, measuring the temperature of wounds is one of the oldest postoperative methods to monitor the wound healing process [97]. These measurements can be performed by direct skin contact or contactless [39,40,47,57,80,98]. Direct skin contact allows precise and continuous measurements with an often low-cost and low-power device over a long period of time. However, it must be ensured that the sensor is not affected by detachment, body fluids or mechanical stress. In contrast, non-contact methods e.g., via thermal imaging cameras, as described in Section 6.2 “Optical Sensors”, are immune to detachment, mechanical stress of the skin and body fluids, and can be used for multiple patients.

For monitoring skin transplants, the temperature difference between a healthy and grafted skin typically varies between 2 °C and 3 °C; larger and suddenly occurring temperature differences indicate some kind of blood occlusion [98]. Chiu et al. examined a reversible, commercially available temperature strip indicator with a colored bar on a temperature scale, indicating the current surface temperature [98]. These temperature test strips were attached to transplanted skin flaps as well as to healthy skin and monitored the temperature during the healing process. A suddenly occurring temperature drop of 3 °C, which indicated some kind of arterial thrombosis, could be successfully observed by the sensor. This simple method allowed both the hospital staff and the patient to overview the healing process. On the other hand, on-line monitoring is not possible, which was addressed by a remote device for continuous temperature recording of porcine skin flaps using infrared thermometry with wireless connection and automatic alarms [99].

A more advanced approach with a wearable multi-sensor setup consisting of four optical reflectance sensors, temperature sensors and electronics was investigated by Gu et al. (Fig. 9(a)) [39].

The optical reflectance as well as temperature changes in skin flaps in a rat model for two types of compromised circulation (ischemia and congestion) were studied. The wearable sensor (around 7 cm long) was placed on healthy skin as well as on the transplanted skin flap bridging the wound edges (Fig. 9(b)). The experiments showed only small

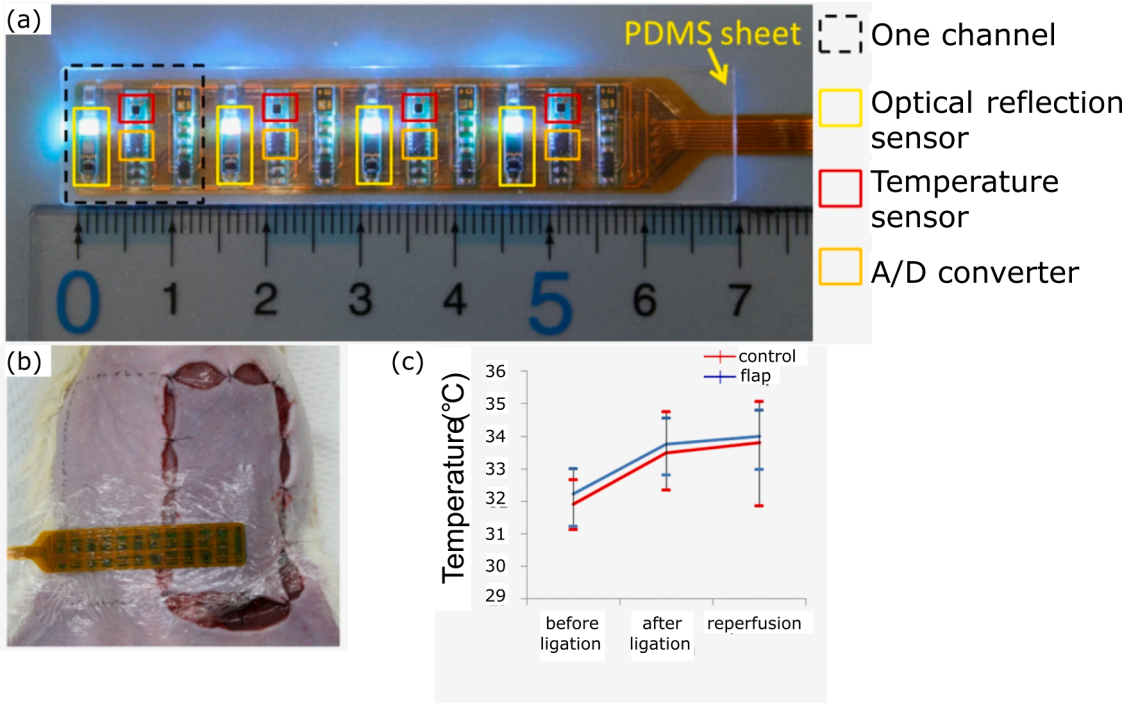

Fig. 9. a) Wearable, multi-sensory probe consisting of color and temperature sensors placed on (b) a rat's control flap (left) and groin flap (right) with venous ligation. (c) Measured average and standard deviation of temperature for the control flap and groin flap for the ischemia model. (Adapted from [39], with permission from Springer Nature, Copyright 2020).

temperature differences (Fig. 9(c)) between "control" and "flap", the blood circulation was proven by the optical reflection sensor. The authors explained the small temperature differences with the thermal equilibration between the small vessels (diameter <0.2 mm) and the surrounding tissues of the rats. In contrast, in a clinical test with humans, the larger arteries and veins in patients (diameter around 4 – 5 mm) led to detect temperature variations in the range of 2 to 3 °C in the case of impaired skin transplants, or 1 to 2 °C in the case of healthy skin grafts (Fig. 10(a)) [40]. In combination with other relevant parameters (color and pulse wave), the sensor setup could detect skin transplant failures, in one case, 13 h prior to the medical staff (Fig. 10(b)).

A rather unconventional method for monitoring skin flaps in a pork model was proposed in [57]. Here, the temperature was not used as a direct marker to monitor the skin flap condition, instead the authors observed the microvascular blood flow in the skin flap by temperature sensors. The biocompatible sensor device consisted of biodegradable barbs, a heating element and four temperature sensors. The heating element heated the blood and four thermistors in certain distances were used to calculate the blood flow. This method was able to distinguish between an occluded and a not occluded skin flap. Implementation of a smart phone for data acquisition, display and analysis reduced the costs of the system and promoted the routine usage. However, receivable experiments must deal with implantation to exclude body response reactions.

In addition to temperature, bioimpedance can also serve as a measure for monitoring the transplanted skin healing process. Bioimpedance describes the response of a living organism to an externally applied electric field and is often used in body fat scales to determine body fat composition [100]. Due to different conductivities in the body (fat and bone have low conductivity, blood has a high conductivity), the resulting current differs from the applied current. In addition, the information obtained depends on the applied frequency, such as low frequencies can penetrate the cell membrane only with difficulty. In general, this technique provides an easy-to-use, safe, and non-invasive method.

A bioimpedance sensor was applied to study the bioimpedance development of transplanted skin flaps on a rat model during its healing process over several hours after surgery [101]. Starting with an impedance value of 1.7 kΩ/cm, an impedance increase (3 h after surgery) corresponds to healthy skin areas, whereas decreasing impedance values showed necrosis. A similar experiment for skin flaps on a rat model proved that the impedance of specimens with vascular complications increased and significantly differed from the control group, see Fig. 11 [72]. In contrast to the observations of Islamoglu et al., here an impedance increase is associated with damaged skin flaps.

The bioimpedance technique was extended to observe the healing process of a skin transplant on human patients [102]. Here, bioimpedance measurements monitored the fluid release through a split-thickness meshed skin graft as indirect method to study the epithelialization process. After complete healing, the impedance value returned to its original value. In all reported cases, bioimpedance measurements seem to be a valuable tool to monitor the status of skin transplant healing. However, bioimpedance has not been used for continuous monitoring so far, and the development of miniaturized sensors is still in its infancy.

