A Quantitative Method for Monitoring Wound Healing

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Abstract. Assessment and monitoring of chronic wounds is primarily based on visual inspection by medical professionals. The method is subjective and its reliability depends on the experience and assessment criteria of the evaluator. This may inflict problems in particular at home care where caretakers may not be wound care specialists. Wound dressings have to be removed for each assessment which may disturb the wound healing process. Additionally this increases both workload and costs, as the wound dressings are then changed without medical necessity. Our research group has developed a quantitative method for evaluation and monitoring the wound healing process. The method is based on differences in electrical conductivity of the wound and undamaged skin and is addressed using bioimpedance measurement. The results of this study indicate that the bioimpedance measurement based method is a promising tool for evaluating the status of a wound.

Keywords: Bioimpedance; Bipolar; Chronic; Healing; Monitoring; Skin; Status; Two-electrode; Wound

1. Introduction

The concept of a chronic wound is not unambiguously defined, however usually a wound that fails to heal within a few weeks or months is considered chronic [Shai and Maibach, 2005]. Chronic wound is often induced by a combination of an internal condition of the body and external trauma. Systemic factors such as diabetes, impaired vascular flow, obesity and aging expose to chronic wounds [Guo and DiPietro, 2010]. Diabetic, vascular and pressure ulcers are responsible for overwhelming majority of all chronic wounds [Mustoe, 2004]. Around 70% of leg ulcers are venous origin [Shai and Maibach, 2005]. It has been estimated that the prevalence of chronic wounds is 1-2% among the population in the developed countries. In the Scandinavian countries the costs associated to chronic wounds account for 2-4% of the total health care expenses. The burden is growing rapidly due to aging population and sharp rise in the incidence of diabetes and obesity. [Sen et al., 2009] A significant proportion of the costs is comprised of inpatient hospital days and wound care products [Sen et al., 2009; Seppänen and Hjerpe, 2008]. In addition to the costs, an individual chronic wound patient is exposed to a variety of psychosocial problems and physical disabilities [Grey et al., 2006].

Assessment of a chronic wound is often based on measuring the size and the depth of the wound and visual evaluation of the wound color [Grey et al., 2006]. Visual assessment is always influenced by a certain degree of subjectivity. Sometimes x-ray, magnetic resonance imaging (MRI) or other imaging methods are used for determining the structure of the wound, and also laboratory tests of exudate samples or biopsied tissue are performed [Paul et al., 2015; Dyson et al., 2003; Baraonski and Ayello, 2011]. These methods are fairly laborious and cannot be applied for daily assessment of healing of a wound. Additionally all these above mentioned methods require removal of the wound dressing.

There is a need for a quantitative at-line method to monitor the healing of chronic wounds while not disturbing the healing process and without necessity to remove the covering dressings. Bioimpedance measurement based assessment of wound healing may provide a solution to this monitoring problem.

Our research group has developed a method for determining the status of a wound. The method is based on an applied two-electrode bioimpedance measurement. In two-electrode bioimpedance
measurement a single electrode pair is used for both feeding the excitation current and measuring the induced voltage (Fig. 1). The output of two-electrode bioimpedance measurement basically consists of the electrode impedances of both electrodes, the electrode-skin interface impedances, the skin impedance under the electrodes and the tissue impedance between the two measurement electrodes [Grimnes and Martinsen, 2008]. The outer layers of skin provide very high impedance compared to underlying tissues. In Eq. 1 $Z_{\text{tot}}$ refers to measured total impedance, $Z_{\text{tissue}}$ to the tissue impedance including the skin impedance, $Z_{\text{EI1}}$ to electrode impedance of electrode 1 and $Z_{\text{EI2}}$ to electrode impedance of electrode 2. In Eq. 1 the electrode-skin interface impedance is included into the electrode-impedance.

$$Z(f)_{\text{tot}} = Z(f)_{\text{tissue}} + Z(f)_{\text{EI1}} + Z(f)_{\text{EI2}}$$  \hspace{1cm} (1)

**Figure 1.** Illustration of two-electrode measurement configuration and the formation of measurement output. Green layer under the electrodes refers to the skin impedance, which provides the largest contribution to $Z_{\text{tissue}}$, in particular at the low measurement frequencies.

## 2. Material and Methods

We conducted a one month bioimpedance spectroscopy follow-up of a superficial acute wound. The measurements were done utilizing a Solartron 1260A Frequency Response Analyzer and Solartron 1294A Impedance Interface and Ambu Blue Sensor BRS – hydrogel electrodes. Table 1 represents the summary of the study.

