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REACTIVE HYPEREMIA RESPONSE AND ULTRASONOGRAPHIC FEATURES IN DETERMINING TISSUE RECOVERY IN RATS

YAPP JONG HENG

FK 2018 70

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By

YAPP JONG HENG

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

July 2018

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

REACTIVE HYPEREMIA RESPONSE AND ULTRASONOGRAPHIC FEATURES IN DETERMINING TISSUE RECOVERY IN RATS

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July 2018

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Faculty : Engineering

Frequent repositioning of patient is important to relief pressure and correct damages on skin areas induced by pressure in order to avoid pressure ulcer (PU) development. Prolonging the recovery time for pressure relief may be beneficial but the amount of recovery time is unknown and worth investigating. In this study, the relationship between different recovery time and weight-bearing tissue conditions subjected to repetitive loading is investigated through histopathology examination in animal model using Sprague-Dawley rats. Furthermore, the effect of different recovery times on non-invasive PU indicators using peak reactive hyperemia (RH) trend and ultrasonographic (US) features are investigated. The hypothesis being tested is that different recovery time that simulates insufficient and sufficient recovery time could affect the RH trend and US feature. This study also compares the peak RH trends and US features with the tissue condition under histopathological examination to determine the potential use of these features in determining the adequate amount of recovery time of weight-bearing tissue in rats non-invasively.

Twenty-one male Sprague-Dawley rats (seven per group), with body weight of 385-485g, were categorised into three groups and subjected to different recovery times, each with three repetitive loading cycles at skin tissues above of right trochanter area. The first, second, and third groups were subjected to short (3 min), moderate (10 min), and prolonged (40 min) recovery, respectively, while applying fixed loading time and pressure (10 min and 50 mmHg, respectively). Peak RH was measured during the three cycles to determine RH trend (increasing, decreasing, and inconsistent). All rat tissues at the trochanter area were evaluated using ultrasound at pre- and post-experiment and rated by two raters to categorise the severity of tissue changes (no, mild, moderate, and severe change). The tissue condition was also evaluated using histopathological examination to distinguish between normal and abnormal tissues.

It was found that as the recovery time increases (3 min vs. 10 min vs. 40 min), the number of samples with normal tissue (43% vs. 43% vs. 100.00%) and inconsistent RH response trend (29% vs. 57% vs. 72%) also increases. In addition, as the recovery time decreases (40 min vs. 10 min vs. 3 min), there is an increased number of samples with abnormal tissue (0% vs. 57% vs. 57%) and increasing RH response trend (14% vs. 29% vs. 57%). Subsequently, most of the samples with increasing RH trend is related to abnormal tissue (71%); while inconsistent RH trends is more related to normal tissue (82%). However, the recovery time has no effect to the tissue condition evaluated under ultrasonographic. Moreover, there is no relationship between the tissue conditions evaluated under ultrasonographic and histopathological examination.

The results suggest that different recovery times affect the tissue condition and RH response trend during repetitive loading. In addition, RH trend over repetitive loading may serve as a new feature for determining tissue condition that leading to pressure ulcer. This animal study may be extended to human studies in the future.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