Oxygen represents an essential element in the wound healing process and the knowledge about the oxygenation status is therefore a critical parameter. It allows the early detection of skin transplant failures. The "gold standard" in the clinical assessment of tissue oxygenation is needle-type Clark electrodes, which can precisely measure oxygen in a tissue [54]. Here, oxygen reacts to water catalyzed by a platinum surface and the electron flow (for this process) will be recorded. However, disadvantageously the sensor probe has to be inserted into the skin and the measurement consumes oxygen, which can influence the wound healing environment. In contrast, transcutaneous oxygen ($TcPO_2$) and carbon dioxide ($TcPCO_2$) measurements describe a non-invasive tool to determine the level of O_2 or CO_2 of the tissue below the skin. $TcPO_2$, as an indirect measure to determine the blood flow, can be used to monitor the wound healing process. Here, the local oxygen release from the capillaries though the skin is measured by a set of electrodes over time. A positive correlation between the skin graft survival rate and the increasing $TcPO_2$ level was demonstrated in [47]. The skin will be

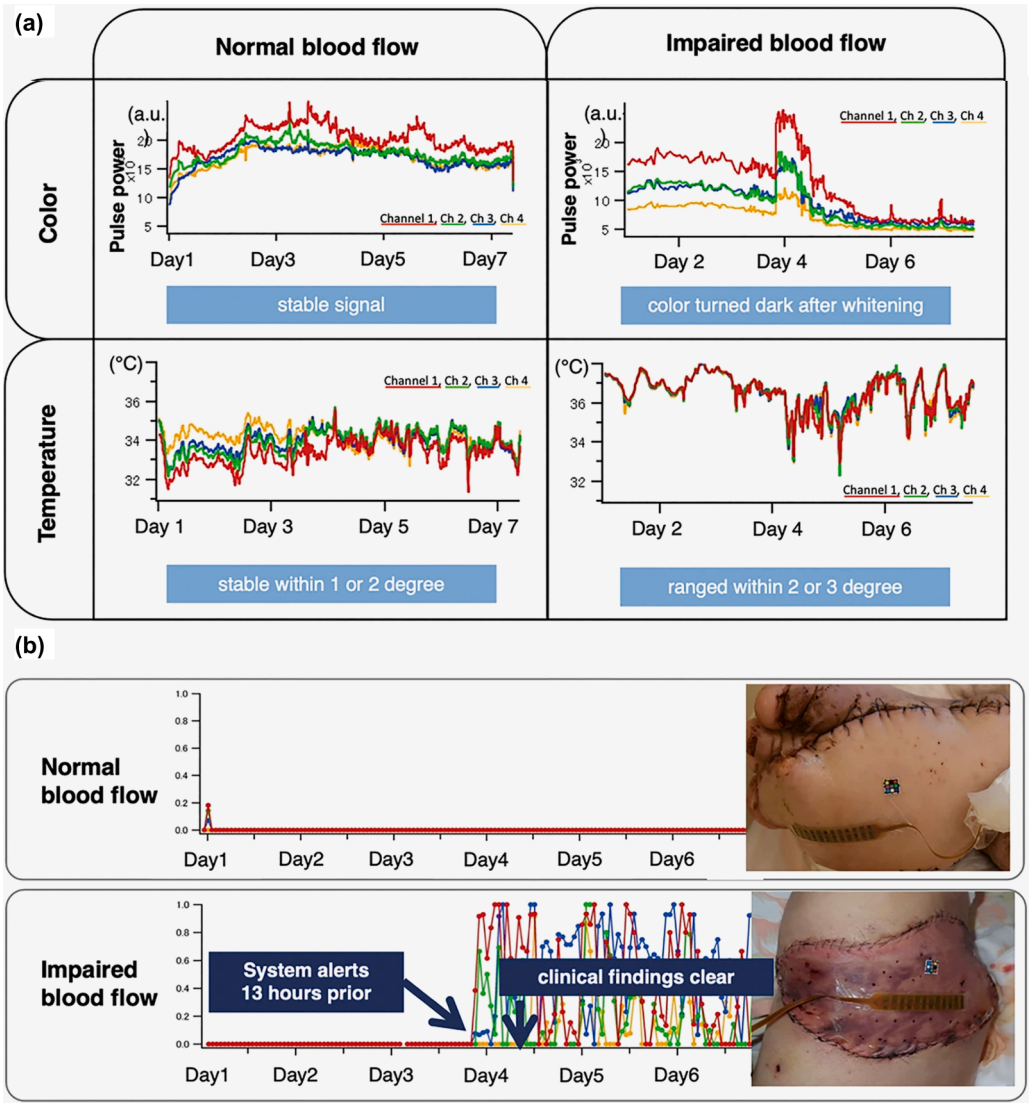

Fig. 10. a) Raw signal data for color (top) and temperature (bottom) measurements on a tissue with normal blood flow (left) and impaired blood flow (right). (b) Comprehensive risk rate calculated from the raw data from temperature, color and pulse wave (not shown here) measurements for normal (top) and impaired (bottom) blood flow in a tissue. (Adapted from [40], with permission from Springer Nature, Copyright 2022).

heated usually during $TcPO_2$ measurement, to enhance the oxygen permeability of the skin. Especially for long-term measurements (>3 h), this could lead to light burns of the skin [44]. Therefore, Abe et al. studied low temperature (37 °C) measurements of $TcPO_2$ to detect circulatory failures of transplanted skin. The recorded values of $TcPO_2$ at 37 °C remained too low to detect circulatory failure, in contrast to measurements of $TcPCO_2$ that displayed a sharp signal for complications in transplanted skin [103]. The increasing $TcPCO_2$ levels can be attributed to an increased cellular respiration or an impaired gas exchange due to a blocked skin microcirculation [104].

Another approach for long-term measurements (up to 5 years), is based on an implanted lithium phthalocyanine (LiPc) crystal, which served as oxygen sensor for electron paramagnetic resonance (EPR) oximetry in a skin flap of a mouse [105]. The unpaired electrons of oxygen interact with the paramagnetic LiPc, which could be recorded in an EPR spectrum. This minimal-invasive procedure allowed a non-invasive measurement of absolute $TcPO_2$ values repeatedly e.g., to record the sharp decrease of oxygen one day after the wounding. In contrast to normal $TcPO_2$ monitoring mentioned before, with this method no oxygen is consumed.

The determination of the oxygenation status of transplanted skin offers well-founded conclusions about the healing process and enables early detection of complications. However, current (implantable) methods are only partially suitable for 24 h continuous patient measurements.

Organic molecules that can easily pass into the gas phase at room temperature (due to their high vapor pressure) are described as volatile organic compounds VOCs. VOCs play an important role in the communication of plants and animals, are responsible for the odor of perfume and pollutants, and are even produced by the human body, like, the skin [106–108]. These volatile compounds (e.g., eccrine, apocrine, sebaceous glands) can vary with the living condition or even by the health state of a person [109].

