Effect of alternating pressure overlay on weight bearing tissue tolerance in people with SCI

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LIST OF ABBREVIATIONS

AIS	American Spinal Injury Association Impairment Scale
AP	Alternating Pressure
ASIA	American Spinal Injury Association
ATP	Adenosine Tri Phosphate
CTRL	Control
FDA	Food and Drug Administration
HH	Heat Hyperemic
IRB	Institutional Review Board
ISCOS	International Spinal Cord Society
LDF	Laser Doppler Flowmetry
OR	Operation Room
PI	Principal Investigator
RH	Reactive Hyperemic
ROM	Range Of Motion
SBF	Skin Blood Flow
SCI	Spinal Cord Injury
STFT	Short Time Fourier Transform
WLRS	White Light Reflectance Spectroscopy

1.0 Project Summary/Abstract

Tissue ischemia (lack of blood flow) is one of the main causes of pressure injury. It is inevitable during bed-ridden condition or prolonged surgery procedure in the operating room. Previous studies demonstrated that the protective mechanisms of alternating pressure (AP) on pressure injury include redistribution of surface pressure, and allowing more blood supplies while lying on the support surface. The Dabir AP overlay is low profile yet possesses similar characteristics as other AP mattresses on the market. The objective of this study is to evaluate the protective mechanisms of Dabir AP overlay on weight bearing tissue of people with chronic spinal cord injury (SCI). Our central hypothesis is that the Dabir AP overlay will cause lower amount of interface pressure and allow more skin blood flow during weight bearing as compared to regular operation room (OR) overlay. In addition, people with SCI will have better tolerance to prolonged weight bearing after preconditioned with the Dabir AP overlay. This study will be repeated measures design, with subjects acting as their own control. Fifteen adults with chronic SCI will be recruited from the Greater Chicago area. Each subject will undergo two study protocols: lying on AP overlay followed by OR overlay (40 minutes each), and lying on OR overlay for 40 minutes only. Laser Doppler flowmetry system will be used to collect data before during and after lying on the overlays, and pressure mapping system will be used to measure interface pressure. Paired *t*-tests will be computed to compare the interface pressure and skin blood flow before, during and after lying on the overlays. Findings of this study will help determine the effectiveness of the Dabir AP overlay on pressure redistribution and ischemia preconditioning.

2.0 Background/Scientific Rationale

Tissue ischemia is one of the main etiologies of pressure injury.[1] It is inevitable during bed-ridden and wheelchair bound conditions, such as spinal cord injury (SCI), or prolonged surgery procedure in the operating room. Active alternating pressure (AP) mattresses are covered by Medicare policy for patients with multiple/large stage 2/ stage 3 pressure injuries to relief interface pressure and prevent recurrence of pressure injuries.[2] Previous studies demonstrated that the protective mechanisms of AP on pressure injury include redistribution of surface pressure, and allowing more blood supplies while lying on the support surface.[3–5] The Dabir AP overlay (DabirAIR™, Dabir Surfaces Inc., Hardwood Heights, IL) is low profile yet possesses similar characteristics as other AP mattresses on the market; it is intended for clinical use, such as operation room (OR) where AP mattresses may not be an option. We expect Dabir AP overlay will be beneficial to people at risk of pressure injury by maintaining the blood supply during weight bearing condition.

In addition to pressure redistribution and increasing blood supplies, we also postulate that the if an AP overlay will be beneficial to the weight-bearing skin by means of preconditioning the skin with short-term ischemia, i.e. when air cells inflate. Ischemic preconditioning is a method used to prevent tissue damage caused by ischemic events, such as stroke and myocardial infarction,[6] by means of slowing down ATP depletion in the short-term subsequent ischemic episodes and washing out the harmful catabolites during each short-term period of reperfusion. Recently, this method is implemented to heal diabetic foot ulcer by remotely precondition the lower limb.[7] We hypothesize that the alternating pressure characteristics of the Dabir AP overlay could be utilized as a method for preconditioning to protect weight-bearing tissue in people with SCI.

To quantify the severity of tissue ischemia, we will collect the non-invasive reactive hyperemic response as an outcome. Reactive hyperemia is characterized by sudden increase in blood flow after temporary obstruction of the blood flow. Previous studies used this response to simulate the tissue response toward ischemia in people that are at risk of pressure ulcer, such as spinal cord injury.[8,9]

People with SCI are at extremely high risk of pressure ulcer formation due to immobility and lack of sensation. In addition, this population may also have underlying change in vascular control mechanisms. To further quantify the vascular control mechanisms in our participants, we plan to use two additional protocols to provide objective measurements of blood supplies. The two non-invasive measurements are heat hyperemia and skin vasomotor response.

Heat hyperemia is an objective and non-invasive method to quantify the degree of impaired thermoregulation. It is characterized by a biphasic pattern with an initial peak (initiated by activity of sensory nerves and modulated by sympathetic nerves), followed by a brief nadir and a plateau phase (mediated by local production of endothelial nitric oxide).[8] A previous study showed that the initial peak was diminished significantly at skin sites below level of injury in patients with complete SCI.[9] Given that increased skin temperature is a well-proven risk factor in ulcer formation in addition to prolonged pressure,[10] adopting measurement of thermoregulatory function may assist in understanding the pathological patterns related to ulcer formation.

