

# Consent Form for Participation in Research

## New York Medical College

Name of Patient/Subject :

Affiliate:

Address:

Chart Number:

**Title of Research Project: Sympathoexcitation in Orthostatic Intolerance – and addendum to Local Vasoconstriction in POTS**

**Note: This project involves the experimental use of a new drug/device/procedure called: Angiotensin-II and L-NMMA**

**This project does not involve the experimental use of a new drug/device/procedure.**

### **Explanation of Research Project:**

You are being asked to participate in this study because you have Orthostatic Intolerance (OI), due to Postural Tachycardia Syndrome (POTS) . These can all be accompanied by problems in blood pressure regulation and fast heart rate when standing. Symptoms can include dizziness, headache, fatigue, and exercise intolerance to name a few. Symptoms are usually relieved by lying down. It is thought that many of these symptoms are caused by abnormalities of the way in which your blood volume shifts when you go from lying to standing. The movement of blood is controlled in part by muscles that line your blood vessels. These muscles are also controlled by chemicals that are produced locally, by circulating chemicals as well as by the activity of your nervous system. The activity of these chemicals and nerves is affected by many different things including your blood pressure, heart rate, blood volume and rate and depth of breathing. Therefore in order to understand why you are orthostatically intolerant we would like to perform the following tests (listed and described individually below), many of which will be done at the same time throughout the performance of this study.

This study is designed to take place over 2 days and will require that you remain on a tilt-table while being hooked-up to the various monitoring devices described below; you will be able to watch movies or sleep during much of the time. While you are being monitored we will perform tests that are designed to stimulate your heart, your nervous system and circulatory system (blood vessels); these include giving you various drugs intravenously (through a needle) and by mouth, and performing incremental tilt-table testing . Intravenous drugs will be given through a catheter that will be placed in your arm at the beginning of the day and will be removed following testing.

Two of these drugs, angiotensin-II and L-NMMA, are regarded as experimental drugs in that they are not currently marketed for the treatment of any disease. They are produced using best manufacturing practices for research and therefore conform to pharmaceutical grade controls.

All of the tests mentioned above will be explained in detail below. To evaluate how your body responds to these tests we need to monitor many things that include the following:

### **MONITORING PROCEDURES:**

1. Muscle Sympathetic Nerve Activity (MSNA) tests the manner in which your nervous system responds to changes in heart rate and blood pressure. To measure this, we will place a very thin needles in the skin behind

one knee. The needle is as thick as an acupuncture needle and most subjects do not feel any discomfort when they are inserted. Once in place, they will be connected to a signal recorder and they will remain in your skin for several hours.

2. Blood Pressure, EKG, Heart Rate, Respiratory Rate, End Tidal pCO<sub>2</sub>, will be recorded to measure how your heart rate, blood pressure and breathing respond. This will be done by placing electrodes (stickers) on various parts of your body and attaching wires to the electrodes. Your breathing rate will be recorded by placing a strap around your chest and the composition of your breath will be measured by placing a thin breathing tube in your nostrils.

3. Impedance Plethysmography, Strain Gauge Plethysmography will allow us to measure how blood shifts in your body during tilt and LBNP. This will be done by placing electrodes (stickers) on various parts of your body and attaching wires to the electrodes and by placing strain gauges (similar to small rubber bands) around your arm and lower leg.

4. Total Blood Volume will be measured by injecting you with Indocyanine Green Dye, which is harmless, and measuring its distribution with a device that is placed on your index finger.

5. Ultrasound examinations of your femoral artery, or portal vein or mesenteric artery will be done throughout testing to evaluate how these blood vessels respond. This painless procedure will be done by placing an ultrasound probe above these blood vessels and recording the signal generated when the sound waves bounce back to the probe from the blood vessels.

As noted above, once we have attached all of the electrodes and measuring devices we will begin our measurements of your blood pressure, heart rate, etc. We will then stimulate your body to change these values by performing different maneuvers. These include giving drugs intravenously, and performing incremental tilt-table testing. Many of the tests will be performed at the same time; for example, drugs may be given during tilt or LBNP or in various combinations.