HYPEREMIA REAKTIF DAN CIRI-CIRI ULTRASONOGRAFI DALAM MENENTUKAN PEMULIHAN TISU TIKUS

Oleh

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Kekerapan mengangkat dan mengalihkan kedudukan pesakit adalah penting untuk memulihkan kawasan kulit yang cedera daripada tertekan supaya tekanan ulser boleh dicegah. Memanjangkan masa pemulihan untuk kawasan kulit tertekan mungkin berfaedah, manakala masa untuk penuh pemulihan adalah kurang dipahami dan patut dikaji. Oleh sebab itu, hubungan antara masa pemulihan yang berbeza terhadap keadaan kulit tertekan semasa tekanan berulang telah dikaji dalam penyelidikan ini dengan menggunakan pemeriksaan histopatologi terhadap jenis tikus Sprague-Dawley. Di samping itu, kesan masa pemulihan yang berbeza semasa takanan berulang terhadap ujian penunjuk tekanan ulser bukan jenis invasif seperti trend hyperemia reaktif (RH) dan ciri-ciri ultrasonografi (US) juga dikaji dalam penyelidikan ini. Hipotesis yang diuji adalah masa pemulihan yang berbeza untuk mensimulasikan masa pemulihan yang tidak mencukupi dan mencukupi boleh memberi kesan terhadap trend RH dan ciri-ciri US. Tambahan pula, puncak trend RH dan ciri-ciri US juga dibandingkan dengan keadaan tisu yang diperiksa melalui ujian histopathology untuk menentukan potensi ujian-ujian penunjuk tersebut dalam menentukan masa pemulihan yang mencukupi untuk kawasan kulit tertekan daripada tikus secara tidak invasif.

Sebanyak dua puluh satu tikus jantan jenis Sprague-Dawley (tujuh tikus bagi setiap kumpulan) dengan berat badan 385-485g telah dikategorikan kepada tiga kumpulan. Setiap kumpulan diberi tiga tekanan berulang terhadap kawasan kulit *trochanter* kanan dengan masa pemulihan yang berbeza. Masa pemulihan untuk kumpulan-kumpulan tersebut adalah masa pendek (3 min) untuk kumpulan pertama, masa sederhana (10 min) untuk kumpulan kedua, dan masa panjang (40 min) untuk kumpulan ketiga. Manakala, masa (10 min) dan magnitud tekanan (50 mmHg) adalah tetap bagi semua kumpulan. Puncak RH semasa tiga tekanan berulang telah direkod untuk menentukan trend RH (meningkat, menuran, dan tidak konsisten). Semua

kawasan tisu di *trochanter* kanan bagi pra- dan pasca-eksperimen diimbas dengan diagnostik ultrasound dan dinilai oleh dua ahli radiologi untuk mengkategorikan keterukan perubahan tisu (tiada, ringan, sederhana, atau perubahan teruk). Di samping itu, kawasan tisu tertekan juga dinilai dengan analisis gambaran histopatologi untuk membezakan sama ada keadaan tisu sihat atau cedera.

Keputusan kajian menunjukan bahawa memanjangkan masa pemulihan (3 min *vs.* 10 min *vs.* 40 min) menambah bilangan subjek dengan keadaan tisu sihat (43% vs. 43% vs. 100%) dan trend RH tidak konsisten (29% vs. 57% vs. 72%). Di samping itu, memendekkan masa pemulihan (40 min *vs.* 10 min *vs.* 3 min) menambah bilangan subjek dengan keadaan tisu cedera (0% vs. 57% vs. 57%) dan trend RH meningkat (14% vs. 29% vs. 57%). Di samping itu, subjek dengan trend RH meningkat adalah lebih berkaitan dengan tisu cedera (71%), manakala trend RH tidak konsisten adalah lebih berkaitan dengan tisu sihat (82%). Manakala, masa pemulihan yang berbeza tidak memberi keberkesanan terhadap tisu diimbas dengan diagnostik ultrasound. Selain itu, tiada perbezaan antara kategori perubahan tisu hasil imbasan ultrasound terhadap keadaan tisu hasil pemeriksaan histopathologi.

Kajian menunjukan masa pemulihan yang berbeza memberi kesan terhadap keadaan tisu dan trend RH semasa tekanan berulang. Selain itu, trend RH dalam tekanan berulang berpotensi untuk berfungsi sebagai penunjuk baru untuk menentukan keadaan kulit tekanan yang berisiko tekanan ulser. Kajian haiwan ini boleh dilanjutkan kepada model manusia pada masa hadapan.

ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude to my advisor Assoc. Prof. Ir. Dr. Raja Mohd Kamil bin Raja Ahmad for the continuous support of my PhD study. I thank him for his kindness, motivation and patient guidance to my research in all the time and writing of this thesis. I appreciate all his contributions of time and ideas to teach me how good experimental and administrative are done.