Typically, VOCs are analyzed by gas chromatograph mass spectrometry (GC–MS). Here, the analyte in gas phase is sent over a stationary phase, which will separate the molecules by their affinity to it. The molecules are retained and will elute the column at different times. Subsequently, these separated molecules will be analyzed by a mass spectrometer, which will break the molecules into ionized fragments and detects these fragments using their mass-to-charge ratio. High-end analytical devices are able to detect and identify infections, at the same time they are also large, expensive, and require high-skilled staff to

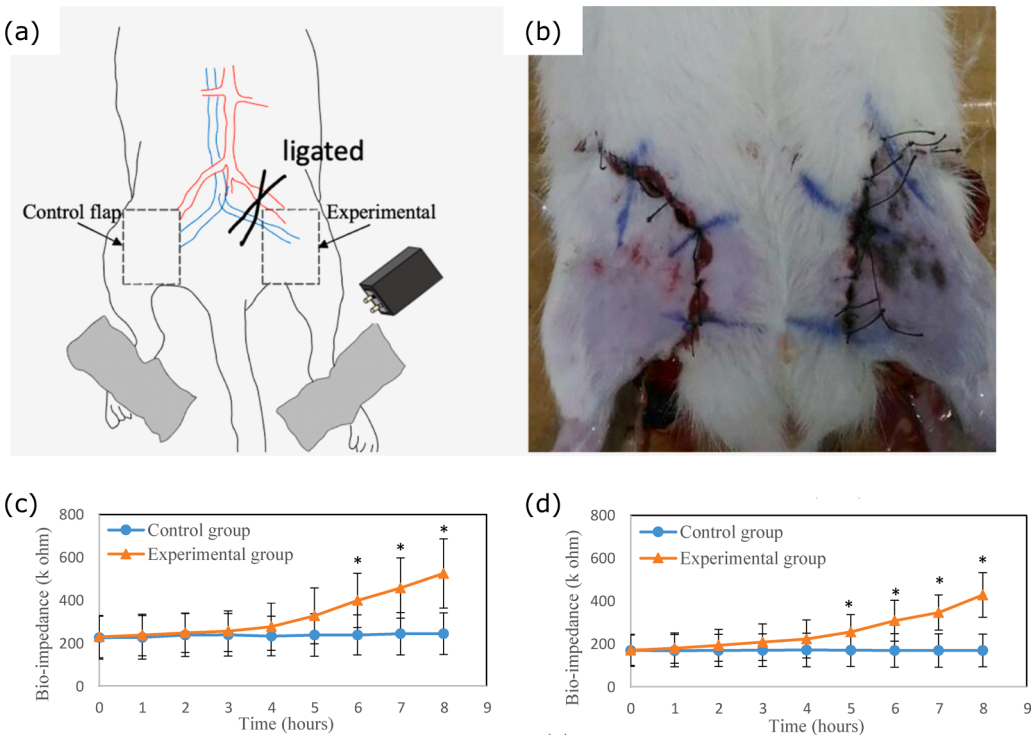

Fig. 11. (a) Schematic of the experimental procedure for animal studies in a rat model and (b) photograph of the initial situation before starting the measurements. (c), (d) Time course of the average bioimpedance in the thigh flaps for the control and experimental group for 1 kHz (c) and 5 kHz (d). $n = 6$ separated trials. (Adapted from [72], with permission from MDPI, Copyright 2021).

operate. A cheaper alternative to monitor transplanted skin presents electrical noses and odor sensors. Such an odor sensor (handheld device based on the GC–MS principle with an additional "sniffer part", which allows a clinical expert to smell the separated components) was used to investigate volatile odorants expressed by patients with osmidrosis (treated by the skin flap method) [108]. After applying the skin flap, the detected VOCs (e.g., heptanal, octanal, nonanal, acetone) were significantly reduced, indicating a successful operation. The VOCs were not detected to monitor the healing process of the transplanted skin, however, bacterial wound infections promote the formation of VOCs. Daulton et al. studied the excretions of VOCs from infected split-skin graft transplantation wounds and compared them with a normal, healthy control group of patients using gas chromatographic ion mobility spectrometry (GC-IMS) [60]. Using this technique, the authors were able to distinguish an infected wound from a healthy one within 10 min, while identifying a pattern for infected wounds. However, individual components or the identification of microorganisms causing the infection could not be analyzed.

Many examination methods in medicine are based on ultrasound, also called sonography. During an ultrasonic examination, high-frequency sound waves (>20 kHz) are sent into the tissue and the pulse echo is recorded and often displayed as an image. A more specialized technique based on the same principle is called Doppler sonography. The Doppler effect describes the change in frequency of a wave depending on the movement of the observer. This effect can be used to measure the speed and direction of blood flow, for example, in an artery. For monitoring transplanted skin, the Doppler probe will be directly connected to a blood vessel (implanted Doppler probe). The importance of implantable Doppler probes in free flap monitoring (>1000 monitored free flaps), which were able to detect intraoperative and postoperative vascular compromises in an early stage, is highlighted in [110]. A further non-invasive flowmetry method, based on the Doppler effect, is the laser Doppler flowmetry (LDF). Here, a laser beam is used instead of ultrasound. For blood flow measurements with LDF, a decrease in perfusion of more than 40% indicates an impaired blood flow [111]. The clear advantage of LDF is its simple handling. Here, the sensor must not be fixed to and removed from the blood vessel. The advantages and disadvantages of implantable Doppler probes, as well as a comparison between implantable Doppler probes and LDF are discussed in detail in [112].

7 Conclusions

Skin grafts and skin flap surgeries have become common in medical centers around the world. Nevertheless, the healing process remains a challenge that can be explained two-folded. First, the human skin happens to be the organ with the highest exposure to the environment. An open wound, and the skin transplant itself, is therefore at high risk for infections. The consequence is a very extensive dressing, which in many cases remains for a long time in order to minimize the risk of infection and physical stress. Healthy skin is supposed to protect the physiological conditions below the skin under as many circumstances as possible. Usually desirable this hinders, in case of large grafts or flaps, the observation of the healing process underneath the graft, leading to delayed conventional diagnoses for e.g., undersupply or even blockage of blood, as well as the associated supply of oxygen and nutrients, or the diagnosis of ongoing infections. Both reasons together can lead to an extremely difficult and, above all, time-delayed conventional assessment of the healing process by the clinic staff.

Failed skin grafts, or complications, have not only an impact on the health of the patient. As well as being a burden to the health care system, they also induce high psychological stress, especially if the areas are affected which are usually visible, such as the face, arms and legs. All these negative consequences could be significantly reduced if problems are detected at an early stage. Monitoring wound healing as continuously as possible, by recording indicators that show possible problems as early as possible, is therefore one of the major trends of current skin graft techniques.

To the best of the authors' knowledge, this review has summarized for the first sensor approaches to monitor skin graft healing. It became

clear that there is currently very little work published, that directly addresses sensor monitoring of skin flap and skin graft healing. Therefore, the authors also searched for and presented work on sensors that have already been investigated for monitoring general wound healing.

In general, the following major trends can currently be identified. First, the monitoring of biochemical parameters on or under the skin graft, foremost, the pH value or the dissolved oxygen concentration, albeit the detection of more complex molecules were demonstrated. For these values, often miniaturized sensor concepts have been developed. However, work is needed here, especially in the areas of biocompatibility, long-term stability and reproducibility, in order to meet the high clinical requirements in the future.

Secondly, the monitoring of physical parameters, like blood flow and temperature or both as a sum parameter, spatially resolved and temporally resolved, is another area of work that has generated much interest. Commercial systems such as (thermal) cameras, ultrasound probes and thermal sensors are applied here. This field needs to be further developed in a much more tailored way for the actual application. The first sensor systems developed explicitly for monitoring wound temperature are promising.

The third emerging trend is the use of electrical metrics. These generally enable non-invasive measurements, even of deeper tissue layers. Even though these methods have been known for some time, further investigations and medical studies are still needed for the explicit monitoring of skin grafts.

The fourth and last trend is the detection of VOCs as environmental parameters in the microenvironment formed by the dressing. This special form of gas analytics is very promising, but further studies on the subject of sample preparation, cross-sensitivity with environmental pollutant and measurement data evaluation are necessary, in order to provide reliable results in everyday clinical use.

