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:**

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

Explanation of Research Project:

Purpose of the Study

Many people are unable to remain upright for long because of symptoms such as dizziness, nausea and headache or fainting. This may occur on a day-to-day basis and may severely compromise lifestyle. The most common cause of this condition is the postural tachycardia syndrome (POTS), which is believed to affect at least a million Americans. POTS is defined by an abnormal increase in heart rate ("tachycardia") that occurs when upright (therefore "postural"). POTS has many causes, some related to excess fluid in the lower limbs. This excess fluid is sometimes called "pooling" because there is often purple discoloration of the arms and legs. Although many scientists expected blood to be collecting abnormally in the arms and legs, previous work shows that this is not true. Instead the pooling effects are due to abnormalities of blood flow. Also, some of these abnormal flow patterns and pooling effects occur in the abdominal circulation where they may be related to local activation of an inflammation-like effect. Blood flow regulation is partly due to the nervous system and partly due to local factors. It is these local factors which we are studying. Many of the local factors relate to regulating properties of the innermost cell layer of blood vessels, which is called the endothelium. "Endothelial cell dysfunction" or ECD is the term used to describe impaired endothelium regulatory ability. ECD is often related to a defect or set of defects in a very simple molecule called nitric oxide or NO whose job it is to control blood vessel size with changes in blood flow, changes in blood vessels during inflammation and blood vessel leakiness. In addition there is recent evidence that a local inflammatory response related to small nerves may play a role in certain types of POTS.

We are asking you to participate in studies to test whether there are abnormalities in NO production or local nerve activity causing POTS. In this study we will perform tests to measure NO, tests to stimulate the release of NO and tests of the effects of chemicals, which can release NO or replace NO if it is missing. We will also use local heating which can provoke local nerves to release chemicals that may affect NO.

Participation

If you decide to participate we will compare clinical information obtained from patients with POTS to information from healthy volunteers. If you have POTS you will already have had a type of screening examination called tilt table testing at our laboratory during which we established that you have POTS and showed how it relates to peripheral blood flow. You will have also had other testing to ensure that you had no other forms of illness such as heart disease, nervous system disease or infectious disease.

All subjects will undergo tests of how the blood vessels function:

1) Strain gauge venous plethysmography which measures leg and arm vein filling using a strain gauge (an elastic band) encircling the limb and detects changes in fluid within the limb caused by rapidly inflating a blood pressure cuff. Plethysmography will be performed in the arm and leg while lying flat.
2) Impedance plethysmography which uses pairs of electrocardiogram stickers to measure small changes in voltage on passing a tiny current (similar to an electrocardiogram). The voltages tell us whether blood volume is increasing or decreasing and also information about blood flow. These measurements will be performed flat and upright during the early part of the study.
3) Tilt Table Testing: We will test the orthostatic response by head-up tilt table testing, a routine test which is used to evaluate patients with POTS. Subjects are placed on an electrically driven table with supporting footboard capable of tilting upright. Subjects are tilted upright from flat to 70^{o} for a maximum of 10 minutes to assess vascular changes and orthostatic tolerance. After this test is complete we will remove all strain gauges and impedance stickers.
4) Blood volume measurement by indocyanine green dye dilution technique. An intravenous catheter (IV) is placed and a small amount of an inert dye is injected and its concentration detected by light absorption over the finger. This will only be performed on the first day of testing.
5) Blood sampling for angiotensin, angiotensinogen, renin, aldosterone, calcitonin gene related peptide, substance P and C-reactive protein because abnormalities in these biochemicals have been shown in some POTS patients. 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. Therefore, blood samples will 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. We will also obtain blood and urine samples for sodium, potassium, and creatinine to estimate renal function and salt status.
6) Laser-Doppler flowmetry (LDF) will be used to measure skin blood flow while lying flat. This uses a small beam of reflected light.
7) LDF will be combined with microdialysis in which we put tiny tubes called microdialysis probes within the skin using a small needle. This will enable us to measure how much NO and related biochemicals are being locally produced and will allow us to administer small amounts of chemicals into the skin, testing the ability of the blood vessels to react normally. We will determine whether certain naturally produced chemicals can reduce NO production in some POTS patients. An advantage of this method 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 can be 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.
8) Along with microdialysis probes we may also place a direct NO sensor within the skin. This is capable of showing relative changes in NO and will help guide our experiments.
9) We will stimulate local blood flow in two ways: One uses local heating over a small area of skin. The other uses a blood pressure cuff that is inflated for 4 minutes on your arm or leg to a pressure above your highest blood pressure. This causes blood vessels to widen and stimulates the production of NO.
10) We will examine blood flow in your nail beds using a microscope and video camera. This allows us to tell whether the smallest blood vessels are smaller in size than normal or are obstructed.