**Table 1. Summary of the study**

<table>
<thead>
<tr>
<th>Study and subject information</th>
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</thead>
<tbody>
<tr>
<td>Gender / Age</td>
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<tr>
<td>Wound type</td>
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<tr>
<td>Wound size</td>
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<tr>
<td>Duration of follow-up</td>
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<tr>
<td>Study equipment</td>
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<tr>
<td>Method and frequency range</td>
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The bioimpedance was measured using a two-electrode configuration. The wound impedance was measured with an electrode placed on the wound (W) and an electrode placed on the reference site located on the undamaged skin (H1) (Fig. 2 and Fig. 3). The wound impedance was compared to the reference impedance measured from the undamaged skin site adjacent to the wound (H1 and H2 electrodes in Fig. 2 and Fig. 3). The skin surrounding the wound was slightly swept with an antiseptic pad before the measurements. The wound status parameter was calculated according to Eq. 2.

$$Wound \ status \, \% = \left( \frac{Z(f_{1})_{W,H1} + Z(f_{2})_{W,H1} + \cdots + Z(f_{n})_{W,H1}}{Z(f_{1})_{H1,H2} + Z(f_{2})_{H1,H2} + \cdots + Z(f_{n})_{H1,H2}} \right) \times 100\%$$  \hspace{1cm} (2)
Figure 2. A descriptive figure representing the measurement setup. Wound impedance is measured with variety of excitation frequencies using electrodes W and H1 and the result is proportioned with the reference measurement taken from electrodes H1 and H2. Electrode Wx is additional electrode for measuring wound impedance using electrode W and Wx.

Figure 3. Photo of the electrode placement on the wound area according to Fig. 2. The wound is a superficial acute wound. The picture on the left was taken 1-2 days after the trauma.

3. Results

Fig. 4 represents the significant difference in the impedance of the open wound (day 4) and the completely healed wound (day 23). The electrodes were placed as shown in Fig. 2 and Fig. 3. The green graph refers to the impedance of undamaged skin measured using the electrodes H1 and H2. This measurement was used as a reference. The orange graph represents the impedance of the wound measured using electrodes H1 and W. The red graph depicts the impedance measured using the electrodes W and Wx, both electrodes were placed on the wound. The red graph is shown to illustrate the significant difference in impedance of wound and undamaged skin. The skin impedance can be tens or even hundreds of times higher than the wound impedance. The blue graph represents the electrode impedance of an electrode pair.

Figure 4. Impedance spectroscopy results of wound and undamaged skin. On day 4, the wound is open. On day 23, the wound is completely healed.
As shown in the Fig. 4 the wound impedance (H1 and W) on day 4 after the injury was approximately half of the reference impedance (H1 and H2) at 10 Hz (Fig. 4). On day 9 the wound had cleared to heal and the impedance of the wound reached the reference at the higher measurement frequencies, 1 kHz to 100 kHz. On day 23, the wound had completely healed and the wound impedance had reached and exceeded the reference impedance throughout the measurement range.

The table in Fig. 5 represents the wound status parameters calculated according to Eq. 2. Wound status is calculated for all measurement frequencies and for selected frequencies (2.5 kHz, 10 kHz and 40 kHz). Colour coding in the table ranges from red to green, low parameter value to high. The wound was photographed on each day of measurement and some of those photos are represented in the Fig. 5.

| Day 1 | 25.9% | 7.1% | 23.1% | ... | 110.5% | 109.7% | 109.0% | 108.4% | 107.9% | 107.3% |
| Day 2 | 32.0% | 8.4% | 28.7% | ... | 112.4% | 109.7% | 109.0% | 108.4% | 107.9% | 107.3% |
| Day 3 | 44.9% | 10.5% | 32.3% | ... | 114.5% | 111.8% | 111.1% | 110.5% | 109.9% | 109.3% |
| Day 4 | 69.7% | 15.5% | 45.6% | ... | 117.4% | 114.7% | 114.0% | 113.4% | 112.8% | 112.2% |
| Day 5 | 93.3% | 19.3% | 58.3% | ... | 119.3% | 116.6% | 116.0% | 115.4% | 114.8% | 114.2% |
| Day 6 | 115.6% | 22.3% | 71.6% | ... | 121.2% | 118.5% | 117.9% | 117.3% | 116.7% | 116.1% |
| Day 7 | 137.9% | 25.2% | 84.9% | ... | 123.0% | 120.3% | 119.7% | 119.1% | 118.5% | 117.9% |
| Day 8 | 159.2% | 28.0% | 98.2% | ... | 124.7% | 121.9% | 121.3% | 120.7% | 120.1% | 119.5% |
| Day 9 | 180.4% | 30.8% | 111.5% | ... | 126.4% | 123.7% | 123.1% | 122.5% | 121.9% | 121.3% |

**Figure 5.** Impedance spectroscopy results of wound in reference to undamaged skin. On day 1, the wound is open. On day 23, the wound is fully healed. On the left the impedance ratios of the wound impedance are reference impedance are calculated for each measurement frequency and then converted to a percentage number. The wound status parameters on the right are calculated according to the Eq. 2.