Common to all trends is the need for flexibility in the measurement setup. Here, a specific focus has to be set on everyday clinical practice. Ideally, future sensor systems will be miniaturized, enable wireless data communication and have an integrated power supply. This would provide longer monitoring times without unnecessary burdening the patient and binding up medical staff and resources. Furthermore, there is a whole series of other works, that propose new solutions or have presented a solution in similar applications. What these generally have in common is that they are often still very much in their infancy and that numerous tasks still need to be carried out for future applications, to make those systems for skin grafts usable in clinical routine.

In summary, solutions so far have shown very promising results, which clearly demonstrate that the use of sensors in the assessment of the healing process of skin grafts has a significant positive impact. In addition, the relief of the hospital staff and the reduced costs of treatment lead to significant economic benefits. Therefore, it is certainly advisable to continue working in this area, in order to provide healthcare facilities with excellent methods and devices of monitoring skin graft status in the future.

CRediT authorship contribution statement

Dua Özsoylu: Writing – original draft, Conceptualization, Investigation, Methodology, Visualization. **Kevin A. Janus:** Writing – original draft, Conceptualization, Investigation, Methodology, Visualization. **Stefan Achtsnicht:** Writing – original draft, Conceptualization, Investigation. **Torsten Wagner:** Conceptualization, Methodology, Writing – review & editing. **Michael Keusgen:** Conceptualization, Methodology, Writing – review & editing. **Michael J. Schöning:** Writing – original draft, Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.snr.2023.100163.

References

[1] A. Przekora, A concise review on tissue engineered artificial skin grafts for chronic wound treatment: can we reconstruct functional skin tissue in vitro? Cells 9 (2020) 1622, https://doi.org/10.3390/cells9071622.
[2] M.H. Mohammadi, B. Heidary Araghi, V. Beydaghi, A. Geraili, F. Moradi, P. Jafari, M. Janmaleki, K.P. Valente, M. Akbari, A. Sanati-Nezhad, Skin diseases modeling using combined tissue engineering and microfluidic technologies, Adv. Healthc. Mater 5 (2016) 2459–2480, https://doi.org/10.1002/adhm.201600439.
[3] H. Sorg, D.J. Tilkorn, S. Hager, J. Hauser, U. Mirastschijski, Skin wound healing: an update on the current knowledge and concepts, Eur. Surg. Res. 58 (2017) 81–94, https://doi.org/10.1159/000454919.
[4] H. Miyazaki, Y. Tsunoi, T. Akagi, S. Sato, M. Akashi, D. Saitoh, A novel strategy to engineer pre-vascularized 3-dimensional skin substitutes to achieve efficient, Func. Engraft., Sci. Rep. 9 (2019) 1–10, https://doi.org/10.1038/s41598-019-44113-6.
[5] R. Serra, A. Rizzuto, A. Rossi, P. Perri, A. Barbetta, K. Abdalla, S. Caroleo, C. Longo, B. Amantea, G. Sammarco, S. de Franciscis, Skin grafting for the treatment of chronic leg ulcers - a systematic review in evidence-based medicine, Int. Wound. J 14 (2017) 149–157, https://doi.org/10.1111/iwj.12575.
[6] B.J. Mehrara, T.D. Santoro, E. Arcilla, J.P. Watson, W.W. Shaw, A.L. Da Lio, Complications after microvascular breast reconstruction: experience with 1195 Flaps, Plast. Reconstr. Surg. 118 (2006) 1100–1109, https://doi.org/10.1097/01.prs.0000236898.87398.d6.
[7] D.T. Bui, P.G. Cordeiro, Q.-Y. Hu, J.J. Disa, A. Pusic, B.J. Mehrara, Free flap reexploration: indications, treatment, and outcomes in 1193 free flaps, Plast. Reconstr. Surg. 119 (2007) 2092–2100, https://doi.org/10.1097/01.prs.0000260598.24376.e1.
[8] K.-T. Chen, S. Mardini, D.C.-C. Chuang, C.-H. Lin, M.-H. Cheng, Y.-T. Lin, W.-C. Huang, C.-K. Tsao, F.-C. Wei, Timing of presentation of the first signs of vascular compromise dictates the salvage outcome of free flap transfers, Plast. Reconstr. Surg. 120 (2007) 187–195, https://doi.org/10.1097/01.prs.0000264077.07779.50.
[9] G. Oganesyan, A.D. Jarell, M. Srivastava, B. Jiang, Efficacy and complication rates of full-thickness skin graft repair of lower extremity wounds after mohs micrographic surgery, Dermatol. Surg. 39 (2013) 1334–1339, https://doi.org/10.1111/dsu.12254.
[10] C. Copelli, K. Tewfik, L. Cassano, N. Pederneschi, S. Catanzaro, A. Manfuso, R. Cocchi, Gestione del Fallimento dei Lembi Liberi in Chirurgia Testa-Collo, Acta. Otorhinolaryngol. Italica 37 (2017) 387–392, https://doi.org/10.14639/0392-100X-1376.
[11] A. Kwok, K. Edwards, D. Donato, E. Tatro, Y. Xu, A. Presson, J. Agarwal, Operative time and flap failure in unilateral and bilateral free flap breast reconstruction, J. Reconstr. Microsurg. 34 (2018) 428–435, https://doi.org/10.1055/s-0038-1627445.
[12] K.O. Nsaful, A.B. Paintsil, J.C.B. Dakubo, J. Nsaful, K. Appiah-Labi, E. Nartey, Evaluation of bacterial infection of split-thickness skin grafts at the Korle Bu teaching hospital, Bali. Medical. Journal 9 (2020) 259–265, https://doi.org/10.15562/bmj.v9i1.1760.
[13] S. Ünal, G. Ersoz, F. Demirkan, E. Arslan, N. Tütüncü, A. Sari, Analysis of skin-graft loss due to infection: infection-related graft loss, Ann. Plast. Surg. 55 (2005) 102–106, https://doi.org/10.1097/01.sap.0000164531.23770.60.
[14] B.O. Mofikoya, A.O. Ugburo, O.M. Belie, Clinical assessment score for monitoring free flaps in the dark skin, Alban. J. Med. Heal. Sci. 49 (2018) 18–22.
[15] B. Gil Rosa, O.E. Akingbade, X. Guo, L. Gonzalez-Macia, M.A. Crone, L. P. Cameron, P. Freemont, K.-L. Choy, F. Güder, E. Yeatman, D.J. Sharp, B. Li, Multiplexed immunosensors for point-of-care diagnostic applications, Biosens. Bioelectron. 203 (2022), 114050, https://doi.org/10.1016/j.bios.2022.114050.
[16] N. Bhalla, Y. Pan, Z. Yang, A.F. Payam, Opportunities and challenges for biosensors and nanoscale analytical tools for pandemics: COVID-19, ACS. Nano 14 (2020) 7783–7807, https://doi.org/10.1021/acsnano.0c04421.
[17] A. Poghossian, M. Jablonski, D. Molinnus, C. Wege, M.J. Schöning, Field-effect sensors for virus detection: from Ebola to SARS-CoV-2 and plant viral enhancers, Front. Plant. Sci. 11 (2020) 1792, https://doi.org/10.3389/fpls.2020.598103.
[18] E. Morales-Narváez, C. Dincer, The impact of biosensing in a pandemic outbreak: COVID-19, Biosens. Bioelectron. 163 (2020), 112274, https://doi.org/10.1016/j.bios.2020.112274.
[19] E. Morales-Narváez, C. Dincer (Eds.), Wearable Physical, Chemical and Biological Sensors, Elsevier, 2022.

[20] D. Özsoylu, T. Wagner, M.J. Schöning, Electrochemical cell-based biosensors for biomedical applications, Curr. Top. Med. Chem. 22 (2022) 713–733, https://doi.org/10.2174/1568026622666220304213617.