#### TESTING PROCEDURES:

1. Drugs will be injected at various times during the studies to increase or decrease your blood pressure by a small amount., An oral drug will also be given during one part of the study.. These drugs may change your heart rate, your nervous system activity and your blood vessel diameters. We will monitor these changes as part of this study. The injected drugs will be given through the intravenous catheter that will be placed in your arm at the beginning of the studies. The drugs that you will receive intravenously and that will increase your blood pressure are: Phenylephrine, Angiotensin-II and NG-monomethyl-L-arginine (L-NMMA); drugs that you will receive intravenously and that will lower your blood pressure are: sodium nitroprusside (SNP) and hydralazine. Losartan will be given orally and can lower your blood pressure by a small amount. Some drugs will be given to help to restore your normal blood pressure when it has increased or decreased. For example, if blood pressure decreases excessively with one drug then it will be counteracted by a blood pressure raising drug. The raising and lowering of your blood pressure is being done deliberately as part of this study.

2. The Rate and Depth of your Breathing will be altered to determine the effect of these changes on the activity of your nervous and circulatory system.

3. To perform Incremental Tilt-table Testing, an electrically driven tilt table with a footboard will be used. First baseline measurements of blood flow will be performed. When these are complete, subjects will be tilted upright incrementally to 20°, 35°, 70° remaining at each angle for 10 minutes. Measurements will be repeated after 5 minutes of tilt at each angle. This will result in blood pressure, heart rate and nervous system changes that will be monitored and recorded.

#### Risks Associated With the Protocol:

If you are a woman and you are pregnant, you cannot participate in this study. If you are not pregnant you must be using an acceptable form of birth control at the time of participation.

If you agree to participate you may experience the following as a result of monitoring and testing.

**Muscle Sympathetic Nerve Activity (MSNA):** The risks associated with MSNA are related to having needles placed into your skin. These could occasionally cause pain and bruising. To minimize pain, we use very thin needles. If you experience pain, we will remove the needles and we will try to insert them in a different location.

**Blood Pressure, EKG, Heart Rate, Respiratory Rate, End Tidal CO<sub>2</sub>:** The only risk associated with this type of monitoring is that some individuals may develop a rash due to sensitivity to the adhesive on the electrodes. If this occurs, electrodes with different adhesive will be used.

**Impedance Plethysmography, Strain Gauge Plethysmography:** The only risk associated with this type of monitoring is that some individuals may develop a rash due to sensitivity to the adhesive on the electrodes. If this occurs, electrodes with different adhesive will be used.

**Total Blood Volume:** There is a small risk of an allergic reaction to the intravenous injection of the indocyanine green dye. If this occurs antihistamines will be administered. There is also a risk of bruising and discomfort associated with the insertion of the intravenous catheter (tube) that will be used for the injection of the dye and the other drugs listed below.

**Ultrasound examination of your blood vessels:** There are no known risks associated with this procedure.

Drugs General Comments: Drugs will either be injected as a bolus (one single amount) or infused over time through the intravenous catheter in your arm and will be used to either increase or decrease your blood pressure. This can cause a change on your heart rate as well. As a result, if your blood pressure falls, you may experience some light-headedness, dizziness or nausea. If your blood pressure rises excessively, you may experience a headache. Because changes in blood pressure can cause an increase in heart rate, you may experience a feeling of your heart pounding. This effect will be minimized because you will be lying down at the time. Also, in all experiments, the heart rate and blood pressure will be deliberately returned to usual baseline levels through the use of another drug. Additional effects of drug-induced changes in heart rate and blood pressure will be minimized due to continuous monitoring of these values. If problems arise or if you do not feel well because of this the drugs will be stopped immediately. There is always a small risk of an allergic reaction to any medication. However, these rarely occur with the drugs that we are using and if they occur we will end the study and administer necessary treatment.

Drugs: Specific Comments: Bolus Administration of sodium nitroprusside and phenylephrine (neosynephrine). The method is used to test your nervous system reflexes and has been in use for approximately 50 years. Typically it produces a decrease in blood pressure of 15 mmHg below your normal value followed by an increase in blood pressure by approximately 15 mmHg. This should be nearly imperceptible. Medications which are infused over time include angiotensin, L-NMMA, and sodium nitroprusside. Angiotensin is a circulating hormone and has effects on blood vessels, on the nervous system and on the kidneys that mostly result in increased blood pressure during short-term experiments such as ours. Long term effects take days at least. L-NMMA is also normally made by the body in small amounts and is a blocker of a blood vessel regulator called nitric oxide. Angiotensin and L-NMMA both decrease nitric oxide which can increase blood pressure. During our experiments we will be deliberately counteracting the blood pressure increasing effects of angiotensin and L-NMMA with another medication called hydralazine (apresoline). Both angiotensin and L-NMMA are regarded as experimental drugs in that they are not currently marketed for the treatment of any disease. They are produced using best manufacturing practices for research and therefore conform to pharmaceutical grade controls. They have both been used for research at least hundreds of times with the results mentioned above.

