Project 9: To Determine the Effects of Normalizing Blood Pressure on Cerebral Blood Flow in Hypotensive Individuals with SCI

STATEMENT OF THE PROBLEM: Dysregulation of BP, secondary to decentralized ANS control of the cardiovascular system, often results in chronic hypotension and orthostatic hypotension (OH) in persons with SCI, particularly in those with high cord lesions (i.e., above T6). While most hypotensive individuals with chronic SCI remain asymptomatic and do not complain of symptoms associated with cerebral hypoperfusion, evidence of reduced resting cerebral blood flow (CBF) has been reported in association with low systemic BP in the SCI (53) and non-SCI populations (54). Reduced CBF in hypotensive individuals may lead to cognitive dysfunction, and we reported significantly impaired memory and marginally impaired attention processing in hypotensive individuals with SCI compared to a normotensive SCI cohort (55). Furthermore, we found that CBF was not increased during cognitive testing in individuals with SCI, which may contribute to impaired cognitive function compared to non-SCI controls (56). Although asymptomatic hypotension may have an adverse impact on cognitive function (54, 57) and quality of QOL clinical management of this condition is extremely low. In fact, we reported that while nearly 40% of Veterans with SCI were hypotensive, less than 1% carried the diagnosis of hypotension or were prescribed an anti-hypotensive medication (58, 59). The discrepancy between incidence and treatment of asymptomatic hypotension in the SCI population may relate to a paucity of treatment options which are supported by rigorous clinical trials documenting the safety and efficacy of anti-hypotensive therapy on BP, CBF and cognitive function.

SPECIFIC AIMS:
In hypotensive individuals with SCI:

1. Study 9.1: To determine the dose of each of 3 agents with anti-hypotensive effects [e.g., beta (3)-adrenoceptor agonist (mirabegron), an alpha agonist (midodrine) and an anti-cholinergic (pyridostigmine)] that will raise systolic BP (SBP) into the normal range (110-130 mmHg).
2. Study 9.2: To determine the effect of each agent at the specified dose (i.e., raises SBP into the normotensive range) on CBF and cognitive function.

PROPOSED STUDY: *Subjects:* Twenty hypotensive individuals with SCI who are chronically injured (> 1 year) and in a healthy stable condition will be recruited. A medical history will be performed prior to investigation; details of the inclusion and exclusion criteria are presented (Human Subjects: Project 9: Anti-HYPO).

Study 9.1: Subjects will visit the laboratory between 3 and 9 times to determine the BP effects of three different anti-HYPO agents. These agents will be administered open label, to determine the effective dose for normalizing SBP (111-130 mmHg). Subjects will remain seated and will be administered the study medication according to the dose titration (Table 4). HR and BP assessments will be recorded every 30 minutes for 4 hours post-drug.

Study 9.2: *Methods:* Subjects will visit the laboratory 3 times and the anti-HYPO agents will be administered in a random and blinded order at the dose determined in *Study 9.1*. Subjects will remain seated and a battery of cognitive tests to assess memory and attention processing will be performed with simultaneous recording of HR, BP, BR and CBF. Study medication will then be administered and HR, BP, and CBF assessments will be recorded every 30 minutes for 4 hours. A second battery of cognitive tests will be administered 2 hours after study medication.

DATA AND STATISTICAL ANALYSES: Repeated measures ANCOVA models will be constructed to compare the effect of study medication on BP and CBF; the covariates in each model will include baseline BP and CBF. The alpha level will be set at 0.05 and significant omnibus effects will be decomposed with pairwise comparisons among anti-HYPO agents using Tukey post hoc tests on the covariate adjusted BP and CBF values. Linear regression models will then be constructed to compare the relationship between change in BP and change in CBF among the anti-HYPO agents tested.

EXPECTED RESULTS AND BENEFITS: In our proposed studies, a more precise identification of the degree of ANS dysfunction (Project 8) and further our understanding of the relationship between systemic BP, CBF and cognitive function in individuals with SCI (Project 9) will be achieved. Data generated from these investigations will be used to guide clinical evaluation and treatment algorithm for improving cardiovascular, cerebrovascular and cognitive function in the SCI population.

Table 4. Dosing Schedule

Drug 1	Visit 1		Visit 2		Visit 3
	Dose	BP response (mmHg)	Dose	BP response (mmHg)	Dose
Mirabegron (beta3 agonist)	**25 mg**	≤ 110*	**50 mg**	≤ 110*	**75 mg**
		111-130	n/a	111-130	n/a
		≥ 140	n/a	≥ 140	n/a
Drug 2	Visit 4		Visit 5		Visit 6
	Dose	BP response (mmHg)	Dose	BP response (mmHg)	Dose
Pyridostigmine (anti-cholinergic)	**60 mg**	≤ 110*	**90 mg**	≤ 110*	**120 mg**
		111-130	n/a	111-130	n/a
		≥ 140	n/a	≥ 140	n/a
Drug 3	Visit 7		Visit 8		Visit 9
	Dose	BP response (mmHg)	Dose	BP response (mmHg)	Dose
Midodrine (alpha agonist)	**10 mg**	≤ 110*	**15 mg**	≤ 110*	**20 mg**
		111-130	n/a	111-130	n/a
		≥ 140	n/a	≥ 140	n/a

VA Department of Veterans Affairs	VA RESEARCH CONSENT FORM

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Subject Name:	Informed Consent Date:
Principal Investigator: Jill M. Wecht, EdD	VAMC: James J Peters

Protocol #: WEC-16-015

Title of Study: **The Effect of Normalizing Blood Pressure on Cerebral Blood Flow in Hypotensive Individuals with SCI: titration**

1. Purpose of study and how long it will last:

The purpose of this study is to determine the dose of three different medications that raise your blood pressure into the normal range (111-139/70-85 mmHg). The three medications which have been approved for experimental use in this study by the FDA (midodrine, mirabegron, and pyridostigmine) have anti-hypotensive effects and will be given escalating doses of each medication on successive study visits, depending on your blood pressure responses, but the order of medication administration will be randomized. You will not know which is being administered, but the investigator and study team will not be blinded to study medication. Your participation will last for no fewer than 3 and no more than 10 visits over the course of about six weeks.

