

Consent Form for Participation in Research

New York Medical College

Name of Patient/Subject :

Affiliate:

Address:

Chart Number:

Title of Research Project: Microvascular function in Metabolic Syndrome

Note:

- 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.
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Explanation of Research Project:

You are being asked to participate in this study because you have obesity, a large increase in your body mass index (weight in kg/height in meter²), i.e. greater than 95%tile of for their age and sex. Obesity can all be accompanied by problems in blood pressure regulation and it increases the risk of damage to the heart and blood vessels. 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 more about vascular changes in you 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 1 day and will require that you remain lying down 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 circulatory system (blood vessels); these include sampling tissue fluid and delivering small amounts of chemicals through microdialysis probes (thin tube inserted at the undersurface of your calf skin) , having you breath at different rates, pulling a string, immerse your hand in cold water, changing your position from lying flat strapped to a tilt table (so that you do not fall, to almost standing up. Microdialysis drugs will be given through a thin tube that will be placed superficially at the undersurface of your leg at the beginning of the day and will be removed following testing. All of these tests 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:

TESTING 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 2 very thin needles in the skin behind one knee. These needles are as thick as acupuncture needles 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 pCO₂, 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 will allow us to measure how blood shifts in your body during tilt. This will be done by placing electrodes (stickers) on various parts of your body and attaching wires to the electrodes around your lower leg and arm.

4. Ultrasound examinations of your femoral artery, portal vein and superior 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.

5) Laser-Doppler flowmetry (LDF) will be used to measure skin blood flow while lying flat. This uses a small beam of reflected light. It will be combined with skin warming stimulation and microdialysis (see below).

4) Local blood properties by Microdialysis: We can also sample tissue fluid and deliver small amounts of chemicals through microdialysis probes, which are tiny tubes inserted within the skin using a small needle. Before the needle is inserted, we will cool your skin with ice to numb the area. The tube is flexible and will remain in place for several hours. This is done to measure the local release of biochemicals that affect the nitric oxide (NO) molecule and the amount of NO present (NO microelectrode), by delivering small amount of chemical to increase NO (ACh), blocking NO(NLA), and also to make sure that no other control mechanisms are involved, we will deliver small amounts of chemical (losartan) through the probes, which test whether we can improve NO (losartan). 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.

5) Direct measurements of nitric oxide by microelectrode. This is a tiny probe placed in the flow path of the microdialysis probe at insertion time and used to monitor NO throughout experiments.

6) We will stimulate local blood flow by using gentle local heating over a small area of skin.

7) We will test the autonomic nervous system effects on blood flow using 2 simple maneuvers:

a. The Valsalva maneuver in which the subject blows against a pressure for approximately 15 seconds.

b. Forearm handgrip test in which the subject grips a dynamometer (a spring that measures grip strength) for 2 minutes exerting about 30% of maximum force.

c. Cold pressor test in which the subject immerses hand in ice cold water for 1 minute.

d. Tilt table testing (HUT): We will strap you to the tilt table and slowly tilt you from lying flat to 20 degrees, 35 degrees, and 70 degrees for five minutes at each angle. This is similar to standing upright without using your muscles. At the end we will tilt you back to flat level at 0 degree.

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 by microdialysis catheter, having you breath at different rates, performing incremental tilt-table testing and performing hand grip test and immersing your hand in cold water.

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.

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 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.

Impedance 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.

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

Measurements : Monitoring and plethysmography contribute no additional risk to your care. Laser-Doppler flowmetry is painless, harmless and contributes no additional risk to your care.

Microdialysis: Microdialysis probes are harmless but could provoke pain, which might potentially lead to stopping the procedure. In general the discomfort of placing the probes is much less than intravenous catheter insertion. Measurements made through the tubes have no effects on overall circulation. Administration of drugs through the probes can at most cause local irritation and redness.

Hyperemia: Gentle heat measurements 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.

Upright Tilt Table Testing: Tilt testing is intended to simulate stress but may potentially cause fainting or pre-fainting symptoms which constitute its primary risk. Tilt testing is standard in the assessment of patients with postural tachycardia syndrome (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.

Drugs General Comments:

Drugs will be infused over time through the intradermal catheter in your leg and will be used to either increase or decrease your blood flow. Normally with the small amount of the drug infused there is no change in blood pressure and heart rate. 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 and procedures: Specific Comments:

The 3 drugs that will be infused alone or in combination through the microdialysis catheters are-

Nitro-L-Arginine (NLA): An inhibitor of nitric oxide synthetase.

Losartan: An angiotensin II receptor antagonist with antihypertensive activity due mainly to selective blockade of AT(1) receptors and the consequent reduced pressor effect of angiotensin II.

Acetylcholine: A receptor mediated stimulus of endothelium dependent generation and release of NO, which is synthesized from endogenous L-arginine by calcium-dependent activation of endothelial NO synthase.

None of these drugs have any sideeffects by intradermal (through the tube under your skin) injection.

Microdialysis: The discomfort associated with this is similar to having a subcutaneous (SC) injection. However we use ice to numb the skin and reduce the discomfort.

Head Up-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.

Cold pressor test may cause some pain and numbness at the site. If the test becomes unbearable we will stop and warm the hand.

Handgrip test: Prolonged pulling of the spring may cause muscle tiredness. We will stop the test if you cannot pull any further.

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 hypertension in obesity. There are no alternatives to participation because this study is not intended to treat or cure obesity.

Alternatives to participation

There are no alternatives to medication as this study is not intended to cure obesity and you can withdraw from the study at any time by informing the principal investigator.

Payments and compensation

\$125 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 two year period we expect to enroll 40 obese patients, and 20 healthy volunteers.

All inquiries will be promptly answered by contacting the investigator, Julian M. Stewart M.D., Ph.D. (914-594-4370)

If you agree to participate, you will be paid \$125 for the 1 day it will take to complete the 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. 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

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

Indu Taneja, MD, PhD
Name of Principal Investigator

914-593-8888
Telephone Number

Childrens Hospital Foundation Research Scholar program
Name of Sponsor

The Committee for Protection of Human Subjects is the Institutional Review Board for:

New York Medical College
RevORA1/05

Metropolitan Hospital Center

Westchester Medical Center