Skin vasomotor response is a reduction in SBF induced by standardized cutaneous electrical stimulation. It is an objective method to assess the integrity of sympathetic pathways,[11] and it is a sensitive tool in identifying sympathetic function below a spinal cord lesion.[12] Measurement of the skin vasomotor response may provide us a comprehensive understanding of the changes in control mechanisms with the pathological pattern in SBF detected before ulcer formation.

By comparing the skin blood flow responses between using Dabir AP overlay vs. standard OR overlay, we might be able to fill the gap of current research by determining the potential benefit of Dabir AP overlay on pressure ulcer prevention.

3.0 Objectives/Aims

The objective of this study is to evaluate the protective mechanisms of Dabir AP overlay on weight bearing tissue of people with chronic spinal cord injury (SCI). Our central hypothesis is that the Dabir AP overlay will cause lower amount of interface pressure and allow more skin blood flow during weight bearing as compared to regular OR overlay. In addition, people with SCI will have better tolerance to prolonged weight bearing after preconditioned with the Dabir AP overlay.

There are three aims (with related hypotheses) for this study:

Aim 1: To determine the effectiveness of pressure redistribution with Dabir AP overlay.

Hypothesis 1. Our participants will demonstrate lower interface pressure at sacrum and heel when lying supine for 40 minutes on Dabir AP overlay as compared to that on regular OR overlay (AliMed®).

Aim 2: To examine the severity of tissue ischemia with the use of Dabir AP overlay.

Hypothesis 2a. Our participants will demonstrate greater skin blood flow at sacrum and heel when lying supine for 40 minutes on Dabir AP overlay as compared to that on regular OR overlay.
Hypothesis 1b. Our participants will demonstrate smaller reactive hyperemic response at sacrum and heel after being relieved from 40 minutes of lying supine on Dabir AP overlay as compared to that on regular OR overlay.

Aim 3: To assess the feasibility of utilizing Dabir AP overlay for ischemic preconditioning for prolonged weight bearing condition.
Hypothesis 3. With 40 minutes of preconditioning using the Dabir AP overlay, our participants will demonstrate smaller reactive hyperemic response at sacrum and heel after being relieved from the regular OR overlay as compared to that without preconditioning.

4.0 Eligibility

Twenty people with chronic SCI will be recruited from the Greater Chicago area. The eligibility of the subjects will be determined by the study team based on the following criteria.

4.1 Inclusion Criteria

- Males and females 18-64 years old
- have had spinal cord injury for more than one year
- have injury level at T10 or above
- not ambulatory and use a wheelchair for mobility
- non smokers or able to refrain from smoking four hours prior to and during the study

4.2 Exclusion Criteria

- current pressure ulcer
- history of diabetes mellitus
- history of cardiovascular diseases
- history of hypertension
- history of pulmonary diseases
- pregnant women (based on screening and pregnancy testing)
- non-English speakers

4.3 Excluded or Vulnerable Populations

No vulnerable population will be included in the study. Since all key investigators are fluent only in English language, non-English speaking subjects will not be included.

5.0 Subject Enrollment

Subjects will be eligible to participate in this study if they meet the study criteria as determined by the telephone screening and face-to-face screening procedures.

Telephone Screening Procedure (approximately 15 minutes)

Subjects will be recruited from the Greater Chicago area through study flyers. The PI or key personnel will recruit the eligible subjects when potential subjects call in response to the flyer. Questions regarding the inclusion and exclusion criteria will be asked to determine the eligibility based on the telephone screening script. Results of the telephone screening will be documented in Forms A, B, C1, C2, and D. If the potential subject is not eligible, results and confidential information will be destroyed immediately. All potential subjects will be scheduled to a study visit at the UIC Applied Health Sciences Building room 272 for further screening. Subjects will be asked to fast and refrain from smoking four hours prior to and during the study, and refrain from consuming any caffeinated foods/drinks for 12 hours prior to the study.

Face-to-face Screening Procedure (approximately 30 minutes)

Upon arrival for the study visit, the PI or key personnel will inform the potential subject of the study procedures and risks and benefits of the study. A consent form with details of all procedures, risks and benefits will be provided to the potential subject. Once the PI or key personnel receive the signed consent form, the subject will proceed to face-to-face screening. During the face-to-face screening procedure, the PI or key personnel will measure the resting heart rate and blood pressure with heart rate monitor and blood pressure cuff respectively and documented in form E1. The PI or key personnel will also examine the remaining motor function, sensation and autonomic function after spinal cord injury. The remaining sensation, motor, and autonomic function are standard physical examination for people with SCI in the clinic. The remaining sensation will be tested with the key personnel performing light touch of the skin below the level of injury (as the picture shown in form E2), and the motor function will be tested with the key personnel instructing subject to perform joint movement below the level of injury. Results of the remaining sensation and motor function will be documented in form E2. The autonomic function will be tested by asking subject questions regarding their ability to sweat, ability to sense the changes in temperature, bladder function, bowel movement and sexual function, and results will be documented in form E3. If the subject demonstrates normal heart rate and blood pressure, the subject will proceed with the study procedures. Women of childbearing age will also be screened for pregnancy using a urine pregnancy test strip. Women who are pregnant will not be eligible to participate.