You are being asked to participate in this research study because you have low blood pressure (hypotension), are between the ages of 18 and 85, and have had a spinal cord injury (SCI) for over one (1) year. This study is sponsored and funded by the National Center for the Medical Consequences of SCI. You will be one of about 30 subjects with SCI who will participate in this study, or one of 60 who will participate across the two sites, which is being conducted at the James J. Peters VA Medical Center (JJP VAMC) and the Kessler Institute for Rehabilitation. Prior to study participation you will be screened for the following:

Inclusion Criteria:

- SCI between the ages of 18 – 85 years old
  - Any level of injury
  - non-ventilator dependent
  - Any AIS grade of SCI
  - SCI duration > 1 year
  - Wheelchair dependent
- Able to provide informed consent
- Low blood pressure
  - Males- systolic blood pressure < 110 mmHg and/or diastolic BP < 70 mmHg
  - Females- systolic blood pressure < 100 mmHg and/or diastolic BP < 70 mmHg

Exclusion Criteria:

- Current illness or infection
- Individuals with frequent or severe autonomic dysreflexia
  - More than 3 symptomatic events per week
  - BP ≥140/90 mmHg
  - Significant adverse subjective symptoms reporting

- Hypertension
- Any neurological condition other than SCI (Alzheimer's disease, dementia, stroke, multiple sclerosis, Parkinson's disease, etc.)
- History of epilepsy or other seizure disorder
- History of traumatic brain injury (TBI)
- Liver or kidney disease
- Bladder problems including blockage of the urine and/or weak urine stream.
- Diagnosis of a psychiatric disorder such as schizophrenia or bipolar disorder
- Known artery disease, heart failure, AV block, and irregular heartbeat
- Any allergies to asprin, mirabegron, pyridostigmine bromide, midodrine hydrochloride, polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide
- Major surgery in the last 30 days
- Illicit drug abuse in the past 6 months
- Your prescription medications will be reviewed by the study investigators and research staff. If you are currently taking medications to treat any of the following please make the investigators aware:
    - Depression, Schizophrenia, ADHA
    - Pain (opioids)
    - Infection or illness (antibiotics)
    - Erectile dysfunction (Viagra, Cialis, etc.)
    - Overactive bladder
    - High or low blood pressure
    - Migraine headaches
    - Malaria
    - Ashtma
- Please talk to the research staff if you have any questions about your medications; we may contact your doctor to discuss.
- Pregnant*

2. Description of the Study Including Procedures to be Used:

If you consent to participate in this research study, you will visit the laboratory at the JJPVAMC (7A-13S) between 3 and 11 times for about 4 hours each visit. You will refrain from caffeine, alcohol, heavy exercise, and smoking for 12 hours prior to arrival and you will refrain from taking sildenafil (Viagra), tadalafil (Cialis), or other similar medications, for 2-days prior to your study visit. You will remain

seated in your wheelchair for a minimum of 20 minutes while the research team applies instrumentation. Three sticky electrodes will be placed on your chest and abdomen area. A blood pressure cuff will be placed around your upper right arm and a small blood pressure cuff will be placed on your left middle or ring finger. Your blood pressure, respiration rate and heart rate will be recorded for 5-minutes while you rest quietly (baseline) before we administer the study medication. After baseline testing you will be asked to swallow a small pill with a glass of water. Blood pressure, respiration rate and heart rate will be monitored for 5-minutes every 30 minutes after you take the medication. For every visit you will be randomized to receive either a midodrine (in a dose escalation manner), pyridostigmine (in a dose escalation manner) or mirabegron (in a dose escalation manner). The table below displays the medication and dose escalation that will be administered on successive study visits, depending on your blood pressure responses. Each of the medications we have chosen have short duration of action so any bad reaction should last for a short period of time. But if at any time you feel uncomfortable, we will immediately stop the study medication and all testing and will monitor your heart rate, breathing rate, and blood pressure very closely until you recover. During 1 of the study visits you will be asked to provide a saliva sample by spitting into a small specialized collection tube.

Table 1: Medication Dose Schedule*

Drug	**Dose 1**	**Dose 2**	**Dose 3**
Mirabegron	50 mg	75 mg	100 mg
Drug	**Dose 1**	**Dose 2**	**Dose 3**
Pyridostigmine	30 mg	60 mg	90 mg**
Drug	**Dose 1**	**Dose 2**	**Dose 3**
Midodrine	5 mg	10 mg	15 mg

*Once the target blood pressure is attained (i.e., **111-139/70-85 mmHg**), you will not be administered a higher dose of that study medication.
** If your blood pressure is unresponsive to Pyridostigmine at these doses, you will receive a higher dose of 120mg.
* If your heart rate slows below 45 bpm you will not be given a higher dose of any study drug
* If your peak BP response to mirabegron is more than 3 hours post drug administration you will not continue the study
* If you completed the medication visits without the saliva collection you may be asked to return provide the sample.