[21] A. Sharma, M. Badea, S. Tiwari, J.L. Marty, Wearable biosensors: an alternative and practical approach in healthcare and disease monitoring, Molecules 26 (2021) 1–32, https://doi.org/10.3390/molecules26030748.

[22] S. Pillai, A. Upadhyay, D. Sayson, B.H. Nguyen, S.D. Tran, Advances in medical wearable biosensors: design, fabrication and materials strategies in healthcare monitoring, Molecules 27 (2021) 165, https://doi.org/10.3390/molecules27010165.

[23] Y. Song, D. Mukasa, H. Zhang, W. Gao, Self-powered Wearable Biosensors, Accounts Mater. Res. 2 (2021) 184–197, https://doi.org/10.1021/accountsmr.1c00002.

[24] D. Rodrigues, A.I. Barbosa, R. Rebelo, I.K. Kwon, R.L. Reis, V.M. Correlo, Skin-integrated wearable systems and implantable biosensors: a comprehensive review, Biosensors 10 (2020) 79, https://doi.org/10.3390/bios10070079.

[25] H.C. Ates, P.Q. Nguyen, L. Gonzalez-Macia, E. Morales-Narváez, F. Güder, J. J. Collins, C. Dincer, End-to-end design of wearable sensors, Nat. Rev. Mater. 7 (2022) 887–907, https://doi.org/10.1038/s41578-022-00460-x.

[26] J. Kim, A.S. Campbell, B.E.F. de Ávila, J. Wang, Wearable biosensors for healthcare monitoring, Nat. Biotechnol. 2019 (37) (2019) 389–406, https://doi.org/10.1038/s41587-019-0045-y.

[27] H.C. Ates, A.K. Yetisen, F. Güder, C. Dincer, Wearable devices for the detection of COVID-19, Nature Electronics 4 (2021) 13–14, https://doi.org/10.1038/s41928-020-00533-1.

[28] S. Cheng, Z. Gu, L. Zhou, M. Hao, H. An, K. Song, X. Wu, K. Zhang, Z. Zhao, Y. Dong, Y. Wen, Recent progress in intelligent wearable sensors for health monitoring and wound healing based on biofluids, Front. Bioeng. Biotechnol. 9 (2021) 1–21, https://doi.org/10.3389/fbioe.2021.765987.

[29] A. Pusta, M. Tertiș, C. Cristea, S. Mirel, Wearable sensors for the detection of biomarkers for wound infection, Biosensors 12 (2022) 1–20, https://doi.org/10.3390/bios12010001.

[30] N. Tang, Y. Zheng, X. Jiang, C. Zhou, H. Jin, K. Jin, W. Wu, H. Haick, Wearable sensors and systems for wound healing-related pH and temperature detection, Micromachines 12 (2021) 430, https://doi.org/10.3390/mi12040430.

[31] S.-H. Lu, M. Samandari, C. Li, H. Li, D. Song, Y. Zhang, A. Tamayol, X. Wang, Multimodal sensing and therapeutic systems for wound healing and management: a review, Sens. Actuators Rep. 4 (2022), 100075, https://doi.org/10.1016/j.snr.2022.100075.

[32] X. Sun, Y. Zhang, C. Ma, Q. Yuan, X. Wang, H. Wan, P. Wang, A review of recent advances in flexible wearable sensors for wound detection based on optical and electrical sensing, Biosensors 12 (2021) 10, https://doi.org/10.3390/bios12010010.

[33] M. Kohlhauser, H. Luze, S.P. Nischwitz, L.P. Kamolz, Historical evolution of skin grafting—a journey through time, Medicina (B. Aires) 57 (2021) 348, https://doi.org/10.3390/medicina57040348.

[34] A. Andreassi, R. Bilenchi, M. Biagioli, C. D'Aniello, Classification and pathophysiology of skin grafts, Clin. Dermatol. 23 (2005) 332–337, https://doi.org/10.1016/j.clindermatol.2004.07.024.

[35] A.Z. Khan, T.P. Utheim, M. Byholt, T. Fiabema, H.C. Sylvester-Jensen, K. A. Tønseth, Skin Grafting,. Tidsskrift. for. Den. Norske, Legeforening 142 (2022) 1–7, https://doi.org/10.4045/tidsskr.21.0671.

[36] P. Martín-Mateos, S. Crespo-Garcia, M. Ruiz-Llata, J.R. Lopez-Fernandez, J. L. Jorcano, M. Del Rio, F. Larcher, P. Acedo, Remote diffuse reflectance spectroscopy sensor for tissue engineering monitoring based on blind signal separation, Biomed. Opt. Express 5 (2014) 3231, https://doi.org/10.1364/BOE.5.003231.

[37] B.L. Dearman, S.T. Boyce, J.E. Greenwood, Advances in skin tissue bioengineering and the challenges of clinical translation, Front. Surg. 8 (2021), 640879, https://doi.org/10.3389/fsurg.2021.640879.

[38] H. Marks, A. Bucknor, E. Roussakis, N. Nowell, P. Kamali, J.P. Cascales, D. Kazei, S.J. Lin, C.L. Evans, A paintable phosphorescent bandage for postoperative tissue oxygen assessment in DIEP flap reconstruction, Sci. Adv. 6 (2020). https://pubmed.ncbi.nlm.nih.gov/33355131/.

[39] J. Gu, Y. Tomioka, K. Kida, Y. Xiao, I. Saito, M. Okazaki, T. Someya, M. Sekino, Measurement of optical reflection and temperature changes after blood occlusion using a wearable device, Sci. Rep. 10 (2020) 11491, https://doi.org/10.1038/s41598-020-68152-6.

[40] Y. Tomioka, M. Sekino, J. Gu, M. Kurita, S. Yamashita, S. Miyamoto, T. Iida, K. Kanayama, K. Yoshimura, M. Nakagawa, S. Akazawa, Y. Kagaya, K. Tanaka, Y. Sunaga, K. Ueda, T. Kawahara, Y. Tahara, M. Okazaki, Wearable, wireless, multi-sensor device for monitoring tissue circulation after free-tissue transplantation: a multicentre clinical trial, Sci. Rep. 12 (2022) 16532, https://doi.org/10.1038/s41598-022-21007-8.

[41] K. Saleh, A.C. Strömdahl, K. Riesbeck, A. Schmidtchen, Inflammation biomarkers and correlation to wound status after full-thickness skin grafting, Front. Med. (Lausanne) 6 (2019) 159, https://doi.org/10.3389/fmed.2019.00159.

[42] J. Palmgren, J. Paoli, A. Schmidtchen, K. Saleh, Variability in the diagnosis of surgical-site infections after full-thickness skin grafting: an international survey, British J. Dermatol. 180 (2019) 1169–1175, https://doi.org/10.1111/bjd.17517.

[43] T. Futoryan, D. Grande, Postoperative wound infection rates in dermatologic surgery, Dermatol. Surg. 21 (1995) 509–514, https://doi.org/10.1111/j.1524-4725.1995.tb00255.x.

[44] S.H. Halani, A.S. Hembd, X. Li, B. Kirby, C.C. Beard, N.T. Haddock, T. M. Suszynski, Flap monitoring using transcutaneous oxygen or carbon dioxide measurements, J. Hand. Microsurg. 14 (2022) 10–18, https://doi.org/10.1055/s-0040-1718862.

[45] T.K. Yun, E.S. Yoon, D.S. Ahn, S.H. Park, B.I. Lee, H.S. Kim, H.J. You, Stabilizing morbidity and predicting the aesthetic results of radial forearm free flap donor sites, Archives of Plastic Surgery 42 (2015) 769–775. doi:10.5999/aps.2015.42.6.769.