I would also like to thank to the rest of my thesis committee: Prof. Datin Dr. Rozi binti Mahmud, Prof. Dr. Md. Zuki bin Abu Bakar, Assoc. Prof. Dr. Siti Anom binti Ahmad, Assoc. Prof. Dr. Norhafizah binti Mohtarrudin, Dr. Loqman Mohamad Yusof, and Dr. Ezamin bin Abdul Rahim, for their insightful comments and encouragement. I thank all of them for their profession in helping my research that has multiple aspects related with electrical and electronics, animal use, US assessment, and histopathology examination. I believe that I am tremendously fortunate to have worked with such a professional and great team.

Last but not the least, a special thanks to my family for supporting me spiritually and financially throughout my PhD life and writing this thesis.

I certify that a Thesis Examination Committee has met on 16 July 2018 to conduct the final examination of Yapp Jong Heng on his thesis entitled "Reactive Hyperemia Response and Ultrasonographic Features in Determining Tissue Recovery in Rats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

PU	Pressure ulcer
RH	Reactive hyperemia
US	Ultrasonographic
HE	Histopathological examination
NI	National Instrument
NPUAP	National PU Advisory Panel
EPUAP	European PU Advisory Panel
LDF	Laser Doppler Flowmetry
PID	Proportional-integral-derivative

GLOSSARY OF TERMS

Endothelium An exceedingly thin single sheet of endothelial cells lining the inner wall of arteries and veins, while capillaries have walls that are only one endothelial cell in thickness (Alberts et al., 2014; Alberts et al., 2002; Chabner, 2013), as shown in Figure 1

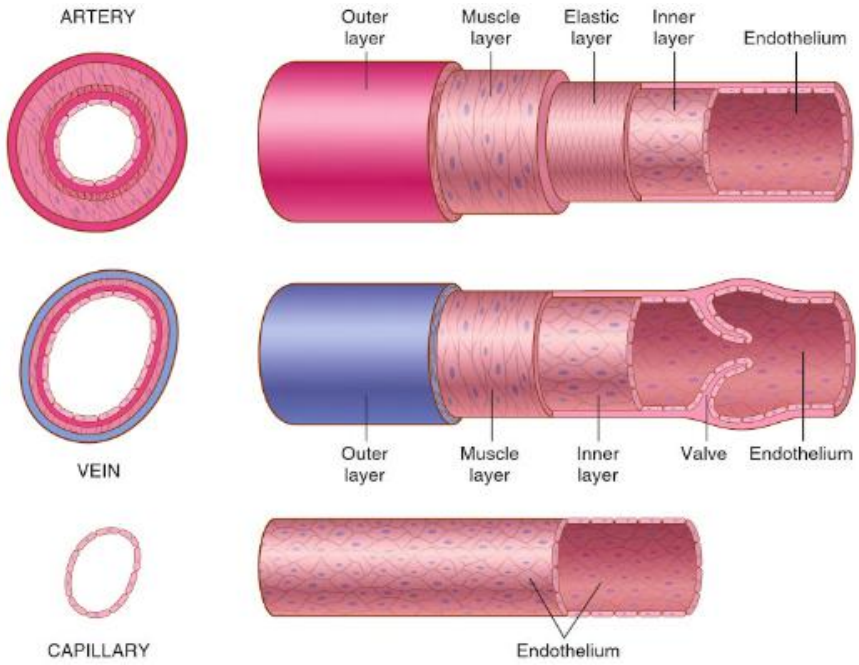

Figure 1 : Blood vessels lined with endothelium
(Source: Chabner, 2013)

Vasodilator An agent that causes vasodilation, such as a nerve or hormone, that widens the blood vessels, which in turn decreases resistance to blood flow and lowers blood pressure (Fundukian, 2011; Soto, 2015)