Heart Rate & Respiration Rate – Three electrodes (small sticky pads) will be placed on your chest and abdomen to continuously monitor your respiration and heart rate during each study visit. Heart and

respiratory rate will be monitored and recorded for 5-minutes during the baseline period and at 30-minute intervals after administration of the study medications.

Blood Pressure – Blood pressure will be monitored and recorded from your right upper arm using standard procedures at 1-minute intervals during baseline and at 30-minute intervals after administration of the study medication. Finger blood pressure will be monitored continuously from your left middle or ring finger on a beat-to-beat basis during the baseline period. Beat-to-beat blood pressure will be recorded for 5-minutes at 30-minute intervals throughout the 4-hour observation period after administration of the study medication.

Autonomic Dysreflexia (AD) Symptoms Survey- Autonomic dysreflexia is a condition where blood pressure increases higher than normal, usually because of a painful or non-painful stimulus below the level of your spinal cord injury. Some of the most common causes of AD relate to bowel or bladder fullness, tight clothing, or pressure from being in a position for too long, but there may be other causes that we are not aware of. You will be asked to complete an AD symptoms survey during each study visit, which will be used to determine your experience with AD over the 7-days prior to the study visit. This survey contains questions related to symptoms you may have experienced, information about your blood pressure at that time, and possible causes of the AD. This survey should take approximately 15 minutes to complete.

Saliva Collection- You will be asked to provide a saliva sample (about 1 teaspoon) into a special collection vessel at one of the study visits. The saliva will be tested by a commercial laboratory for several genetic markers including the Apolipoprotein E (ApoE), cholinergic muscarinic receptors, alpha adrenergic receptors, beta adrenergic receptors, dopamine receptor 1, 2 and serotonin receptor genotypes. This test will describe genetic characteristics that are inherited from your parents that may be related to how your heart and blood vessels respond to the study intervention. The introduction of genetic testing from saliva is allowing scientists to develop an understanding of how different combinations of genes may influence health or disease states. The results from the saliva test will be used only for research purposes only and these particular genetic markers are related to the heart, blood vessels and how the nervous system controls their function. Their use in the study will assist the research team in explaining the study results.

3. Description of any Procedures that may Result in Discomfort or Inconvenience:
You have been told that the study described above may involve the following discomforts:

- You may experience some discomfort when electrodes are removed from your skin and some skin irritation at the site of electrode placement.
- You may experience some discomfort when the blood pressure cuffs around your upper arm and your finger are inflated.
- Since this research may have unknown effects on an unborn child and should not be done during pregnancy, it is necessary for a pregnancy test to be done first. To your knowledge you are not pregnant at the present time. You also agree to avoid becoming pregnant (use contraceptives, take precautions against becoming pregnant, etc.) during this study.

4. Expected Risks of Study:

- The monitoring of heart rate, breathing rate, and blood pressure are all non-invasive measurements and are not associated with any known risks.
- Saliva sample- There should be minimal discomfort associated with providing a saliva sample. You may experience a brief moment of dry mouth after placing the saliva sample into the collection vessel. The dry mouth will go away after consuming a small amount of liquid.
- Your blood pressure may be elevated above what is considered to be the normal range (>140/90 mm Hg) following administration of the study medications (i.e., midodrine, pyridostigmine, and mirabegron). If this happens, we will take action to help reduce your blood pressure; we will loosen any tight clothing or braces that you may be wearing; we will shift your position in your wheelchair, and we will help you check and empty your bladder or bowel. If your blood pressure remains high for more than 30 minutes after we take these measures, we will provide medication to lower your blood pressure. The medication of choice will be sub-lingual (under the tongue) nitroglycerin.
- If after 4-hours of testing your BP remains above your baseline, but not in the hypertensive range (>139/89 mmHg), you will be sent home with a 24-hour BP Holter monitor (Vasomedical-BIOX™ 2301 Wuxi, Jiangsu, China). The monitor will be programmed to obtain BP readings every 20 minutes during the day and 30-minute intervals during the night. Study coordinator or the PI will follow-up with phone calls to you while you are at home to asses any side effects and document BP changes.
- You will be asked to immediately report any significant AE you may feel after leaving the laboratory. Symptoms which you should be particularly aware of include: headache, pounding in the ears, blurry vision, nausea, goosebumps, chills and spasms; please alert the research staff if you experience any of these symptoms in greater frequency or severity during the experiment or after you leave the laboratory.