In another part of the study you will receive losartan by mouth and an infusion of sodium nitroprusside. These produce effects that are opposite to angiotensin and L-NMMA. Losartan blocks the effects of angiotensin while sodium nitroprusside donates nitric oxide to the body. They can lower your blood pressure. However, during our experiments we will be deliberately counteracting the blood pressure decreasing effects of losartan and sodium nitroprusside with another medication called phenylephrine which can be very accurately adjusted. Losartan can sometimes produce gastrointestinal discomfort which will be grounds for terminating the experiment. Dizziness may happen with either drug but should disappear with the proper counteracting dose of phenylephrine Hypersensitivity or low blood cells can happen but are very rare and will be promptly recognized and treated. Apart from low blood pressure sodium nitroprusside in the dose given has few side effects over the short time course of the study.

Effects of counteracting medications: Hydralazine will be used to counteract increased blood pressure. Hydralazine can cause headache and abdominal discomfort sometimes. If this occurs we will end the study. There can be dizziness and tingling and hypersensitivity reactions. Sometimes nasal congestion and tearing occurs. Phenylephrine is also known as neosynephrine. Phenylephrine infusion will be used to counteract decreased blood pressure. Side effects include increased blood pressure, headache, slower heart rate, excitability, restlessness, and rarely irregular heart beats. These disappear rapidly when the drug is stopped. The drug can be very accurately adjusted.

Incremental Tilt-table Testing: This may cause you to experience light-headedness, dizziness or nausea. Since we will be performing continuous monitoring of your heart rate and blood pressure, we should be able to anticipate the start of these symptoms. If they occur, or if you become uncomfortable at any time during testing we will return the table to the supine (flat) position.

There are no direct benefits to you for participating in this study. There may be future benefits to society after completion of the studies as the information may increase our understanding of the mechanisms that lead to Orthostatic Intolerance. There are no alternatives to participation because this study is not intended to treat or cure Orthostatic Intolerance.

If you agree to participate, you will be paid \$300 for the 2 days it will take to complete the studies.

## Consent Form for Participation in Research (continued)

### Research-related Injury

New York Medical College and its affiliated institutions (Metropolitan Hospital Center and Westchester Medical Center) do not provide financial compensation for injury or illness resulting from participation in research, but essential medical care is available. Unless the sponsor provides otherwise, payment for treatment of any injury or illness resulting from participation in research will be assumed by you personally or through your medical insurance. You should contact the investigator in the event of a research-related injury.

### Confidentiality

This consent form and your medical records are subject to review by representatives of New York Medical College, the study sponsor, cooperative study groups, and State and federal regulatory agencies. By signing this form you agree that your medical records (or those of the person for whom you are signing this form) may be copied by study doctors and their representatives, by study sponsors and their representatives, and by regulatory agencies of the State of New York or of the federal government. If this investigation is published, you will not be identified by any personal data. You will be given a copy of the signed consent form. Other copies will be kept in confidential files in the investigator's office and (if appropriate) with your medical chart.

### Voluntary participation

Your signature indicates that you understand this consent form and freely consent to participate in this study. You are free to refuse or to discontinue participation in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

### Offer to answer questions

You may call the investigator if you have any questions about your participation in the study. You may call the Office of Research Administration at (914) 594-4480 if you have questions about your rights as a research subject.

Not valid without the Committee stamp    Subject's Signature    Date

Signature of person authorized to consent    Position    Date for subject or witness if consentor is illiterate or unable to sign

Signature of person obtaining consent    Date

**Julian M. Stewart, MD, PhD 914-593-8888**

Name of Principal Investigator    Telephone Number

Void one year from above date    Name of Sponsor

**The Committee for Protection of Human Subjects is the Institutional Review Board for: New York Medical College  
Metropolitan Hospital Center Westchester Medical Center**