There will be 2 separate testing sessions each lasting approximately 5-6 hours.

If there is sufficient evidence for a local nervous inflammatory response during our laser heating tests and if there is other evidence for pooling in the abdominal circulation then you may be eligible to receive a medication called octreotide (Sandostatin). This is an FDA improved medication that can selectively contract blood vessels in the abdominal circulation and improve pooling there. The medication is given by injection, initially using a

short acting form which needs to be given daily. Later, if there is a beneficial response, we will test a long acting version of the same drug called Sandostatin LAR Depot.

Risks and discomforts
Monitoring, and plethysmography contribute no additional risk to your care. Laser-Doppler flowmetry is painless, harmless and contributes no additional risk to your care. Gentle heat measurements and reactive hyperemia have no foreseeable risks and have been performed many times in our laboratory without bad outcome. Heating can possibly result in reversible redness over the heated area. Intravenous placement for indocyanine dye dilution experiments may be uncomfortable and produce some bruising. Indocyanine green dye is inert and possesses no known allergic properties. However, should any signs of an allergic response occur we will take immediate corrective measures. Blood sampling will be performed at the time of dye dilution and will not add to risk. Microdialysis probes are harmless but could provoke pain, which might potentially lead to stopping the procedure. In general the discomfort involved is less than intravenous insertion. Measurements made through the tubes have no effects on overall circulation. Administration of chemicals through the probes can at most cause local irritation and redness. Nail bed examination of the skin is completely passive and harmless. Sandostatin can have side effects which are mostly gastrointestinal such as diarrhea and abdominal distension. These are very short-lived when the short-acting form of the drug is given which is another reason that we will use the short acting drug first.

Benefits
There may be direct benefit from this study to POTS patients with ECD. The testing may reveal potential forms of effective treatment. You may therefore derive immediate benefit from the study because it may directly improve your health. If you have normal flow POTS and elect to receive octreotide, this may improve your condition. Also the study will enable us to detect changes in blood vessel function, which may furnish data important for determining other suitable medical therapy in POTS patients. There is no direct benefit to healthy volunteers, although their contribution is essential for purposes of experimental control. Healthy patients will contribute to general medical knowledge.

Tilt testing is standard in the assessment of patients with POTS. Short tilts for 10 minutes are usually very well tolerated by patients and control subjects alike. However, should there be fainting, near fainting or excessive patient discomfort, subjects will be promptly returned to the recumbent position. Intravenous fluids can be given if needed at the end of the tilt test and invariably improve overall well-being after fainting although this is often superfluous. In recent testing neither POTS patients nor volunteers have actually fainted.

Alternatives to participation
The alternative is standard medical care.

Payments and compensation
$300 per subject.

Additional information
There will be no additional cost for testing to the patients. Significant new findings, which may relate to your willingness to continue participation, will be provided. Any change in your health detected during monitoring and testing will be promptly treated. Over a four year period we expect to enroll 60 patients with POTS, and 30 healthy volunteers.

All inquiries will be promptly answered by contacting the investigator, Julian M. Stewart M.D., Ph.D. (914-593-8888)

Consent Form for Participation in Research (continued)

Research-related Injury
New York Medical College and its affiliated institutions (Metropolitan Hospital Center, St. Agnes Hospital, 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 may be 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 -- Offer to answer questions
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. 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

Void one year from above date

_____ _____
Subject's Signature Date

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

_____ _____
Signature of person obtaining consent Date

Julian Stewart, MD, PhD 593-8888
Name of Principal Investigator Telephone Number

National Heart Lung and Blood Institute of the National Institutes of Health
Name of Sponsor

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