

# Consent Form for Participation in Research

## New York Medical College

Affiliate \_\_\_\_\_

Name of Patient/Subject \_\_\_\_\_

Address \_\_\_\_\_

Chart Number \_\_\_\_\_

Title of Research Project: **Local Vasoconstriction in Postural Tachycardia Syndrome**

- This project involves the experimental use of a new drug/device/procedure called: angiotensin-II, angiotensin-1-7, apocynin, ebselen, HOE-140, and tempol delivered by microdialysis.
- This project does not involve the experimental use of a new drug/device/procedure.

### Explanation of Research Project:

#### Purpose of the Study

You are being asked to participate in this study because you have Orthostatic Intolerance (OI), due to Postural Tachycardia Syndrome (POTS) or you are a healthy volunteer. OI is defined by symptoms such as dizziness, headache, fatigue, nausea, palpitations, sweating and exercise intolerance which are relieved by lying down. POTS is OI associated with a rapid heart rate (tachycardia=fast heart rate). It is thought that many of these symptoms are caused by abnormalities of the way in which your blood volume (the amount of blood in your circulatory system) 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, and 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, and blood volume. 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.

For some patients and all healthy volunteers the study will take place over 4 days and will require that you remain lying down on a tilt-table for 6 hours for the first 2 days while being hooked-up to microdialysis apparatus comprising tiny tubes inserted within the skin. We will also perform very small skin biopsies (skin samples) under local anesthesia. During the third day you will be 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 performing tilt-table testing. Intravenous drugs will be given through a catheter (a small plastic tube) that will be placed in your arm at the beginning of the day and will be removed following testing.

POTS patients with low blood flow will be also be enrolled in a chronic study to test whether the medication, losartan, will benefit them. The effects of losartan are explained in following pages. If you are a low flow POTS patient then during one month you will receive either losartan or placebo (a pill with no effects) which will be made to look like losartan. During a second month losartan or placebo will be switched. After each month we will retest the way your nervous system works and whether there is improvement with respect to the effects of angiotensin-II and blood flow. Thus, low flow POTS patients will have the 4 visits that all patients and healthy volunteers have, and also two additional visits to find out whether losartan is beneficial compared to placebo.

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:

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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 upright tilt. 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 popliteal artery (behind the knee) and of the middle cerebral artery (at the temple) will measure leg and brain blood flow throughout testing on the third day to evaluate how these blood vessels respond to different medications and procedures. 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.
6. Measurement of cerebral hemoglobin oxygen saturation using near infrared spectroscopy (NIRS). It is entirely noninvasive and obtains information by illuminating the head with a small amount of near infrared laser light similar to light used in finger pulse oximetry and to laser Doppler flowmetry.

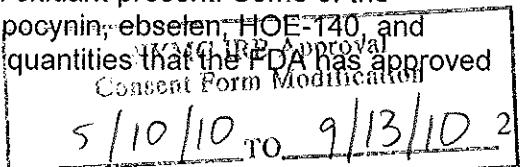
As noted above, once we have attached all of the electrodes and measuring devices we will begin our measurements of your blood pressure, heart rate, etc. We will then stimulate your body to change these values by performing different maneuvers. These include giving drugs intravenously, performing tilt-table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

Testing Procedures:

Risks of testing procedures are located on following pages where they are explained in detail.

1. Local blood properties by Microdialysis: We can also sample tissue fluid for biological molecules and deliver small amounts of chemicals through microdialysis probes, which are tiny tubes inserted within the skin using a small needle. This is done to measure the local release of biochemicals that affect release and destruction of nitric oxide (NO) and angiotensin-II (Ang-II), two very small molecules which are important for blood vessel regulation and also for the release of oxidants.

In addition, we will deliver small amounts of chemicals (Ang-II, angiotensin-(1-7), ebselen, apocynin, tempol, HOE-140, enalaprilat, ACE2 inhibitors, and ascorbate) through the probes, which test how Ang-II and NO works, whether we can improve blood flow with antioxidants (apocynin and ascorbate), and whether vessel widening chemicals such as angiotensin-(1-7) improves NO and local blood flow. Some of the biochemicals which affect NO are oxidants and we will test whether there is too much oxidant present. Some of the biochemicals are experimental drugs (angiotensin-II, angiotensin-1-7, apocynin, ebselen, HOE-140, and tempol). However, all of the experimental drugs are given in such small quantities that the FDA has approved



the experimental drugs for use in this study. An advantage of local administration of medication is that it only affects the tiny area of skin tested and has no effect on overall circulation or on the rest of the body. Side effects, if any, are at most minor and local. We can test how blood vessels work without disturbing the natural workings of the heart and circulation. We will also be able to tell how well nerves are working by gently heating an area of skin and looking at LDF.

2. Blood sampling for angiotensin, angiotensin(1-7), oxidants, renin, aldosterone, because abnormalities in these biochemicals have been shown in some POTS patients. We will also obtain blood and urine samples for sodium, potassium, and creatinine to estimate renal function and salt status.

Recent preliminary work suggests that some of the blood flow problems in POTS may be inherited and could be responsible for local activation of inflammation. Blood samples will be analyzed for gene and protein expression (i.e. how much of a particular molecule is being made).

Blood samples will also be collected for analysis of genetic material (DNA) to look for the gene or genes that can cause blood flow problems and inflammation. Blood samples may be kept up to five years. Blood may also be sent anonymously without identifiers to other laboratories for testing. Collecting genetic material, while a key aspect of the research, requires your specific permission. If you agree to the collection of blood for this purpose please initial the "Yes" box.