CHAPTER 1

INTRODUCTION

Pressure ulcer (PU) is an area of localised tissue breakdown due to pressure and/or shear force sustained (Porter-Armstrong et al., 2018; Yarkony, 1994), causing prolonged tissue ischemia (lack of blood supply) (Jan et al., 2010; Liao, Burns, et al., 2013) which results in ulceration. The development of PU can also be accelerated with increasing temperature (Kokate et al., 1995; Romanelli et al., 2018) or moisture on skin (Kanj et al., 1998; Niezgoda et al., 2006; Romanelli et al., 2018; Thomas, 2006). PU can occur when subjects are bedridden, or wearing a poorly fitted medical devices, prosthesis or orthosis (Bouten et al., 2003; Boyko et al., 2018). They are more commonly developed once spinal-cord patients become wheelchair-bound and the risk remains high throughout their lifetime (Bhattacharya et al., 2015; Boyko et al., 2018; Krause et al., 2004; Raghavan et al., 2003; Salzberg et al., 1998; Sonenblum et al., 2011; Vidal et al., 1991). PU is a life-threatening complication due to breakdown tissue interacting with the external environment resulting in fatal septic infection. Therefore, the mortality rate of patients is increased compare with other conditions in hospital (9.1 - 11.6% death with PUs vs. 1.8 - 2.6% death for other conditions) (Bauer et al., 2016; Russo et al., 2008). It is also reported that the presence of PU in the patient has nearly three-fold increase in in-hospital death risk (Bo et al., 2003; Clough, 1994; Raju et al., 2015; Thomas et al., 1996). The ulcers could results in longer hospital stay (Chetter et al., 2016) with an additional 8.2 to 42 days (New et al., 2004; Whitty et al., 2017) or approximately three times longer (Gill, 2015; Russo et al., 2008) than those patients without PU. Additional care cost is needed to prevent further deterioration (costs US health care system $9.1 billion to $11.6 billion per year (Bauer et al., 2016), and costs National Health Service (NHS) in UK at between £1.4 billion and £2.1 billion, annually (Baillie, 2014; Dealey et al., 2012)). PUs can be developed at any parts of the body like the sacrum, heel, and buttock (Clark et al., 2017; Reger et al., 2009).

An effective protocol for PUs prevention is therefore needed to reduce the heavy burden on society caused by PUs. Repositioning the patients for at least every two hours is the gold standard (Gill, 2015; Lyder et al., 2008) to relieve prolonged pressure exerted on skin tissues repetitively for PUs prevention. In addition, special support surface is used to prevent skin breakdown by changing or redistributing pressure exerted on skin to restore and/or promote blood perfusion at underlying skin. However, from a survey, only 57 percent of respondents agreed on the effectiveness of the 2 hours repositioning in their intensive care units and remain at high risk of PU development (Latimer et al., 2015; Lyder et al., 2008), and using a different support surface with different repositioning frequencies does not influence the incidence of early PU (stage I) (Defloor et al., 2005; Yap et al., 2018).

Personalizing the repositioning interval has also been suggested to relieve the pressure on the skin for a sufficient amount of time and may alleviate the development of PU (Barnett et al., 1995; Pickham et al., 2016). In estimating an optimal body repositioning interval, the full tissue recovery time must be investigated. In order to know the full tissue recovery time, the tissue condition of an individual with applied recovery time must be evaluated in-vivo and non-invasive evaluation method is the only options for patient.