- In order to diminish the possible risks of interaction between the study medications and other medications you may be taking, you may be asked to avoid taking prescription medications on the day of the study, which should be approved by your primary physician.
- There may be interactions between the study medication and prescription medications you my be taking. In order to lower the risk to you the research staff will monitor your medications and may contact your doctor if needed. Medications prescribed for conditions not mentioned in the exclusion criteria, may have minor or moderate risks, (meaning the effects are considered tolerable and in most cases there is no need for medical intervention), and may be permitted, but decisions about your study participation should be made by study personnel in conjunction with you and your doctor.
- Symptoms of autonomic dysreflexia (AD) may become more frequent or worse while taking these study medications.
- Common side effects of all three medications are dizziness, nausea, blurred vision, headache, bladder pain, difficulty, painful, and/or burning urination. Also, an urge to urinate or urine retention.
- **Midodrine** risks (≤8% likely) include: cardiac awareness (irregular heartbeat or shortness of breath), pounding in the ears, increased dizziness, slow pulse, fainting, tingling and itching of the scalp, goosebumps, chills, constipation, superficial venous thrombosis (a blood clot in a vein), vascular ischemia (blockage of blood supply in an artery), and temporary muscle spasms.
- **Pyridostigmine** risks: (≤2% likely) include; upset stomach, abdominal cramps, increased saliva/mucus, urinary frequency and/or urgency, nausea, increased flatulence, wheezing, decreased pupil size, increased sweating or cold sweat, pale skin, watery eyes, warmth or tingly feeling, and rash or itching.
- **Mirabegron** risks (0.2% likely) include: abdominal or stomach pain, dry mouth, difficultly with breathing, muscle aches, diarrhea, constipation, bloating, sinus pain, and sore throat.
- Since this research may have unknown effects on an unborn child and should not be done during pregnancy, it is necessary for a pregnancy test to be done first. To your knowledge you are not pregnant at the present time. You also agree to avoid becoming pregnant (use contraceptives, take precautions against becoming pregnant, etc.) during this study.
- As with any research, there may be unforeseen risks and discomforts. A medical doctor associated with the study will be available to treat any medical emergency that may develop.

5. Expected Benefits of the Study:
There may be no direct benefit to you from this study, but information learned may help others.

6. Other Treatments Available:
Participation in the study is voluntary and you understand that the only alternative is to not participate.

7. Use of Research Results:
We will let you and your physician know of any significant new findings made during this study which may affect your willingness to participate. All research material generated from the study will remain in the possession of Dr. Wecht and her study team. De-identified electronic data will be stored on secured VA networks, behind VA firewalls, in access-restricted folders. Coded physical data will be stored at the JJP VA Medical Center in locked file cabinets behind locked doors. Access to the research materials generated from the study will be restricted to Dr. Wecht's research team. Your medical records will be maintained according to this medical center's requirements and all electronic and hard copy Research Records will be retained according to National Archives and Records Administration, Records Schedule Number RCS-10-1.

If you wish to participate, please check your answers to the following questions.
May we collect your tissue samples, health information and genetic information to study to explore genetics markers related to apolipoprotein E, cholinergic muscarinic receptors, alpha adrenergic receptors, beta adrenergic receptors, dopamine receptor 1, 2 and serotonin receptor genotypes?
Yes_____ No_____

May we share your tissue samples, health information and genetic information with other researchers to study genetics markers related to apolipoprotein E, cholinergic muscarinic receptors, alpha adrenergic receptors, beta adrenergic receptors, dopamine receptor 1, 2 and serotonin receptor genotypes?
Yes_____ No_____

May we share your tissue samples, health information and genetic information with other researchers for future research projects related to other topics?
Yes_____ No_____

Researchers might want to ask you to participate in additional studies. In some cases, you might be a particularly good candidate for a particular study because of your health history or genomic information.

May we contact you in the future to get your permission to use your samples, health information and genomic information for additional studies?
Yes_____ No_____

May we contact you in the future to ask your permission for additional samples or follow-up information about your health or medical care?
Yes_____ No_____

□_____ By checking this box and initialing, you agree to be contacted by the Principal Investigator or her investigative team at a future date for additional studies being conducted in the National Center for the Medical Consequences of SCI.

If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. No information by which you can be identified will be released or published unless required by law. In order to comply with federal regulations, research records identifying you may be reviewed by the following: Authorized representatives of the Bronx VAMC (e.g. Institutional Review Board, Research Compliance Officer) and VA, including the Office of Research Oversight (ORO), Federal Agencies such as the Government Accounting Office (GAO), VA Office of Inspector General (OIG), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP).

Because this research involves articles regulated by the FDA, the FDA may choose to inspect and copy medical or research records that identify individual research subjects". If this study was initiated on or after March 7, 2012, a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include a summary of the results. You can search this web site at any time.

8. Special Circumstances:
If you are a patient, a copy of this consent form will be placed in your medical record.

9. Compensation and/or Treatment in the Event of Injury:
The VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Further information about compensation and medical treatment may be obtained from the medical administration service at this VA medical center. A veteran-participant does not have to pay for care received as a participant in a research project, except in accordance with federal law that certain veterans have to pay co-payments for medical care and services provided by the VA.

10. Voluntary Participation:
You are not required to take part in this study; your participation is entirely voluntary. You can refuse to participate or withdraw your participation in this study after you consent without penalty or loss of VA or other benefits to which you are entitled. During the course of the study, you will be told about any new findings within the investigation or about information reported in the literature or reported verbally to the investigators that might affect your willingness to remain in the study. A signed copy of this consent form will be given to you.

11. Termination of Participation:
You can refuse to participate now or you can withdraw from the study at any time after giving your consent. This will not interfere with your regular medical treatment, if you are a patient. The investigator also has the right to withdraw you from the study at any time for reasons including, but not limited to, medical concerns (your health and safety are in jeopardy with continued participation in the study), non-compliance (you miss several scheduled appointments without notification) and protocol deviations (exclusion/inclusion criteria change and you are no longer eligible to participate).

12. Costs and Reimbursements:
As a veteran or non-veteran, you will not be charged for any treatments or procedures that are part of this study. For veterans who are required to pay co-payments for medical care and services provided by VA, these co-payments will continue to apply for medical care and services provided by VA that are not part of this study. Reimbursement typically takes 6-8 weeks to arrive by Electronic Transfer Fund (EFT) and 12-14 weeks to arrive by check. You understand that if you choose to receive reimbursement through EFT, you will be required to provide the research staff information that includes; name of your bank, routing number and account number.