[46] G. Nicoletti, F. Brenta, M. Bleve, T. Pellegatta, A. Malovini, A. Faga, P. Perugini, Long-term in vivo assessment of bioengineered skin substitutes: a clinical study, J. Tissue. Eng. Regen. Med 9 (2015) 460–468, https://doi.org/10.1002/term.1939.

[47] T. Oda, H. Kato, M. Nakamura, A. Morita, Analysis of biomonitoring data after full-thickness skin grafting, J. Dermatol. 48 (2021) 1035–1043, https://doi.org/10.1111/1346-8138.15873.

[48] N.F. Jones, Intraoperative and postoperative monitoring of microsurgical free tissue transfers, Clin. Plast. Surg. 19 (1992) 783–797, https://doi.org/10.1016/S0094-1298(20)30796-3.

[49] Y. Ashitate, B.T. Lee, R.G. Laurence, E. Lunsford, M. Hutteman, R. Oketokoun, H. S. Choi, J.V. Frangioni, Intraoperative prediction of postoperative flap outcome using the near-infrared fluorophore methylene blue, Ann. Plast. Surg. 70 (2013) 360–365, https://doi.org/10.1097/SAP.0b013e318236babe.

[50] H. Wada, C.R. Vargas, J. Angelo, B. Faulkner-Jones, M.A. Paul, O.A. Ho, B.T. Lee, J.V. Frangioni, Accurate prediction of tissue viability at postoperative day 7 using only two intraoperative subsecond near-infrared fluorescence images, Plast. Reconstr. Surg. 139 (2017) 354–363, https://doi.org/10.1097/PRS.0000000000003009.

[51] A. Keller, A new diagnostic algorithm for early prediction of vascular compromise in 208 microsurgical flaps using tissue oxygen saturation measurements, Ann. Plast. Surg. 62 (2009) 538–543, https://doi.org/10.1097/SAP.0b013e3181a47ce8.

[52] H.Z. Bian, C.H. Pek, J. Hwee, Current evidence on the use of near-infrared spectroscopy for postoperative free flap monitoring: a systematic review, Chinese. J. Plastic Reconstruc. Surg. 4 (2022) 194–202, https://doi.org/10.1016/j.cjprs.2022.08.008.

[53] A. Ogawa, T. Nakagawa, G. Oda, T. Hosoya, K. Hayashi, M. Yoshino, H. Mori, N. Uemura, T. Fujioka, M. Mori, I. Onishi, K. Igari, H. Uetake, Study of the protocol used to evaluate skin-flap perfusion in mastectomy based on the characteristics of indocyanine green, Photodiagn. Photodyn. Ther. 35 (2021), 102401, https://doi.org/10.1016/j.pdpdt.2021.102401.

[54] Z. Li, E. Roussakis, P.G.L. Koolen, A.M.S. Ibrahim, K. Kim, L.F. Rose, J. Wu, A. J. Nichols, Y. Baek, R. Birngruber, G. Apiou-Sbirlea, R. Matyal, T. Huang, R. Chan, S.J. Lin, C.L. Evans, Non-invasive transdermal two-dimensional mapping of cutaneous oxygenation with a rapid-drying liquid bandage, Biomed. Opt. Express 5 (2014) 3748, https://doi.org/10.1364/BOE.5.003748.

[55] S. Sonmezoglu, J.R. Fineman, E. Maltepe, M.M. Maharbiz, Monitoring deep-tissue oxygenation with a millimeter-scale ultrasonic implant, Nat. Biotechnol. 39 (2021) 855–864, https://doi.org/10.1038/s41587-021-00866-y.

[56] M. Berthelot, F.P. Henry, J. Hunter, D. Leff, S. Wood, N. Jallali, E. Dex, L. Lysakova, B. Lo, G.-Z. Yang, Pervasive wearable device for free tissue transfer monitoring based on advanced data analysis: clinical study report, J. Biomed. Opt. 24 (2019) 1, https://doi.org/10.1117/1.JBO.24.6.067001.

[57] Di Lu, S. Li, Q. Yang, H.M. Arafa, Y. Xu, Y. Yan, D. Ostojich, W. Bai, H. Guo, C. Wu, S. Li, L. Jacobson, A.M. Westman, M.R. MacEwan, Y. Huang, M. Pet, J. A. Rogers, Implantable, wireless, self-fixing thermal sensors for continuous measurements of microvascular blood flow in flaps and organ grafts, Biosensors. Bioelect. 206 (2022), 114145, https://doi.org/10.1016/j.bios.2022.114145.

[58] H. Guo, W. Bai, W. Ouyang, Y. Liu, C. Wu, Y. Xu, Y. Weng, H. Zang, Y. Liu, L. Jacobson, Z. Hu, Y. Wang, H.M. Arafa, Q. Yang, Di Lu, S. Li, L. Zhang, X. Xiao, A. Vázquez-Guardado, J. Ciatti, E. Dempsey, N. Ghoreishi-Haack, E.A. Waters, C. R. Haney, A.M. Westman, M.R. MacEwan, M.A. Pet, J.A. Rogers, Wireless implantable optical probe for continuous monitoring of oxygen saturation in flaps and organ grafts, Nat. Commun. 13 (2022) 3009, https://doi.org/10.1038/s41467-022-30594-z.

[59] P.-L. Tremblay, V. Hudon, F. Berthod, L. Germain, F.A. Auger, Inosculation of tissue-engineered capillaries with the host's vasculature in a reconstructed skin transplanted on mice, Am. J. Transp. 5 (2005) 1002–1010, https://doi.org/10.1111/j.1600-6143.2005.00790.x.

[60] E. Daulton, A. Wicaksono, J. Bechar, J.A. Covington, J. Hardwicke, The detection of wound infection by ion mobility chemical analysis, Biosensors 10 (2020) 19, https://doi.org/10.3390/bios10030019.

[61] T. Yoshinobu, M.J. Schöning, Light-addressable potentiometric sensors for cell monitoring and biosensing, Curr. Opinion. Electrochem. 28 (2021), 100727, https://doi.org/10.1016/j.coelec.2021.100727.

[62] A. Poghossian, M.J. Schöning, Capacitive field-effect EIS chemical sensors and biosensors: a status report, Sensors 20 (2020), https://doi.org/10.3390/s20195639.

[63] A. Poghossian, M.J. Schöning, Recent progress in silicon-based biologically sensitive field-effect devices, Curr. Opinion. Electrochem. 29 (2021), 100811, https://doi.org/10.1016/j.coelec.2021.100811.

[64] D. Özsoylu, T. Isık, M.M. Demir, M.J. Schöning, T. Wagner, Cryopreservation of a cell-based biosensor chip modified with elastic polymer fibers enabling ready-to-use on-site applications, Biosens. Bioelectr. 177 (2021), 112983, https://doi.org/10.1016/j.bios.2021.112983.

[65] V. Naresh, N. Lee, A review on biosensors and recent development of nanostructured materials-enabled biosensors, Sensors 21 (2021), https://doi.org/10.3390/s21041109.

[66] M.G. Dickson, D.T. Sharpe, Continuous subcutaneous tissue pH measurement as a monitor of blood flow in skin flaps: an experimental study, Br. J. Plast. Surg. 38 (1985) 39–42, https://doi.org/10.1016/0007-1226(85)90084-0.

[67] W. Lee, S.H. Jeong, Y.W. Lim, H. Lee, J. Kang, H. Lee, I. Lee, H.S. Han, S. Kobayashi, M. Tanaka, B.S. Bae, Conformable microneedle pH sensors via the integration of two different siloxane polymers for mapping peripheral artery disease, Sci. Adv. 7 (2021) 6290, https://doi.org/10.1126/SCIADV.ABI6290/SUPPL_FILE/SCIADV.ABI6290_SM.PDF.