Reactive hyperemia (RH) response and ultrasonographic (US) features have been suggested as suitable features to identify people at risk of PU non-invasively (Liao, Burns, et al., 2013; Lucas et al., 2014). Previous skin blood flow and PU studies found that the degree of RH is related to the degree of ischemic event (a restriction in blood supply to tissues), and proportional to the pressure magnitude (Lachenbruch et al., 2015; Manorama et al., 2010), loading duration (Liao, Burns, et al., 2013; Matsubara et al., 1998; Thorfinn et al., 2007; Thorfinn et al., 2006), and increased temperature (Lachenbruch et al., 2015; Tzen et al., 2010). Studies related to early detection of PU using US features shows that the patients with at risk of PUs may be presented with oedema (Schäfer et al., 2015), distorted layered structure (Schäfer et al., 2015) and increased dermal and hypodermal thickness (Grap et al., 2015) that are considered as features of tissue changes induced by pressure (Schäfer et al., 2015) associated with inflammation (Grap et al., 2015).

1.1 Problem statements

The incidences of PU still exist even with two hours body repositioning and/or applying special support surface to relieve the pressure (Defloor et al., 2005; Latimer et al., 2015; Lyder et al., 2008; Salisbury, 1985). Reactive hyperemia response occurred after pressure relief could allow tissue prevented and recovered from pressure-induced ischemia (Jan, Liao, Rice, et al., 2013; Thorfinn et al., 2007). Therefore, pressure relief with sufficient recovery time can probably prevent pressure ulcer by fully reversing the tissue damages induced on weight-bearing tissues. The problem is how much recovery time is sufficient? This problem is investigated here.

Furthermore, the existing prevention approaches may not be sufficient for all individuals due to individual characteristics and tolerance for pressure (Braden et al., 2000; Coleman et al., 2014). Both individual susceptibility and local tolerance for pressure are affected by the conditions of individual such as health status and exposure to risk factors (Coleman et al., 2014). This results in varying development time of pressure ulcers between subjects. Therefore, individualised PU prevention method (Barnett et al., 1995; Källman, 2015; Kwong et al., 2016) is essential to alleviate the PU development. An effective protocol for determining tissue condition is therefore needed to indicate the effectiveness of prevention strategy that applied on the individual. The problem is how to determine the weight-bearing tissues condition accurately and non-invasively. The RH trend and US features that can be potentially used in determining weight bearing tissue condition non-invasively need to be

validated with histopathological examination and is addressed in this prospective study.

1.2 Hypothesis

The following hypotheses are tested:

I. Different recovery time during repetitive loading can affects the tissue condition and response.

   a. Short recovery time gives insufficient tissue recovery during repetitive loading and is presented as abnormal tissue under histopathological examination; while prolonged recovery time can promote tissue recovery and presented as normal tissue.
   b. Peak RH increases from cycle to cycle of repetitive loading with short recovery time, and the peak does not increase with prolonged recovery time.
   c. US assessment detects severe tissue changes induced by repetitive loading with short recovery time; while no/mild tissue changes with prolonged recovery time.

II. Peak RH trend and US features can be used to indicate tissue condition non-invasively.

   a. Peak RH increases from cycle to cycle of repetitive loading indicates accumulation of ischemic event at weight-bearing tissue and the tissue is in abnormal condition under histopathological examination; and the peak RH with non-increases from cycle to cycle is in normal condition under histopathological examination.
   b. No tissue changes under US assessment has normal tissue condition under histopathological examination; while mild to severe tissue changes under US assessment has abnormal tissue condition under histopathological examination.

1.3 Aim and objectives

The aim of this study is to investigate the possibility of using certain features (RH trends and US features) measured using non-invasive modalities in determining sufficient recovery time and the condition of weight-bearing tissue of rat during repetitive loading. Firstly, the tissue condition under histopathology (for validating the effect of different recovery time), RH response trend and US feature changes were

investigated with different recovery time that simulate sufficient and insufficient recovery time during repetitive loading. Secondly, the tissue condition with RH response trends and US feature changes were examined using histopathology study.

The objectives of this study are listed below.

1. To establish a relationship between tissue recovery time and tissue condition examined under histopathology.
2. To establish a relationship between tissue recovery time and RH trend.
3. To establish a relationship between tissue recovery time and US feature changes.
4. To establish a relationship between RH trends and tissue condition examined under histopathology.
5. To establish a relationship between US features and tissue condition examined under histopathology.