You have been told that you will receive up to $770 for participation in this research study according to the following schedule:

- Visit 1 - $75.00
- Visit 2 - $75.00
- Visit 3 - $75.00
- Visit 4 - $75.00
- Visit 5 - $75.00
- Visit 6 - $75.00
- Visit 7 - $75.00
- Visit 8 - $75.00
- Visit 8 - $75.00
- Visit 9 - $75.00
- Visit 10 - $75.00
- Visit 11 - $20.00

You understand that payment will be processed after each study visit based on the above schedule, and that you will be paid for each study visit you attend and complete. You understand that if you cannot complete all study visits you will be paid for the testing sessions that you complete.

13. Contact Person(s):

If you have any questions, at any time, about this research, or want to discuss any possible study-related injuries, please call telephone number 718-584-9000, ext. 3122 for Dr. Wecht. In addition after-hours you can contact Dr. Wecht at (201) 390-0487 or the medical doctor affiliated with this study: Dr. William Bauman at (914) 329-4772.

I understand that should I wish to discuss my participation in this study with any other doctor or layperson, I can contact Mary Sano, Ph.D. ACOS/R&D Program by requesting an appointment at (718) 741-4228 hospital extension 4228, first floor in the research building, room 1F-01 If I have questions, concerns and/or complaints
or to offer input.

RESEARCH SUBJECTS' RIGHTS:
You have read or have had read to you all of the above. Dr. Jill M. Wecht, EdD or her delegate has explained the study to you and answered all of my questions. You have been told of the risks or discomforts and possible benefits of the study. You have been informed of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but my records will not be revealed unless required by law. This study has been explained to me. I have had a chance to ask questions. I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

Subject Signature	Date	Time

Person Obtaining Informed Consent (Print Name) (Investigator or Delegate as indicated on Assurance Page)	Signature of Person Obtaining Informed Consent	Date

VERBAL CONSENT IF THE PARTICIPANT LACKS UPPER LIMB FUNCTIONS TO COMFORTABLY WRITE

_____ is unable to sign the consent form due to impaired arm function. I certify that I have carefully explained the purpose and nature of this research to him/her in appropriate language and he/she has had an opportunity to discuss it with me in detail. I have answered all of his/her questions and he/she has consented to participate in this research. I, therefore, am signing the consent form to document that he/she has given his/her consent to participate in this research study.

Person Obtaining Consent: _____

Name: _____

Signature: _____

Date: _____

Witness Name: _____

Signature: _____

Date: _____

VA Department of Veterans Affairs

VA RESEARCH CONSENT FORM

Version Date: February 4, 2021	**Page: 1 of 12**
Subject Name:	**Informed Consent Date:**
Principal Investigator: Jill M. Wecht, EdD	**VAMC: James J Peters**
Protocol #: WEC-16-015 **Title of Study: The Effect of Normalizing Blood Pressure on Cerebral Blood Flow in Hypotensive Individuals with SCI: blinded**	

1. Purpose of study and how long it will last:

The purpose of this study is to measure blood pressure and blood flow to the brain during cognitive tests before and after the administration of the 3 study medications, which may have increased your blood pressure in Study 1. The 3 medications have been approved for experimental use in this study by the FDA for phase 2 clinical trial. You will be asked to visit the laboratory on 4 separate days. The drugs are midodrine, pyridostigmine , and mirabegron will be given to you as a pill on 3 of the study visits, which will be randomized and compared to placebo (no medication). Neither you nor the study investigators will know what the pill contains on each of the 4 study visits.

You are being asked to participate in this research study because you are between the age of 18 and 85, and have had SCI for over one (1) year. This study is sponsored and funded by the National Center for the Medical Consequences of Spinal Cord Injury (SCI).

You will be one of about 20 subjects with SCI who will participate in this study, or one of 40 who will participate across the two sites, which is being conducted at the James J. Peters VA Medical Center (JJP VAMC) and the Kessler Institute for Rehabilitation The time allotted for your participation in each of the 4 study visits will be about 4-hours, which will occur over the course of about four weeks. Prior to study participation you will be screened for the following:

Inclusion Criteria:

- Participation in Study 1a: "titration/open label" trial
- SCI between the ages of 18 – 85 years old
  - Any level of injury
  - non-ventilator dependent
  - Any AIS grade of SCI
  - SCI duration > 1 year
  - Wheelchair dependent
- Able to provide informed consent
- Low blood pressure
  - Males- systolic blood pressure < 110 mmHg and/or diastolic BP < 70 mmHg
  - Females- systolic blood pressure < 100 mmHg and/or diastolic BP < 70 mmHg

Exclusion Criteria:

- Current illness or infection
- Individuals with frequent or severe autonomic dysreflexia
  - More than 3 symptomatic events per week

- BP ≥140/90 mmHg
- Significant adverse subjective symptoms reporting

- Hypertension
- Any neurological condition other than SCI (Alzheimer's disease, dementia, stroke, multiple sclerosis, Parkinson's disease, etc.)
- History of epilepsy or other seizure disorder
- History of traumatic brain injury (TBI)
- Liver or kidney disease.
- Bladder issuing including blockage of the urine and/or weak urine stream.
- Diagnosis of a psychiatric disorder such as schizophrenia or bipolar disorder
- Known artery disease, heart failure, AV block, and irregular heartbeat.
- Any allergies to aspirin, mirabegron, pyridostigmine bromide, midodrine hydrochloride, polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide.
- Mini mental status exam score of less than 24
- Vision impaired- more than 20/60 in worst eye (with prescription eyewear)
- Major surgery in the last 30 days
- Your prescription medications will be reviewed by the study investigators and research staff. If you are currently taking medications to treat any of the following please make the investigators aware:
  - Depression, Schizophrenia, ADHA
  - Pain (opioids)
  - Infection or illness (antibiotics)
  - Erectile dysfunction (Viagra, Cialis, etc.)
  - Overactive bladder
  - High or low blood pressure
  - Migraine headaches
  - Malaria
  - Asthma
  - Please talk to the research staff if you have any questions about your medicaitons; we may contact your doctor to discuss.
- Pregnant*