6.0 Study Design and Procedures

Study Design. This study uses a repeated measures design, and each subject will act as his/her own control. Each subject will undergo the two protocols in the experimental procedures: AP protocol and Control protocol. To ensure the order of the two protocols are randomized, the order of AP and Control protocols will be determined by drawing one envelope from the envelope pool. We will start with a pool of total 20 envelopes (10 envelopes indicating AP protocol first, and 10 envelopes indicating control protocol first). Once the envelope is drawn from the pool, it will not return to the pool.

Study Procedures (Research purpose). After enrollment, subjects will proceed to the following procedures: 1) experimental procedures, 2) vascular control measures, 3) pressure mapping of wheelchair and 4) blood withdraw.

1) Experimental procedure (approximately 4.5 hours)

Each subject will undergo two study protocols: AP and control (figure 1), and the order of the protocols will be randomized as described previously. A 30-minute washout period will be provided in between the two protocols. Two Laser Doppler flowmetry (LDF) flat probes (moor instrument, Wilmington, DE) will be taped to the sacrum and one heel to collect the skin blood flow response throughout both AP and control protocols. A whole body pressure mapping system (Xsensor, Xsensor Technology Corp., Alberta, Canada) will be used between the subject and the overlay to collect the inter pressure data. For the AP cycle, we will use four 10-minute cycles (5 minutes of high pressure and 5 minutes of low pressure).

AP protocol: The subject will first lie on his/her side quietly for 10 minutes to collect the baseline skin blood flow, followed by lying supine on the Dabir AP overlay for 40 minutes, and then side lying for 30 minutes to collect the first reactive hyperemic response. To test the effect of preconditioning, the subject will then lie supine on the OR overlay for 40 minutes followed by side lying for 30 minutes for the second reactive hyperemic response.

Control protocol: The subject will first lie on his/her side quietly for 10 minutes to collect the baseline skin blood flow, followed by lying supine on the OR overlay (AliMed®) for 40 minutes, and then side lying for 30 minutes to collect the reactive hyperemic response for control protocol.

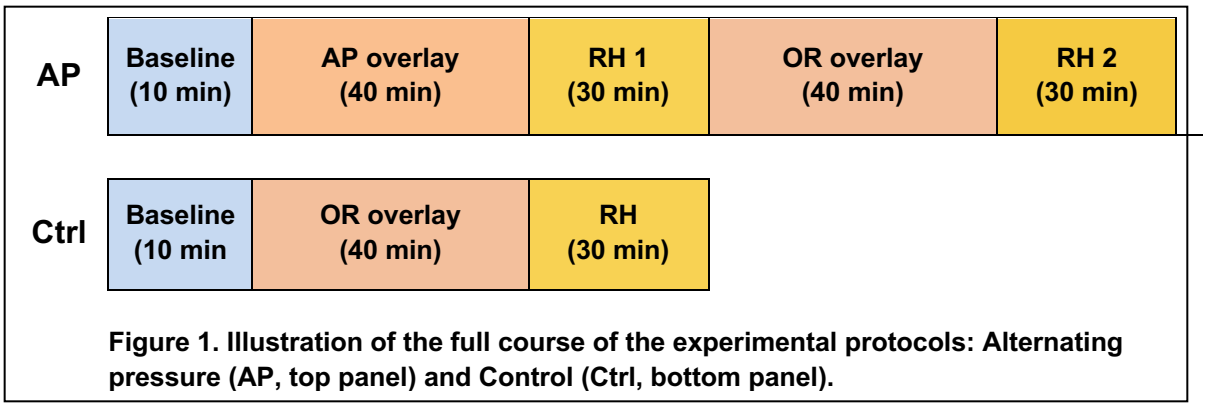

Figure 1. Illustration of the full course of the experimental protocols: Alternating pressure (AP, top panel) and Control (Ctrl, bottom panel).

2) Vascular control measures (approximately 30 minutes)

The PI, or key personnel will then collect the vascular control measures, including the heat hyperemic (HH) blood flow response, and the skin vasomotor response. A non-invasive combined laser Doppler and white light reflectance spectroscopy (LDF-WLRS) probe (CP2T-1000, Moor Instrument, Wilmington, DE) will be used for both measures.

HH blood flow response will be measured at the sacrum and one heel while the subject is in side-lying position. Figure 2 demonstrates the HH measurement setting. HH will be induced with the heater at the tip of the probe head (41°C for 5 minutes). This HH measure will take approximately 7 minutes (2 min-baseline, 5 min-heating) per location. In total, the HH measures will take up to 15 minutes to complete.

The skin vasomotor response will be induced using cutaneous electrical stimulation (3-10 mA, 0.2-1.0 ms pulses at 20 Hz, 1 s trains) delivered via 1 cm Ag-AgCl surface electrodes applied bilaterally (4 cm apart) to the forehead (above lesion) and the abdominal wall (below lesion) while the subject is in a semi-reclined position.[12] For each site, 5-8 stimuli will be delivered randomly. CP2T-1000 probe will be used to collect SBF and tissue oxygenation data at pulp of the second finger and toe. Subject will be in a semi-reclined position (about 30° from horizontal plane) during this protocol, and it will take up to 15 minutes to complete this protocol.