[68] L.A. Schneider, A. Korber, S. Grabbe, J. Dissemond, Influence of pH on wound-healing: a new perspective for wound-therapy? Arch. Dermatol. Res. 298 (2007) 413–420. https://pubmed.ncbi.nlm.nih.gov/17091276/.

[69] Y. Gao, D.T. Nguyen, T. Yeo, S.B. Lim, W.X. Tan, L.E. Madden, L. Jin, J.Y.K. Long, F.A.B. Aloweni, Y.J.A. Liew, M.L.L. Tan, S.Y. Ang, S.D. Maniya, I. Abdelwahab, K. P. Loh, C.-H. Chen, D.L. Becker, D. Leavesley, J.S. Ho, C.T. Lim, A flexible multiplexed immunosensor for point-of-care in situ wound monitoring, Sci. Adv. 7 (2021) eabg9614, https://doi.org/10.1126/sciadv.abg9614.

[70] T. Guinovart, G. Valdés-Ramírez, J.R. Windmiller, F.J. Andrade, J. Wang, Bandage-based wearable potentiometric sensor for monitoring wound pH, Electroanalysis 26 (2014) 1345–1353, https://doi.org/10.1002/elan.201300558.

[71] R. Rahimi, M. Ochoa, T. Parupudi, X. Zhao, I.K. Yazdi, M.R. Dokmeci, A. Tamayol, A. Khademhosseini, B. Ziaie, A low-cost flexible pH sensor array for wound assessment, Sensors Actuators B 229 (2016) 609–617, https://doi.org/10.1016/j.snb.2015.12.082.

[72] Y.-K. Huang, M.Y. Wong, C.-R. Wu, Y.-Z. Cheng, B.-S. Lin, Free myocutaneous flap assessment in a rat model: verification of a wireless bioelectrical impedance assessment (BIA) system for vascular compromise following microsurgery, J. Pers. Med. 11 (2021) 373, https://doi.org/10.3390/jpm11050373.

[73] L. Natta, V.M. Mastronardi, F. Guido, L. Algieri, S. Puce, F. Pisano, F. Rizzi, R. Pulli, A. Qualtieri, M. de Vittorio, Soft and flexible piezoelectric smart patch for vascular graft monitoring based on aluminum nitride thin film, Sci. Rep. 9 (2019) 8392, https://doi.org/10.1038/s41598-019-44784-1.

[74] J.R. Marland, M.E. Gray, C. Dunare, E.O. Blair, A. Tsiamis, P. Sullivan, E. González-Fernández, S.N. Greenhalgh, R. Gregson, R.E. Clutton, M.M. Parys, A. Dyson, M. Singer, I.H. Kunkler, M.A. Potter, S. Mitra, J.G. Terry, S. Smith, A.R. Mount, I. Underwood, A.J. Walton, D.J. Argyle, A.F. Murray, Real-time measurement of tumour hypoxia using an implantable microfabricated oxygen sensor, Sensing and Bio-sensing Research 30 (2020) 100375. doi:10.1016/j.sbsr.2020.100375.

[75] C. Lim, Y.J. Hong, J. Jung, Y. Shin, S.H. Sunwoo, S. Baik, O.K. Park, S.H. Choi, T. Hyeon, J.H. Kim, S. Lee, D.H. Kim, Tissue-like skin-device interface for wearable bioelectronics by using ultrasoft, mass-permeable, and low-impedance hydrogels, Sci. Adv. 7 (2021) eabd3716, https://doi.org/10.1126/sciadv.abd3716.

[76] B. Kollar, A. Shubin, T.J. Borges, S. Tasigiorgos, T.S. Win, C.G. Lian, S.T. Dillon, X. Gu, I. Wyrobnik, G.F. Murphy, B. Pomahac, T.A. Libermann, L.V. Riella, Increased levels of circulating MMP3 correlate with severe rejection in face transplantation, Sci. Rep. 8 (2018) 1–12, https://doi.org/10.1038/s41598-018-33272-7.

[77] J. Jang, J. Kim, H. Shin, Y.G. Park, B.J. Joo, H. Seo, J.E. Won, D.W. Kim, C.Y. Lee, H.K. Kim, J.U. Park, Smart contact lens and transparent heat patch for remote monitoring and therapy of chronic ocular surface inflammation using mobiles, Sci. Adv. 7 (2021) 7194–7225, https://doi.org/10.1126/sciadv.abf7194.

[78] T.O.H. Prasetyono, S. Adianto, The relationship between oxygen saturation and color alteration of a compromised skin flap: experimental study on the rabbit, Arch. Plast. Surg. 40 (2013) 505–509, https://doi.org/10.5999/aps.2013.40.5.505.

[79] A.A. Sagaidachnyi, A.V. Fomin, D.A. Usanov, A.V. Skripal, Thermography-based blood flow imaging in human skin of the hands and feet: a spectral filtering approach, Physiol. Meas. 38 (2017) 272–288, https://doi.org/10.1088/1361-6579/aa4eaf.

[80] S. Hummelink, A.S. Kruit, A.R. van Vlaenderen, M.J. Schreinemachers, W. Steenbergen, D.J. Ulrich, Post-operative monitoring of free flaps using a low-cost thermal camera: a pilot study, Eur. J. Plast. Surg. 43 (2020) 589–596. https://link.springer.com/article/10.1007/s00238-020-01642-y.

[81] G.G. Hallock, Dynamic infrared thermography and smartphone thermal imaging as an adjunct for preoperative, intraoperative, and postoperative perforator free flap monitoring, Plastic Aesth. Res. 6 (2019) 1–12, https://doi.org/10.20517/2347-9264.2019.029.

[82] T. Sjøberg, J.B. Mercer, S. Weum, L. de Weerd, The value of dynamic infrared thermography in pedicled thoracodorsal artery perforator flap surgery, Plastic and Reconstructive Surgery Global Open 8 (2020) e2799. doi:10.1097/GOX.0000000000002799.

[83] Y. Khan, D. Han, A. Pierre, J. Ting, X. Wang, C.M. Lochner, G. Bovo, N. Yaacobi-Gross, C. Newsome, R. Wilson, A.C. Arias, A flexible organic reflectance oximeter array, Proc. Natl. Acad. Sci. U.S.A. 115 (2018) E11015–E11024. https://www.pnas.org/doi/10.1073/pnas.1813053115.

[84] E. Newton, O. Butskiy, B. Shadgan, E. Prisman, D.W. Anderson, Outcomes of free flap reconstructions with near-infrared spectroscopy (NIRS) monitoring: a systematic review, Microsurgery 40 (2020) 268–275, https://doi.org/10.1002/micr.30526.

[85] M.N. Ericson, M.A. Wilson, G.L. Coté, J.S. Baba, W. Xu, M. Bobrek, C.L. Britton, M.S. Hileman, M.R. Moore, M.S. Emery, R. Lenarduzzi, Implantable sensor for blood flow monitoring after transplant surgery, Minimally Invasive Therapy and Allied Technologies 13 (2004) 87–94. doi:10.1080/13645700410027866.

[86] S. Maly, L. Janousek, R. Bortel, J. Sebek, J. Hospodka, J. Skapa, J. Fronek, A. Dalla Mora, NIRS-based monitoring of kidney graft perfusion, PLoS. ONE 15 (2020), e0243154, https://doi.org/10.1371/journal.pone.0243154.

[87] H. Zhang, P. Gutruf, K. Meacham, M.C. Montana, X. Zhao, A.M. Chiarelli, A. Vázquez-Guardado, A. Norris, L. Lu, Q. Guo, C. Xu, Y. Wu, H. Zhao, X. Ning, W. Bai, I. Kandela, C.R. Haney, D. Chanda, R.W. Gereau, J.A. Rogers, Wireless, battery-free optoelectronic systems as subdermal implants for local tissue oximetry, Sci. Adv. 5 (2019), https://doi.org/10.1126/sciadv.aaw0873.