2. Description of the Study Including Procedures to be Used:

If you consent to participate in this research study, you will visit the laboratory at the JJPVAMC (7A-13S) 4 times for about 4 hours each visit. You will refrain from caffeine, alcohol, heavy exercise, and smoking for 12 hours prior to arrival and **you will refrain from taking sildenafil (Viagra), tadalafil (Cialis), or other similar medications, for 2-days prior to each of your study visits**. Prior to data collection a baseline blood draw will be collected. You will remain seated in your wheelchair for a minimum of 20 minutes while the research team applies instrumentation. Three sticky electrodes will be placed on your chest and abdomen area to monitor your heart rate and respiratory (breathing) rate. A blood pressure cuff will be placed around your upper right arm and a small blood pressure cuff will be placed on your left middle or ring finger. We will place a plastic harness on your head, apply gel to your forehead and place an ultrasound probe against your head. We will monitor your blood pressure, respiration rate, heart rate and blood flow to your brain (CBF) for 5 minutes while you rest quietly (baseline) prior to administration of the study medication. Following the baseline data collection a series of cognitive tests focused on assessing memory and attention will be administered. You will then be given pills with a glass of water. The pills will contain either placebo, pyridostigmine, mirabegron, or midodrine. During each of the four visits, you will take only 1 type of medication or placebo. If you complete all 4 visits, you will have taken one of each medication including placebo. You will not know which of the study medications or placebo you will be taking at any given visit. The effective dosage for each medication was determined from your participation in the previous "titration" trial. After taking the study medication, heart rate, respiratory rate, blood pressure and blood flow to the brain will be monitored for 4-hours and a second battery of cognitive tests, similar to the first battery, will be administered 2 hours after taking the medication. After you finish the second cognitive tests a final blood draw will be performed. Each of the medications we have chosen have short duration of action so any bad reaction should last for a short period of time. But if at any time you feel uncomfortable, we will immediately stop the study medication and all testing and will monitor your heart rate, breathing rate, and blood pressure very closely until you recover.

Table 1: Protocol Timeline

Time Point	**Pre-1**	**Pre-2**	**Pre-3**	**Drug**	**Post-1**	**Post-2**	**Post-3**	**Post-4**
Time (min)	0-10	10-25	25-30	30	60-120	120-180	180-240	240-300
Heart Rate	instrumentation	1x	1x		2x	2x	2x	2x
Breathing Rate		1x	1x		2x	2x	2x	2x
Drug administration				x				
Beat-to-beat BP		1x	1x		2x	2x	2x	2x
Manual BP		5x	5x		4x	4x	4x	4x
CBFv		1x	1x		1x	1x	1x	1x
AD Survey		1x	1x		1x	1x	1x	1x
Blood Draws		1x (3.6) teaspoons or 18mL				1x (3.6) teaspoons or 18mL		
Cognitive Tests		1x				1x		

Heart Rate & Respiration Rate : Three electrodes (small sticky pads) will be placed on your chest and abdomen to continuously monitor your heart rate and respiratory rate during each study visit. Heart rate will be monitored and recorded for 5-minutes during the baseline period and at 30-minute intervals after administration of the study medications and during the cognitive test.

Blood Pressure: Blood pressure will be monitored and recorded from your right upper arm using standard procedures at 1-minute intervals during baseline and at 30-minute intervals after administration of the study medications. Finger blood pressure will be monitored continuously from your left middle or ring finger on a beat-to-beat basis during the baseline period. Beat-to-beat blood pressure will be recorded throughout the cognitive tests and at 30-minute intervals throughout the 4-hour period following administration of the study medications.

Cerebral Blood Flow: CBF will be monitored and recorded using a small Doppler ultrasound probe (a noninvasive test that measures brain blood flow) with ultrasound gel that will be placed over your left temple to measure blood flow velocity through your middle cerebral artery. The Doppler probe will

be held in place with a head harness which will be tightened so that the probe doesn't move around during testing.

Cognitive Tests: These tests evaluate different types of cognitive function such as your short-term, and long-term memory, attention processing speed, and executive function. During this time we will continuously monitor and record your heart rate, breathing rate, blood pressure and blood flow to your brain using the equipment attached to you.

Autonomic Dysreflexia (AD) Symptoms Survey: Autonomic dysreflexia is a condition where blood pressure increases higher than normal, usually because of a painful or non-painful stimulus below the level of your spinal cord injury. Some of the most common causes of AD relate to bowel or bladder fullness, tight clothing, or pressure from being in a position for too long, but there may be other causes that we are not aware of. You will be asked to complete an AD symptoms survey during each study visit, which will be used to determine your experience with AD over the 7-days prior to the study visit. This survey contains questions related to symptoms you may have experienced, information about your blood pressure at that time, and possible causes of the AD.