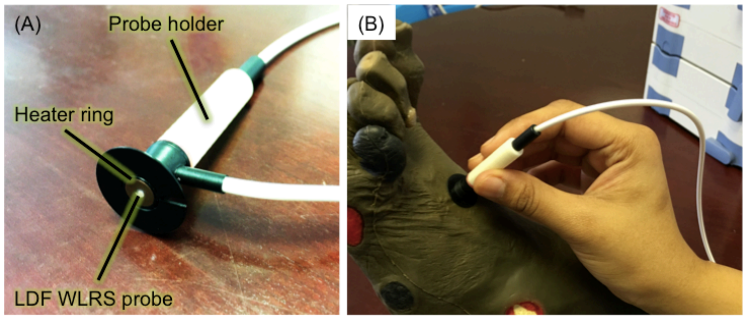

Figure 2. (A) hand held LDF-WLRS probe with heater ring, (B) HH measure.

3) Pressure mapping of wheelchair (approximately 10 minutes)

The subject will be asked to transfer back to his/her wheelchair with the pressure mapping system placed between the wheelchair and the subject to collect the interface pressure data. The pressure mapping system is the same as that used between the subject and overlay to collect the interface pressure data.

4) Blood withdraw (approximately 15 minutes)

The key personnel will draw venous blood samples (total 20 mL) via venipuncture for standard blood tests, including glycated hemoglobin (HbA1C), plasma glucose, lipid and lipoprotein concentrations (i.e. total-cholesterol, low-density lipoprotein, triglycerides, and high-density lipoprotein). The rationale for making these measurements is to collect potential covariates that might affect skin blood flow responses. Blood samples not used to probe for blood sugar and lipid profile tests will be stored up to five years (or until exhausted) for further analyses, since latest trend in literatures demonstrated metabolic syndrome after spinal cord injury had an effect on pressure ulcer formation.[13]

7.0 Expected Risks/Benefits

Expected Risks

Overall, potential risks associated with participation in the study are unlikely and of low risk. Subjects will be advised to speak with the PI if they believe they have been hurt by the study. Potential risks associated with the non-invasive protocols of our study are as followed:

1) Emotional stress: The risk of having emotional stress with our telephone screening procedure and examination of remaining sensation, motor and autonomic function is no more than minimal. Participants may feel uncomfortable answering personal health related questions. The examinations of remaining sensation, motor and autonomic function are regularly performed at the physician's office. Participants may feel uncomfortable that he or she could not feel or move the body below the level of injury. In addition, female subjects may feel added emotional stress if their screening pregnancy test results are positive and they were unaware that they were pregnant.

2) Discomfort: The risk of having discomfort with our heart rate, blood pressure, exams is no more than minimal. These examinations are regularly performed at the physician's office. Participants may feel discomfort caused by the blood pressure cuff and heart rate monitor belt.

3) Localized Ischemia. The risk of tissue ischemia associated with reactive hyperemia (caused by lying on OR or AP overlays) is low. Reactive

hyperemia is a normal physiological response induced by short-term non-damaging ischemia of the loaded area. The amount of pressure expected on sacrum and heels is very low (~60mmHg) and for a short period of time (40 minutes), which simulates the amount of pressure lying or sitting on a mattress or seat cushion. The amount, duration and area of localized pressure on the skin is within the current clinical practice guideline of pressure ulcer prevention, which is making turning the patient in bed every two hours. The skin breakdown risk associated with lying on OR or AP overlay is considered as rare (less than 1 out of 100 people).

4) Localized Heating. The risk of burn associated with heat hyperemia is low. Heat hyperemia will be induced by short-term heating of the skin. The temperature of heating is very low (41°C or 106°F) and for a short period of time (5 minutes). This temperature and duration is far lower and shorter than the therapeutic hot packs used regularly in clinic (45-54°C) for more than 10 minutes covering the whole joint or lower back. Previous published literatures that investigated microcirculatory response in people with SCI induced heat hyperemia with 20-30 minutes heating at 41°C. No tissue burn or damage to the skin was noted in these published studies. The amount and duration of localized heating of the skin is far shorter than that causing burn of the skin. The skin breakdown risk associated with the heating protocol is considered as rare (less than 1 out of 100 people).

5) Electrical Stimulation. The risk of skin or muscle damage associated with electrical stimulation is low. The skin vasomotor response will be induced using cutaneous electrical stimulation (3-10 mA, 0.2-1.0 ms pulses at 20 Hz, 1 s trains) delivered via 1 cm Ag-AgCl surface electrodes applied bilaterally (4 cm apart) to the forehead (above lesion) and the abdominal wall (below lesion). This is a standard protocol used to measure the sympathetic outflow of the microcirculatory response. The same protocol was used in previous studies on chronic spinal cord injury patients, and no damage to the skin or underlying muscle was noted. Electrical stimulation at a higher intensity and duration (10-50mA for 10 minutes) is one of the standard clinical practice protocol in nerve stimulation and pain reduction for patients with SCI. Therefore the skin or muscle damage associated with electrical stimulation is considered as rare (less than 1 out of 100 people).

6) Skin Blood Flow (SBF) and Tissue Oxygenation Testing will be performed using an FDA cleared non-invasive device. The amount of energy used with the laser light during the measurement is similar to that of a bar code scanner, and the white light is similar to that of ordinary daylight.