**4. Discussion**

The healing of a wound starts from the base as the granulation tissue forms. Gradually the edges of the wound begin to close in and eventually the wound is re-epithelized. [Shai and Maibach, 2005]. It is beneficial to not only monitor the spatial changes of the wound area but also the changes in the lateral direction.

Our proposal to evaluate the status of a wound is based on an applied two-electrode bioimpedance measurement. The two-electrode configuration represents so called “true impedance”, in which areas of negative sensitivity do not exist unlike in the other conventional bioimpedance measurement configurations. In two-electrode measurement the sensitivity is dictated by current density which peaks proximal to the electrode surfaces and decreases with distance from the electrodes. [Bronzino and Peterson, 2015; Grimnes and Martinsen, 2008; Martinsen and Grimmes, 2009b]

However, if excitation voltage and electrode dimensions are kept constant, there are at least two ways to affect the measurement depth. One is inter-electrode spacing and the other is measurement frequency [Grimnes and Martinsen, 2008]. Martinsen et al. 2009a investigated the effect of frequency to measurement depth in two-electrode configuration using a finite element model of the skin and electrodes. The study suggested that at a low frequency (less than 1 kHz) the Stratum Corneum, the dead cell layer of epidermis provides by far the largest contribution to the measured total impedance. The contribution seems to decline as the measurement frequency increases. This effect could be
explained using a simplistic and descriptive electrical equivalent of the skin and subcutaneous tissue. In the model the epidermis is represented using a parallel combination resistance and capacitance, the dermis and subcutaneous tissues are represented by a resistor [Birlea et al., 2014; Meziane et al., 2013]. According to this representation the epidermal layers provide a high frequency dependency in reference to the viable skin layers and subcutaneous tissue. At a low measurement frequency the impedance of tissue is mainly comprised of the impedance of epidermis. As the measurement frequency is increases, more current flows through the capacitive element of epidermis. Parallel combination of capacitive and resistive element results in a major decrease in the impedance of the epidermis. Frequency dependency of the dermis and subcutaneous tissue is much lower; therefore their relative contribution to the measured total impedance increases as the measurement frequency increases. Appropriate frequency selection may enable the monitoring of changes in electrical properties in tissue layers at different depths.

We measured the wound impedance by placing one electrode on the wound and the other on the undamaged skin. The electrode placed on the undamaged skin is shared by the skin impedance measurement, which is used as a reference. The mutual (H1) electrode binds the wound measurement and reference measurement together in a way that the mutual electrode creates an impedance baseline into the wound impedance measurement. The electrode setup decreases possibility of electrical short-circuit through highly conductive ionic wound exudate, which is typical for venous ulcers.

The results represented in Fig. 5 depict that the increase in the wound status parameters between day 5 and day 9 is primarily due increase of wound impedance at frequencies 1 kHz and above. After day 9 also frequencies below 1 kHz start to show significant increase. At the first two days of the follow-up the level of reference impedance at the lower measurement frequencies was observed as very small in comparison to the rest follow-up period. This has affected on the impedance ratios represented in Fig. 5 at the lower end of frequency range in the first two days. At the reference site the lowest measurement frequencies correspond mainly the superficial layers of epidermis. The stratum corneum layer of epidermis is volatile and fairly high daily variations may be observed due to constant reformation and exposure to external environment. To increase the reliability of the reference measurement it may be advisable to measure impedance at somewhat higher frequencies so that the contribution of stratum corneum layer is reduced and measurement depth is increased.

The well-known downside of the two-electrode configuration is that the measurement results also include the impedance originating from the electrodes and leads. Because of this high and even quality electrodes should be used and the effect of the electrode impedance minimized or controlled. In most cases it is also impossible to make a distinction between electrode impedance and tissue impedance [Brown et al., 2000]. Despite of this the total electrode-impedance can be easily measured by connecting electrodes face-to-face. We did measure the electrode-impedance of the Ambu Blue Sensor BRS electrodes and the electrode-impedance was at the same level as the impedance measured using the wound electrode W and Wx at the first day of follow up. The level of electrode-impedance (Fig. 4) was such low in comparison to the results of the skin measurement or wound measurement using H1 and W electrodes, especially at lower frequencies, that we did not perceive it as seriously detrimental to the results. The higher the measurement frequency is, the larger the relative effect of electrode-impedance seems to be. If the electrode impedance is proven to have an adverse effect on the results, a simple subtraction might be enough to overcome this problem.

5. Conclusions

The developed bioimpedance based method is an auspicious tool for quantitative evaluation of the status of a wound. The follow-up of the superficial wound did show that the applied two-electrode method is suitable for wound monitoring. The results also indicated that frequency selection may have a role in detecting of early changes in the wound base. In the future more and different types of wounds should be monitored using the method.

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