[88] J.S. Chien, M. Mohammed, H. Eldik, M.M. Ibrahim, J. Martinez, S.P. Nichols, N. Wisniewski, B. Klitzman, Injectable phosphorescence-based oxygen biosensors identify post ischemic reactive hyperoxia, Sci. Rep. 7 (2017) 8255, https://doi.org/10.1038/s41598-017-08490-0.

[89] M. Corsi, A. Paghi, S. Mariani, G. Golinelli, A. Debrassi, G. Egri, G. Leo, E. Vandini, A. Vilella, L. Dähne, D. Giuliani, G. Barillaro, Bioresorbable nanostructured chemical sensor for monitoring of pH level in vivo, Adv. Sci. 9 (2022), 2202062, https://doi.org/10.1002/advs.202202062.

[90] G.T. Kennedy, R. Stone, A.C. Kowalczewski, R. Rowland, J.H. Chen, M. L. Baldado, A. Ponticorvo, N. Bernal, R.J. Christy, A.J. Durkin, Spatial frequency domain imaging: a quantitative, noninvasive tool for in vivo monitoring of burn wound and skin graft healing, J. Biomed. Opt. 24 (2019) 1, https://doi.org/10.1117/1.JBO.24.7.071615.

[91] A.J. Deegan, J. Lu, R. Sharma, S.P. Mandell, R.K. Wang, Imaging human skin autograft integration with optical coherence tomography, Quant. Imaging. Med. Surg 11 (2021) 784–796, https://doi.org/10.21037/qims-20-750.

[92] S. Guo, L.A. DiPietro, Factors affecting wound healing, J. Dent. Res. 89 (2010) 219–229, https://doi.org/10.1177/0022034509359125.

[93] S.A. Eming, P.J. Murray, E.J. Pearce, Metabolic orchestration of the wound healing response, Cell Metab. 33 (2021) 1726–1743, https://doi.org/10.1016/j.cmet.2021.07.017.

[94] P. Salvo, V. Dini, A. Kirchhain, A. Janowska, T. Oranges, A. Chiricozzi, T. Lomonaco, F. Di Francesco, M. Romanelli, Sensors and biosensors for C-reactive protein, temperature and pH, and their applications for monitoring wound healing: a review, Sensors 17 (2017) 2952, https://doi.org/10.3390/s17122952.

[95] M. Fierheller, R.G. Sibbald, A clinical investigation into the relationship between increased periwound skin temperature and local wound infection in patients with chronic leg ulcers, Adv. Skin Wound Care 23 (2010) 369–379, https://doi.org/10.1097/01.ASW.0000383197.28192.98.

[96] A.G. Gaiziunas, M.H. Hast, Temperature gradients and prediction of flap viability, J. Otolaryngol. 5 (1976) 399–402.

[97] A.G. Leonard, M.D. Brennen, J. Colville, The use of continuous temperature monitoring in the post-operative management of microvascular cases, Br. J. Plast. Surg. 35 (1982) 337–342, https://doi.org/10.1016/S0007-1226(82)90123-0.

[98] E.S. Chiu, A. Altman, R.J. Allen, Free flap monitoring using skin temperature strip indicators: adjunct to clinical examination, Plast. Reconstr. Surg. 122 (2008) 144e–145e, https://doi.org/10.1097/PRS.0b013e318186caf3.

[99] R. Xie, Q. Liu, Y. Zhang, C. Guo, X. Huang, M. Liu, A wireless infrared thermometry device for postoperative flap monitoring: proof of concept in a porcine flap model, Int. Wound. J. (2022) 1–10, https://doi.org/10.1111/iwj.14034.

[100] J. Frija-Masson, J. Mullaert, E. Vidal-Petiot, N. Pons-Kerjean, M. Flamant, M.-P. D'Ortho, Accuracy of smart scales on weight and body composition: observational study, JMIR. Mhealth. Uhealth 9 (2021) e22487, https://doi.org/10.2196/22487.

[101] K. Islamoglu, E. Ozgentas, Monitoring of rat skin flap ischemia by bioelectrical impedance measurements, Ann. Plast. Surg. 47 (2001) 534–539, https://doi.org/10.1097/00000637-200111000-00011.

[102] J. Hauser, M. Lehnhardt, A. Daigeler, S. Langer, H.U. Steinau, P.M. Vogt, Photoplanimetric evaluation and impedance measurement of split-thickness skin grafts: a new model for objective wound-healing assessment in clinical trials, Skin Res. Technol. 15 (2009) 168–171, https://doi.org/10.1111/j.1600-0846.2008.00343.x.

[103] Y. Abe, I. Hashimoto, K. Goishi, K. Kashiwagi, M. Yamano, H. Nakanishi, Transcutaneous pCO_2 measurement at low temperature for reliable and continuous free flap monitoring, Plastic Reconstruc. Surg. Global Open 1 (2013) 1–8, https://doi.org/10.1097/GOX.0b013e3182936cd0.

[104] T. Nakano, T. Kudo, Y. Sano, H. Minehara, M. Suzuki, K. Aoki, T. Matsushita, Transcutaneous CO_2 pressure monitoring increases salvage rates after free tissue transplantation for extremity reconstruction, Plastic Reconstruc. Surg. Global Open 10 (2022) e4467, https://doi.org/10.1097/GOX.0000000000004467.

[105] C.M. Desmet, A. Lafosse, S. Vériter, P.E. Porporato, P. Sonveaux, D. Dufrane, P. Levêque, B. Gallez, D. Hinderberger, Application of electron paramagnetic resonance (EPR) oximetry to monitor oxygen in wounds in diabetic models, PLoS. ONE 10 (2015), e0144914, https://doi.org/10.1371/journal.pone.0144914.

[106] H. Bouwmeester, R.C. Schuurink, P.M. Bleeker, F. Schiestl, The role of volatiles in plant communication, The Plant J. 100 (2019) 892–907, https://doi.org/10.1111/tpj.14496.

[107] M. Singal, D. Vitale, L. Smith, Fragranced products and VOCs, Environ. Health. Perspect. 119 (2011) 200–202, https://doi.org/10.1289/ehp.1103497.

[108] K. Kubomura, R. Ogawa, N. Sasaki, S. Ichinose, S. Akaishi, H. Kuwahara, Objective odor assessment in patients with Osmidrosis, Plastic and Reconstructive Surgery Global Open 10 (2022) e4622. doi:10.1097/GOX.0000000000004622.

[109] M. Gallagher, C.J. Wysocki, J.J. Leyden, A.I. Spielman, X. Sun, G. Preti, Analyses of volatile organic compounds from human skin, British J. Dermatol. 159 (2008) 780–791, https://doi.org/10.1111/j.1365-2133.2008.08748.x.

[110] M.K. Wax, The role of the implantable doppler probe in free flap surgery, Laryngoscope 124 (2014) S1–S12, https://doi.org/10.1002/lary.24569.
[111] L. Heller, L.S. Levin, B. Klitzman, Laser doppler flowmeter monitoring of free-tissue transfers: blood flow in normal and complicated cases, Plast. Reconstr. Surg. 107 (2001) 1739–1745, https://doi.org/10.1097/00006534-200106000-00015.
[112] F.J. Paprottka, D. Klimas, N. Krezdorn, D. Schlarb, A.E.J. Trevatt, D. Hebebrand, Cook–Swartz doppler probe surveillance for free flaps—defining pros and cons, The Surg. J. 06 (2020) e42–e46, https://doi.org/10.1055/s-0040-1702922.