7) Bruising and swelling with venipuncture The risks of drawing blood from a vein includes discomfort at the site of the needle stick, possible bruising and swelling around the site of the needle stick is minimal. The risks of infection is very rare, and feeling faint from this procedure is uncommon.

8) Bare skin measurements. Bare skin measurements will be collected during this study. Some of the locations for the measurements, such as the sacrum

(low back) is very private, so the subject may feel embarrassed. A bed sheet will be provided to cover the subjects upon request.

9) Breach of confidentiality. The risk of breach of confidentiality is minimal since the only key to link subject ID and confidential information is locked in the file cabinet of the PI's locked office. The key will only be accessible to the PI's team. All other data is only coded with a subject ID in hard copy and electronic files. All hard copy files with subject ID only will be stored in a locked cabinet in the PI's locked laboratory, which is three floors away from the PI's office. All electronic data do not contain any confidential information, and they will be stored on the laptop used to collect data, and the hard drive located in the PI's Laboratory. Both computers are password protected, and the data are only accessible to the PI's team. All study personnel are trained in the maintenance of security and confidentiality of research data.

Benefits.

There is no direct benefit for the participants in this study, however findings from these participants will help us understand the potential benefit of the Dabir AP overlay as compared to the regular OR overlay, and the potential use of Dabir AP overlay on ischemia-preconditioning.

8.0 Data Collection and Management Procedures

Three sets of data (and one biological sample) will be collected from the subjects. The following listed the details of data procurement, storage, and encryption: All data will be stored at UIC, and data will not be shared or stored at Schwab.

1) Confidential information (hard copy only): Confidential information that includes direct identifiers such as name, date of birth and phone number will be recorded on **Form A**. A subject ID (code) will be assigned to the subject by PI upon study enrollment for the purpose of protecting the confidentiality of the subject data for analysis purpose. Form A will serve as the key to the code. **Form G** is the compensation form. Participants will be asked to sign the form once the payment is received. Form A and G will be stored in a locked file cabinet in PI's locked office (UIC Applied Health Science Building, Rm 506H). Only the PI will have access to this locked file cabinet. A portable lock cash box will be used to transport Form A and G between the DHSP building and Department of Physical Therapy. Form A and G will be stored up to five years and destroyed afterwards so that all data will be de-identified for future analyses only.

2) Paper-based data (hard copy and excel spread sheet) will be coded using the subject ID on forms: B, C, D, E and F. These forms will be stored in a locked file cabinet in PI's locked laboratory (UIC Applied Health Science Building, Rm 272; different from the room that stores Forms A and G). The PI's team will be responsible for incorporating data on these forms to an excel

spreadsheet for further statistical analyses. Two layers of encryption will be used to ensure the security of excel file. These coded data will be stored up to seven years after completion of this study.

3) Skin blood flow data (electronic text file generated automatically with data acquisition system): Skin blood flow data will be collected directly via the LDF. These analog signals are automatically stored on the UIC laptop used for data collection. Only Dr. Tzen's team can log on to the password protection laptop to collect and access the blood flow and tissue oxygenation data. The assigned subject ID will be the only identifier of the data set collected from each subject. These coded data will be stored up to seven years after completion of this study.

4) Blood sample: The blood samples not used to probe for blood glucose and lipid profile will be stored coded at co-investigator Dr. Haus' lab (UIC Applied Health Science Building, Rm 106). Dr. Haus will not have access to the key of the code.

5) Urine sample: Urine will be collected from women of childbearing age for pregnancy testing during visit one for eligibility screening. Any urine remaining after the testing will be disposed of.

9.0 Data Analysis

The MatLab program (The MathWorks Natick, MA) will be used to process the skin blood flow signal. The signals will be analyzed with two signal processing methods to characterize the responses in both time and frequency domains. Details of both methods were published previously by the PI.[14]

1) *Exponential curve-fitting technique*:
To select the time-domain parameters of the reactive hyperemia and heat hyperemia objectively. A tenth ordered Chebyshev I low pass filter (with cut off frequency at 0.15 Hz) will be applied to remove the noise caused by respiration and cardiac movement.[10] We will use a least squares model to fit the filtered reactive and heat hyperemic curves, and all parameters (including peak, time to peak, area under curve of reactive hyperemia; and first peak, second peak and time to first and second peaks, area under curve of heat hyperemia) will be derived from the fit curves.

2) *Time-frequency analysis*:
To further examine the different control mechanisms of SBF by decomposing the signal in frequency domain. Short-time Fourier transform will be used to decompose the signal by breaking the signal into short-time segments (windows), then computed Fourier analysis within each segment to calculate

spectral densities. A 256-sample Hanning window (512 seconds) will be used to compute the spectrogram.

Please see section 12.0 for details of all statistical analyses.

10.0 Quality Control and Quality Assurance

Dr. Tzen will be responsible for quality control and quality assurance of the data collected. Dr. Tzen has more than ten years of experiences in pressure ulcer research using non-invasive blood flow measurements, and she will perform the protocols in person and shadow her research team on the first two subjects. Dr. Tzen will then supervise the data collection on site for the next three subjects recruited in this study. Dr. Tzen will check all the data within two days of collection (paper and electronic formats). If the study team encounter any issues related to data collection, Dr. Tzen is available through phone calls to address the concerns. Dr. Tzen will meet with her team every two weeks to check the laboratory notes and monitor the study regularly.