Blood Draws: Blood will be drawn from a vein in your arm or hand twice over the course of each study visit. Each blood collection tube will contain about 1.2 teaspoon (6mL) of your blood. Three blood samples will be taken before baseline data collection in the seated position. Three more samples will be taken after the second cognitive test while you are seated. A certified and trained researcher will gently insert a very small needle into the vein in your arm to collect the blood. Once the blood has been collected, the needle will be removed and the puncture site will be cleaned and covered. At each study visit, six tubes of 6mL of blood will be collected. A total amount of 144mL of blood will be collected at the end of the four study visits.

All specimens obtained during this study will be stored in the Basic Science Laboratory at The Center of Excellence on the Medical Consequences of Spinal Cord Injury located at the James J. Peters Veterans Affairs Medical Center, Bronx, NY. All samples will be labeled with a number randomly assigned to you, along with the date and information regarding the study. Samples will be stored for future analysis specifically related to this study. Samples will be stored until all data related to this study has been analyzed and at the end of this period specimens will be destroyed.

3. Description of any Procedures that may Result in Discomfort or Inconvenience:

You have been told that the study described above may involve the following discomforts:

- You may experience some discomfort when electrodes are removed from skin and some skin irritation at the site of electrode placement.
- You may experience some discomfort when the blood pressure cuffs around your upper arm and your finger is inflated.
- You may feel discomfort with the harness around your head that is used to secure the ultrasound probe to your head for assessment of brain blood flow.
- Possibly frustration may occur during the thinking tests. You will be encouraged to take breaks as needed and you may stop a test at any time and for any reason.
- Since this research may have unknown effects on an unborn child and should not be done during pregnancy, it is necessary for a pregnancy test to be done first. To your knowledge you are not pregnant at the present time. You also agree to avoid becoming pregnant (use contraceptives, take precautions against becoming pregnant, etc.) during this study.
- You may experience some discomfort when the needle is being placed in your arm vein during the blood draws.

4. Expected Risks of Study:

- Heart rate, breathing rate, and blood pressure: are all non-invasive measurements and are not associated with any known risks.
- You may experience pain, bruising, and rarely fainting or infection from the blood draws.
- Your blood pressure may be elevated above what is considered to be the normal range (>140/90 mm Hg) following midodrine, pyridostigmine, and mirabegron administration. If this happens, we will take action to help reduce higher pressure; we will loosen any tight clothing or braces that you may be wearing; and we will help you check and empty your bladder or bowel. If your blood pressure remains high for more than 30 minutes after we take these measures, then we may provide medication to lower your pressure back to normal. The medication of choice will be sub-lingual (under the tongue) nitroglycerin.
- If after 4-hours of testing your BP remains above your baseline but is not in the hypertensive range (>139/89 mmHg), you will be sent home with a 24-hour BP Holter monitor (Vasomedical-BIOX™ 2301 Wuxi, Jiangsu, China). The monitor will be programmed to obtain BP readings every 20 minutes during the daytime and at 30-minute intervals during the nighttime. A study coordinator or the PI will follow-up with phone calls to you while you are at home to assess any side effects and document BP changes.
- You will be asked to immediately report any significant AE you may feel after leaving the laboratory. Symptoms which you should be particularly aware of include: headache,

pounding in the ears, blurry vision, nausea, goosebumps, chills and spasms; please alert the research staff if you experience any of these symptoms in greater frequency or severity during the experiment or after you leave the laboratory.

- In order to diminish the possible risks of interaction between the study medications and other medications you may be taking, you may be asked to avoid taking prescription medications on the day of the study, which should be approved by your primary physician.
- There may be interactions between the study medication and prescription medications you may be taking. In order to lower the risk to you the research staff will monitor your medications and may contact your doctor if needed. Medications prescribed for conditions not mentioned in the exclusion criteria, may have minor or moderate risks, (meaning the effects are considered tolerable and in most cases there is no need for medical intervention), and may be permitted, but decisions about your study participation should be made by study personnel in conjunction with you and your doctor.
- Symptoms of autonomic dysreflexia (AD) may become more frequent or worse while taking midodrine, mirabegron and pyridostigmine.
- Common side effects of all three medications are dizziness, nausea, blurred vision , headache, bladder pain, difficulty, painful, and/or burning urination. Also, an urge to urinate or urine retention.
- **Midodrine** risks (≤8% likely) include: cardiac awareness (irregular heartbeat or shortness of breath), pounding in the ears, increased dizziness, slow pulse, fainting, tingling and itching of the scalp, goosebumps, chills, constipation, superficial venous thrombosis (a blood clot in a vein), vascular ischemia (blockage of blood supply in an artery), and temporary muscle spasms.
- **Pyridostigmine** risks: (≤2% likely) include; upset stomach, abdominal cramps, increased saliva/mucus, urinary frequency and/or urgency, nausea, increased flatulence, wheezing, decreased pupil size, increased sweating or cold sweat, pale skin, watery eyes, warmth or tingly feeling, and rash or itching.
- **Mirabegron** risks (0.2% likely) include: abdominal or stomach pain, dry mouth, difficultly with breathing, muscle aches, diarrhea, constipation , bloating, sinus pain, and sore throat.
- Since this research may have unknown effects on an unborn child and should not be done during pregnancy, it is necessary for a pregnancy test to be done first. To your knowledge you are not pregnant at the present time. You also agree to avoid becoming pregnant (use contraceptives, take precautions against becoming pregnant, etc.) during this study.
- As with any research, there may be unforeseen risks and discomforts. A medical doctor associated with the study will be available to treat any medical emergency that may develop.