1.4 Project scope

In this project a pressure control system that applies repetitive loading on the skin of anaesthetised rats is developed. The repetitive loading is able to restrict and restore blood perfusion at underlying skin to induce ischemic-reperfusion event that simulates the loading and recovery condition on the skin of bedridden patients with interval repositioning. This prospective study employed 21 rats (seven rats per group); as such, the findings are derived from a limited population size to explore the effects of recovery time on tissue condition, RH trend, and US features during repetitive loading. Nevertheless, the number of samples in this study (n = 21 rats divided into three groups) is bigger than previous related PU studies (Anke Stekelenburg et al., 2007: 10 Brown-Norway rats divided into three groups; Herrman *et al.*, 1999: 7 fuzzy rats; Sari *et al.*, 2008: 8 rats divided into three groups). Inducing pressure on human subject with unknown effect and histopathology examination could lead to tissue damage and will violate ethics consideration. This strengthen the reason of using animal model to test the hypothesis stated in this study. Once the hypothesis is proven, transitioning to human study is possible to validate the findings in this study on human subject.

Three recovery times (prolonged-40 min, moderate-10 min, and short-3 min) during repetitive loading was applied on the skin of 21 male rats to simulate sufficient and insufficient recovery time for the weight-bearing tissues in reversing the damages induced by repetitive loading. The scope of this implementation is related to preventative interventions for early PU from the aspect of pressure relief during recovery time, with the use of RH trends (peak RH) and US featured to detect changes (presence of oedema, distorted layered structure, and increased dermal and hypodermal thickness) measured using laser Doppler perfusion and ultrasound, respectively. The project investigates the effects of different recovery time on tissue condition, RH trends, and US feature changes. The investigations were performed to

determine the relationship of different recovery time in term of tissue condition and responses. Besides, the potential features used for estimating optimal tissue recovery time non-invasively can be determined.

Furthermore, the potential features were also related with tissue condition examined using histopathology study to determine the use of the features in determining tissue condition non-invasively.

1.5 Research significance

This study enhanced the understanding of PU by establishing the relationship between weight-bearing tissue and different recovery time during repetitive loading. Findings from this study supports the use of recovery time in preventing weight-bearing tissue approaches to early stage of PU. In addition, this study investigates the prospect of using RH response trends and/or US features for determining condition of weight-bearing tissues of an individual during repetitive loading. The RH response trend and/or US features that are associated with the tissue condition examined under histopathology should be further included into clinical protocol as a diagnostic strategy in determining tissue condition non-invasively. Furthermore, this study may contribute towards the development of PU preventive strategy in the aspect of achieving optimal recovery time during repetitive loading. Findings from this study may assist in future design of clinical protocol, e.g. achieve optimal body repositioning time interval or optimal time of alternating pressure on air mattress, using the features (RH trend and/or US features) to prevent the development of PU.

1.6 Thesis outline

This thesis is divided into five chapters consisting of thorough details of the study.

Chapter 1 provides the research background, existing problems to carry out this thesis, aims and objectives to accomplish this work, project scopes and research significance.

Chapter 2 covers a comprehensive review on PU, and the detection and prevention methods of PU development. In recent research, the RH and US features were introduced to have the benefits go further in preventing PU by determining the optimal recovery time and tissue condition of an individual.

Chapter 3 describes the methodology of the research. In this chapter the number and type of subject, measurement equipment, measurement considerations, and data collection protocol are detailed.

Chapter 4 shows the results of RH trend, US feature, and histopathology examination that induced by the three different recovery times. The RH trend and US feature are compared with the tissue condition based histopathology examination to determine the potential use of these features in determining weight-bearing tissues condition.

Chapter 5 discusses the results. The potential and limitation of the features in responding recovery time and determining tissue condition were presented to determine their potential use in preventing PU.

Chapter 6 presents the major findings of the study. Future work and recommendations are also highlighted in this chapter.

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