11.0 Data and Safety Monitoring

The PI of this study (Tzen) will be responsible for monitoring the data and safety of this study. Dr. Tzen will meet with the research team every two weeks to monitor the overall conduct of the study (including issues with safety, ethics, recruitment, retention, adequacy of study design to achieve the specific aims) and provide feedback to the study team for the possible protocol amendments, and input from this study on future studies. Serious adverse events are not expected, but all such events will be reported according to the UIC IRB, and will be handled with the standard of Good Clinical Practice Guidelines including informing the PI, and IRB within 24 hours of the event, following up and reporting on the event until resolved, and subsequently reported to the PI.

The risk of breach of confidentiality is minimal since the only key to link subject ID and confidential information is a hard copy of Form A, which is locked in the file cabinet of the PI's locked office. All other data is only coded with a subject ID in hard copy and electronic file. All hard copy files with subject ID only will be stored in a locked cabinet in the PI's locked laboratory, which is three floors away from the PI's office. All electronic data are also coded and encrypted using Symantec software, and they will be stored on the laptop used to collect data, and the hard drive located in the PI's laboratory. Both computers are password protected, and the data are only accessible to the PI's team. All study personnel are trained in the maintenance of security and confidentiality of research data.

12.0 Statistical Considerations

For aims 1 and 2, paired *t*-tests will be computed to compare the interface pressure and skin blood flow during 40 minutes of AP overlay (AP protocol) vs. OR overlay (Ctrl protocol). Paired *t*-tests will also be used to compare the reactive hyperemic response during RH1 (AP protocol) vs. RH (Ctrl protocol). For aim 3, paired *t*-tests will be computed to compare the skin blood flow during OR overlay (AP protocol) vs. OR overlay (Ctrl protocol), and the reactive hyperemic response during RH2 (AP protocol) vs. RH (Ctrl protocol). SPSS will be used for all statistical analyses. Since this is a pilot study, we will test the study on 15 subjects. Results form this study will be used to calculate sample size for future studies. In case of dropout or subject decease during this study, we propose to recruit up to 20 subjects for this study.

13.0 Regulatory Requirements

13.1 Informed Consent

Oral consent will be obtained by phone during the initial telephone screen. Eligible subjects will be scheduled for a study visit where written informed consent will be obtained prior to conducting any study procedures. The PI's team is responsible for obtaining the signed consent form. The PI's team members were trained by the PI in obtaining informed consent, including thorough explanation of the research protocols and allowing potential subjects sufficient amount of time to ask any questions and to make the decision in participating in this study. To ensure the quality of the informed consent process, the PI will consent the first two subjects by herself and shadow her team members, and the PI will supervise her team members to consent the next three potential subjects of this study.

The informed consent documents will be stored in a locked file cabinet in PI's locked office (UIC Applied Health Science Building, Rm 506H), only the PI have access to the locked file cabinet. A portable lock cash box will be used to transport the signed consent forms from the DHSP building to the PI's office. Only the PI's team will have access to the consent form. Subjects will receive a signed copy.

13.2 Subject Confidentiality

As described in 8.0 Data Collection and Management Procedures, the only document that contains confidential information is a hard copy of Forms A and G. To guard the confidentiality, Forms A and G will be stored in a locked file cabinet in PI's locked office (UIC Applied Health Science Building, Rm 506H), only the PI has access to this locked file cabinet. A portable lock cash box will be used to transport Form A between DHSP

building and the PI's office. Form A and G will be destroyed at the end of the study so that all data will be de-identified for future analyses only.

Other data, including Forms B, C, D, E, F, blood flow and tissue oxygenation data in text files and excel spreadsheets will only contain an assigned subject ID, and Form A is the only document to link the subject ID to the subjects' confidential information. To guard the confidential information, Forms B, C, D, E, F will be stored in a locked file cabinet in PI's locked laboratory (UIC Applied Health Science Building, Rm 272; different from the room that stores Forms A and G). The PI's team will be responsible for incorporating data on Form B to a excel spreadsheet that contains information of all subjects on a password protected desktop located in the PI's locked laboratory. Two layers of encryption will be used. The analog signals of blood flow and tissue oxygenation will be stored on the password protected UIC laptop used for data collection. Only the PI's team can access the laptop to collect and access data. The assigned subject ID will be the only identifier of the data set collected from each subject. These coded data will be stored up to seven years after completion of this study. The password of the laptop and desktop used in this study will be changed quarterly and known only by the PI's team.

13.3 Unanticipated Problems

The PI will be responsible for monitoring and overseeing all procedures of the study. With the previous experiences, there should be no unanticipated problems with this study. However, should any unanticipated problems occur, the incident will be handled with the standard of Good Clinical Practice Guidelines including informing the PI, and IRB within 24 hours of the event, following up and reporting on the event until resolved, and subsequently reported to the PI.

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APPENDICES

American Spinal Injury Association (ASIA) Impairment Scale

A = Complete: No motor or sensory function is preserved in the sacral segments S4-S5.

B = Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

C = Incomplete: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

D = Incomplete: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

E = Normal: motor and sensory function are normal.