I agree to the collection of blood for genetic purposes      Yes-       No-

3. On the third day of testing drugs will be injected at various times during the studies to increase or decrease your blood pressure by a small amount., An oral drug, losartan, that blocks Ang-II 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 third study day. The drugs that you will receive intravenously and that will increase your blood pressure is called phenylephrine, the drug that you will receive intravenously and that will lower your blood pressure is sodium nitroprusside (SNP). Either ascorbic acid (vitamin C) will be given intravenously or saline (intravenous salt water). If ascorbic acid is given on the first day then saline will be given on a second day as a control and vice versa. It is possible but unlikely that ascorbic acid can lower your blood pressure by a small amount. Some drugs or intravenous fluids 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.

POTS patients with low blood flow will be also be enrolled in a chronic study to test whether the medication, losartan, will be of benefit. During one month you will receive either losartan or placebo (a pill with no effects) which will be made to look like losartan. During a second month losartan or placebo will be switched. After each month we will retest the way your nervous system works and whether there is improvement with respect to the effects of angiotensin-II and blood flow.

4. Tilt-table Testing is performed using an electrically driven tilt table with a footboard. First baseline measurements of blood flow will be performed. When these are complete, subjects will be tilted upright incrementally to 45 to 70 degrees remaining upright for 10 minutes. This will result in blood pressure, heart rate and nervous system changes that will be monitored and recorded.

5. Skin Punch Biopsy: Biopsies will be performed using local anesthesia with local anesthetic after cleansing the skin with iodine and alcohol. Two 3mm (1/4 inch) biopsy samples will be obtained from the skin of the calf using a disposable skin punch. Samples will be analyzed for gene and protein expression (i.e. how much of a particular molecule is being made).

Collecting genetic material, while a key aspect of the research, requires your specific permission. If you agree to the collection of skin for this purpose please initial the "Yes" box.

I agree to the skin biopsy      Yes-       No-

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Risks and Discomforts 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.

Risks of Monitoring:

1. Muscle Sympathetic Nerve Activity (MSNA): The risks associated with MSNA are related to having electrodes 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.
2. Blood Pressure, EKG, Heart Rate, Respiratory Rate, End Tidal CO2: 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.
3. 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.
4. 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.
5. Ultrasound examination of your blood vessels: There are no known risks associated with this procedure.
6. Near Infrared Spectroscopy (NIRS): There are no known risks associated with this procedure.

Risks of Testing:

1. Microdialysis: This procedure requires the placement of small flexible tubes into the skin. It could therefore cause some pain and bruising. The risk is comparable to receiving a shot. To minimize discomfort an area of your leg will be numbed with ice before inserting the needle. Once this needle is inserted it should not cause any discomfort because it is made of plastic and is flexible.
2. Blood sampling and intravenous catheter insertion may result in a small amount of discomfort and the potential for later bruising
3. Drugs: Drugs General Comments: Drugs will be briefly injected as a bolus (one single amount) through the intravenous catheter in your arm and will be used to either increase or decrease your blood pressure for a very short period of time. 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

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decrease in blood pressure of 15 mmHg below your normal value followed by an increase in blood pressure by approximately 15 mmHg.

Ascorbic acid will be given by intravenous infusion to all subjects. Its main potential side effect is transient mild soreness at the site of injection. Very rapid intravenous administration can cause temporary faintness or dizziness. These effects immediately dissipate if the infusion rate is lowered. Healthy volunteers usually experience no changes in vital signs but this may not pertain to POTS patients. If decreased blood pressure becomes a symptomatic issue, the experiment will terminate and the patient will receive intravenous saline which invariably leads to symptomatic and blood pressure improvement. Phenylephrine is also available.

Losartan will also be given to low flow POTS patients as part of a chronic drug study. A gradual increase in dose forms part of the regimen. If there are symptoms at one dose then the dose will be reduced. Blood pressure and heart rate will be monitored at home using automated devices. All patients will be closely followed by the Nurse-Research Coordinator and by the Principal Investigator. If there are symptoms and signs of persistently low blood pressure or progressive orthostatic intolerance then rescue can be easily effected through volume loading and phenylephrine as needed.

Effects of counteracting medications: 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.

4. 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.
5. Skin Biopsy: The 3 mm skin biopsies will be performed under local anesthesia using standard sterile technique and sterile disposable biopsy punches which will be discarded after use. It is possible that a small scar may remain after the biopsy site has healed. Sutures are not used in clinical biopsies of <4mm in diameter.

#### Benefits

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.

#### Costs

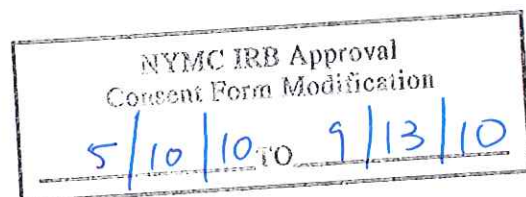
There will be no costs to study participants for any testing or monitoring.

#### Payments and compensation

Subjects will receive \$150 for each day of testing. All subjects are asked to participate in 4 days of testing for a total of \$600. Low flow POTS patients will be asked to participate in a drug trial comparing losartan to placebo which will require 2 additional days of testing for which they will receive an additional \$150 per day. Requests for payment will be submitted after each testing day.

#### Alternatives to Participation

The alternative is to not participate in this study.



**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, including the Food and Drug Administration (FDA). 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.

\_\_\_\_\_  
Subject's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of person authorized to consent  
or subject or witness if consentor is illiterate or unable to sign

\_\_\_\_\_  
Position

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of person obtaining consent

\_\_\_\_\_  
Date

Julian Stewart, M.D., Ph.D.  
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Name of Principal Investigator

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\_\_\_\_\_  
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, and Westchester Institute for Human Development