5. Expected Benefits of the Study:

There may be no direct benefit to you from this study, but information learned may help others.

6. Other Treatments Available:

Participation in the study is voluntary and you understand that the only alternative is to not participate.

7. Use of Research Results:

We will let you and your physician know of any significant new findings made during this study which may affect your willingness to participate. All research material generated from the study will remain in the possession of Dr. Wecht and her study team. De-identified electronic data will be stored on secured VA networks, behind VA firewalls, in access-restricted folders. Coded physical data will be stored at the JJP VAMC in locked file cabinets behind locked doors. Access to the research materials generated from the study will be restricted to Dr. Wecht's research team. Your medical records will be maintained according to this medical center's requirements and all electronic and hard copy Research Records will be retained according to National Archives and Records Administration, Records Schedule Number RCS-10-1.

☐_____ By checking this box and initialing, you agree to be contacted by the Principal Investigator or her investigative team at a future date for additional studies being conducted in the National Center for the Medical Consequences of SCI.

If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. No information by which you can be identified will be released or published unless required by law. In order to comply with federal regulations, research records identifying you may be reviewed by the following: Authorized representatives of the Bronx VAMC (e.g. Institutional Review Board, Research Compliance Officer) and VA, including the Office of Research Oversight (ORO), Federal Agencies such as the Government Accounting Office (GAO), VA Office of Inspector General (OIG), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP).
Because this research involves articles regulated by the FDA, the FDA may choose to inspect and copy medical or research records that identify individual research subjects". If this study was initiated on

or after March 7, 2012, a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include a summary of the results. You can search this web site at any time.

8. Special Circumstances:
If you are a patient, a copy of this consent form will be placed in your medical record.

9. Compensation and/or Treatment in the Event of Injury:
The VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Further information about compensation and medical treatment may be obtained from the medical administration service at this VA medical center. A veteran-participant does not have to pay for care received as a participant in a research project, except in accordance with federal law that certain veterans have to pay co-payments for medical care and services provided by the VA.

10. Voluntary Participation:
You are not required to take part in this study; your participation is entirely voluntary. You can refuse to participate in this study or withdraw your participation in this study after you consent without penalty or loss of VA or other benefits to which you are entitled. During the course of the study, you will be told about any new findings within the investigation or about information reported in the literature or reported verbally to the investigators that might affect your willingness to remain in the study. A signed copy of this consent form will be given to you.

11. Termination of Participation:
You can refuse to participate now or you can withdraw from the study at any time after giving your consent. This will not interfere with your regular medical treatment, if you are a patient. The investigator also has the right to withdraw you from the study at any time for reasons including, but not limited to, medical concerns (your health and safety are in jeopardy with continued participation in the study), non-compliance (you miss several scheduled appointments without notification) and protocol deviations (exclusion/inclusion criteria change and you are no longer eligible to participate).

12. Costs and Reimbursements:
As a veteran or non-veteran, you will not be charged for any treatments or procedures that are part of this study. For veterans who are required to pay co-payments for medical care and services provided

by VA, these co-payments will continue to apply for medical care and services provided by VA that are not part of this study. Reimbursement typically takes 6-8 weeks to arrive by Electronic Transfer Fund (EFT) and 12-14 weeks to arrive by check. You understand that if you choose to receive reimbursement through EFT, you will be required to provide the research staff information that includes; name of your bank, routing number and account number.

You have been told that you will receive up to $300 for participation in this research study according to the following schedule:

- Visit 1 - $75.00
- Visit 2 - $75.00
- Visit 3-$75.00
- Visit 4- $75.00

You understand that payment will be processed after each study visit based on the above schedule, and that you will be paid for each study visit you attend and complete. You understand that if you cannot complete all study visits you will be paid for the testing sessions that you complete.

13. Contact Person(s):

If you have any questions, at any time, about this research, or want to discuss any possible study-related injuries, please call telephone number 718-584-9000, ext. 3122 for Dr. Wecht. In addition after-hours you can contact Dr. Wecht at (201) 390-0487 or the medical doctor affiliated with this study: Dr. William Bauman at (914) 329-4772.

I understand that should I wish to discuss my participation in this study with any other doctor or layperson, I can contact Mary Sano, Ph.D. ACOS/R&D Program by requesting an appointment at (718) 741-4228 hospital extension 4228, first floor in the research building, room 1F-01 If I have questions, concerns and/or complaints or to offer input.

RESEARCH SUBJECTS' RIGHTS:

You have read or have had read to you all of the above. Dr. Jill M. Wecht, EdD or her delegate has explained the study to you and answered all of my questions. You have been told of the risks or

discomforts and possible benefits of the study. You have been informed of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but my records will not be revealed unless required by law. This study has been explained to me. I have had a chance to ask questions. I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

Subject Signature	Date	Time

Person Obtaining Informed Consent (Print Name) (Investigator or Delegate as indicated on Assurance Page)	Signature of Person Obtaining Informed Consent	Date

VERBAL CONSENT IF THE PARTICIPANT LACKS UPPER LIMB FUNCTIONS TO COMFORTABLY WRITE

_____ is unable to sign the consent form due to impaired arm function. I certify that I have carefully explained the purpose and nature of this research to him/her

in appropriate language and he/she has had an opportunity to discuss it with me in detail. I have answered all of his/her questions and he/she has consented to participate in this research. I, therefore, am signing the consent form to document that he/she has given his/her consent to participate in this research study.

Person Obtaining Consent: _____

Name: _____

Signature: _____

Date: _____

Witness Name: _____

Signature: _____

Date: _____