FORM A: CONFIDENTIAL INFO

(to complete during telephone screening)

Name of subject: _____

Date of birth: ___/___/____

Address:

Street: _____

City: _____ State: _____ Zip Code: _____

Phone: (Work) _____ (Home) _____

E-mail: _____

IRB approval

Researcher's Initials:_____

Date: _____

FORM B: DEMOGRAPHIC INFO

(to complete during telephone screening)

- Gender: _____ Male _____ Female
- Weight: _____ Height: _____
- (Body Mass Index: _____ (To be calculated by the investigator)
- Race/Origin: _____African-American _____Asian-American/Asian
  _____Caucasian _____Hispanic
  _____Others (please specify_____)

IRB approval

FORM C1 – SELF-REPORT MEDICAL HISTORY

(to complete during telephone screening)

Spinal Cord Injury History

- Date of injury: _____/_____/_____
- Level of injury: Cervical ___ Thoracic___ Lumbar___
- AIS: ___ A ___ B___ C
- Wheelchair: ____ manual ____ power

Pregnant: _____ yes _____ no

IRB approval

Other Medical history

_____ Cardiovascular Disease

_____ Hypertension

_____ Diabetes Mellitus

_____ Neuropathy

_____ Lung Disease

_____ **Others, please list**

_____

_____ **None of above diseases**

Pressure Ulcer history

If had pressure ulcers in the past, please indicate the location and time:

_____

_____

_____

_____

FORM C2 – SELF-REPORT CURRENT MEDICATION

(to complete during telephone screening)

Name of Medication	Dosage	Frequency	Reason for Taking
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

IRB approval

FORM D – SELF-REPORT SOCIAL HISTORY

(to complete during telephone screening)

Please indicate Yes or No to the following:

Do you smoke? _____Yes _____No

If yes, packs per day? _____ Number of years? _____

Do you exercise on a regular basis? ____Yes ____No

If yes, describe

_____

_____

_____

IRB approval

Researcher's Initials:_____

Date: _____

FORM E1 – RESTING VITALS

(to complete during face-to-face screening)

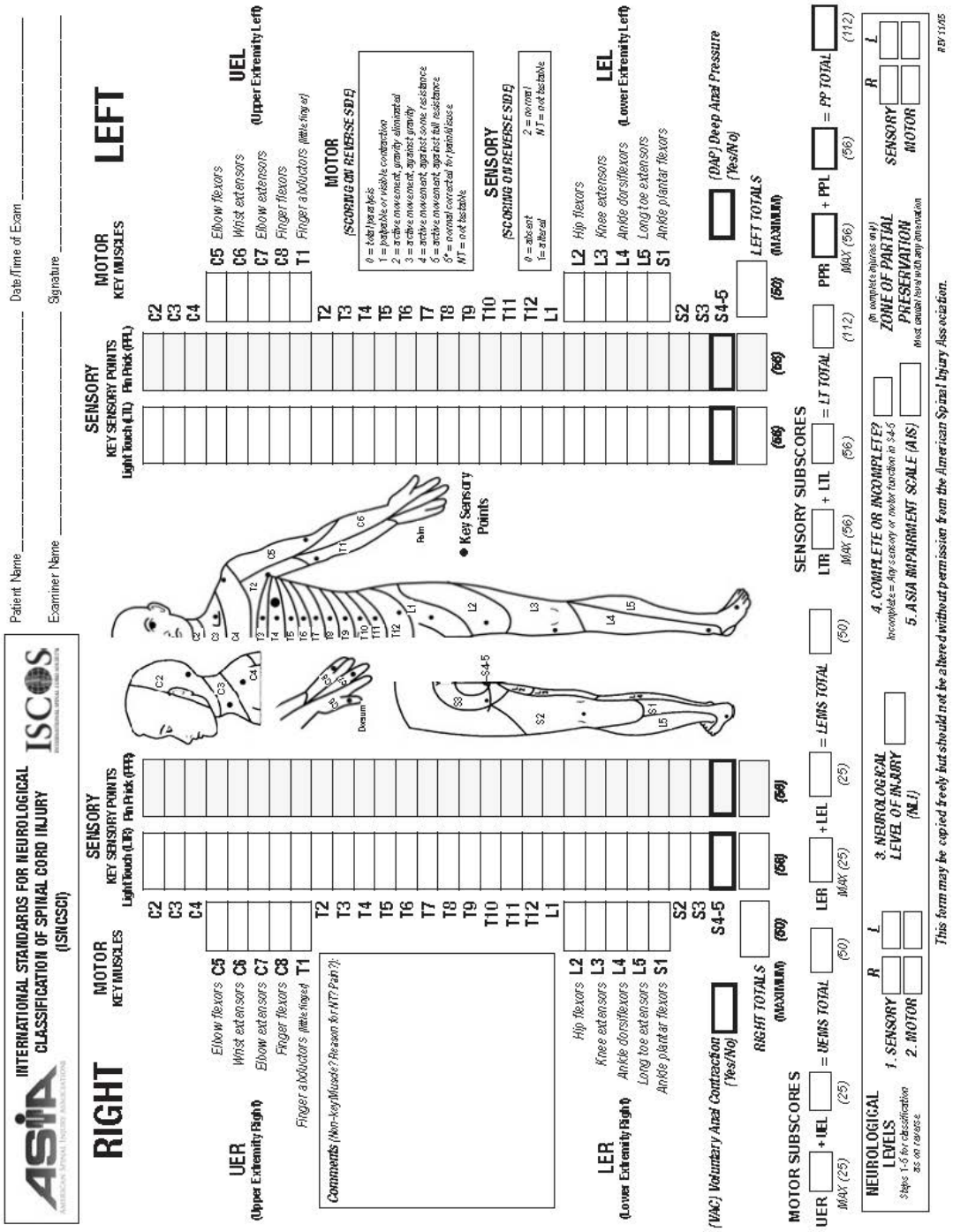
Resting heart rate: _____

Resting blood pressure: _____

Pregnant: _____ yes _____ no (based on urine test result)

FORM E2 – ASIA IMPAIRMENT SCALE

(to complete during face-to-face screening)



Muscle Function Grading

0 = total paralysis

1 = palpable or visible contraction

2 = active movement, full range of motion (ROM) with gravity eliminated

3 = active movement, full ROM against gravity

4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position

5 = (normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present

NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

Sensory Grading

0 = Absent

1 = Altered, either decreased/impaired sensation or hypersensitivity

2 = Normal

NT = Not testable

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, abduction, adduction, internal and external rotation	C5
Elbow: Supination	
Elbow: Pronation Wrist: Flexion	C6
Finger: Flexion at proximal joint, extension. Thumb: Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint Thumb: Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation Knee: Flexion Ankle: Inversion and eversion Toe: MP and IP extension	L4
Hallux and Toe: DIP and PIP flexion and adduction	L5
Hallux: Abduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pinprick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments (S4-S5) by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI having a muscle grade ≥ 3.

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

ASIA
AMERICAN SPINAL INJURY ASSOCIATION

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ISCOS
INTERNATIONAL SPINAL CORD SOCIETY

Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI)
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most caudal level of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
If voluntary anal contraction = No AND all S4-5 sensory scores = 0
AND deep anal pressure = No, then injury is Complete.
Otherwise, injury is Incomplete.

5. Determine ASIA Impairment Scale (AIS) Grade:
Is injury Complete? If YES, AIS=A and can record ZPP (lowest dermatome or myotome on each side with some preservation)
NO →
Is injury Motor Complete? If YES, AIS=B
NO → (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)
Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?
NO → AIS=C
YES → AIS=D

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

FORM E3 – AUTONOMIC FUNCTION SCALE

ASIA AMERICAN SPINAL INJURY ASSOCIATION ISCOS INTERNATIONAL SPINAL CORD SOCIETY

Autonomic Standards Assessment Form

Patient Name:_____
(Document Subject ID instead)

Autonomic Diagnosis: (Supraconal ☐, Conal ☐, Cauda Equina ☐)

General Autonomic Function

System/Organ	Findings	Abnormal conditions	Check mark
Autonomic control of the heart	Normal		
	Abnormal	Bradycardia	
		Tachycardia	
		Other dysrhythmias	
	Unknown		
	Unable to assess		
Autonomic control of blood pressure	Normal		
	Abnormal	Resting systolic blood pressure below 90 mmHg	
		Orthostatic hypotension	
		Autonomic dysreflexia	
	Unknown		
	Unable to assess		
Autonomic control of sweating	Normal		
	Abnormal	Hyperhydrosis above lesion	
		Hyperhydrosis below lesion	
		Hypohydrosis below lesion	
	Unknown		
	Unable to assess		
Temperature regulations	Normal		
	Abnormal	Hyperthermia	
		Hypothermia	
	Unknown		
	Unable to assess		
Autonomic and Somatic Control of Broncho-pulmonary System	Normal		
	Abnormal	Unable to voluntarily breathe requiring full ventilatory support	
		Impaired voluntary breathing requiring partial vent support	
		Voluntary respiration impaired does not require vent support	
	Unknown		
	Unable to assess		

Lower Urinary Tract, Bowel and Sexual Function

System/Organ		Score
Lower Urinary Tract		
Awareness of the need to empty the bladder		
Ability to prevent leakage (continence)		
Bladder emptying method (specify)_____		
Bowel		
Sensation of need for a bowel movement		
Ability to Prevent Stool Leakage (continence)		
Voluntary sphincter contraction		
Sexual Function		
Genital arousal (erection or lubrication)	Psychogenic	
	Reflex	
Orgasm		
Ejaculation (male only)		
Sensation of Menses (female only)		

2=Normal function, 1=Reduced or Altered Neurological Function
0=Complete loss of control, NT=Unable to assess due to preexisting or concomitant problems

Date of Injury_____ Date of Assessment_____

Examiner_____

FORM F – TEST DATA

_____ Envelope A: CTRL → AP

Session	Heart Rate		Blood Pressure	
	Before	After	Before	After
CTRL				
AP				

_____ Envelope B: AP → CTRL

Session	Heart Rate		Blood Pressure	
	Before	After	Before	After
AP				
CTRL				

(Signature of Investigator) **(Date)**

FORM G – COMPENSATION

I, _____, acknowledge that I am to receive compensation for participating in this study $_____ on _____/_____/_____.

Participant's signature _____Date _____

Researcher's signature _____Date_____