Document Date: 07-14-2021

Trial # NCT04553484

Study Title:
Measuring Cardiovascular Performance and Blood Flow Using Common But Never Compared Methods

Reference, WCG Connexus IRB Review Tracking # 120190515

Semler Protocol

Title of the study:	Measuring Cardiovascular Performance Using Common but Never Compared Methods in Subjects
Sponsor:	Semler Scientific, Inc. 2344 Walsh Avenue Santa Clara, CA 95051 (877) 774-4211 www.semlerscientific.com Douglas Murphy-Chutorian, M.D. Chief Executive Officer

This observational study will conduct measurements of cardiovascular performance by echocardiography, Brain Natriuretic Peptide (BNP) blood serum levels and blood flow by volume plethysmography in subjects who meet the AHA/ACC criteria for screening for PAD.

Research Plan

1. Specific Aims

The aims of this observational study are to measure these three frequently performed tests: measurements of cardiovascular performance by echocardiography (Echo), Brain Natriuretic Peptide (BNP) blood serum levels and blood flow by volume plethysmography (VP) in human subjects.

2. Background and Significance

No studies have ever compared these three cardiac performance measures.

3. Description of the Semler QuantaFlo® device

QuantaFlo® aids clinicians in the diagnosis of vascular disease by measuring blood volume changes in the brachial arterial distributions.

The clinician places a sensor and makes a measurement on an upper extremity. The sensor includes a transducer, which detects changes in arterial blood volume. This signal is digitized and sent to a computer, which runs a specifically-designed software application. The application calculates the result via a proprietary algorithm, which is based on the features of the volume signals from the brachial arterial distributions.

QuantaFlo® is an FDA-cleared device that has been used on more than 1 million patients with no adverse effects reported.

4. Description of Brain Natriuretic Peptide (BNP) Blood Serum Level

Brain Natriuretic Peptide (BNP) is a hormone secreted primarily by the ventricular myocardium in response to wall stress. BNP levels can be predictive of cardiovascular abnormalities.

The clinician will perform a blood draw to collect some venous blood. The clinician will then send the blood sample to a diagnostic laboratory for evaluation of blood serum BNP levels.

5. Description of Trans-Thoracic Echocardiography (Echo)

Echocardiography is a routine diagnostic test, used to characterize cardiac function.

The clinician places an ultrasound probe at various points on the chest while the subject holds their breath (minimizing lung and chest movement improves image clarity). This allows the Echo equipment to create a model of the heart and compute various cardiac attributes (see Case Report Form).

The Echo equipment used in this study may vary, but all are FDA cleared for computation of LVEF (such as GE Vivid iq, Siemens Syngo US, Phillips Affiniti, Phillips CX50).

6. Research Design and Methods

6.1. Objectives:

6.1.1. Collect blood flow data.

6.1.2. Measure cardiac performance using echocardiography.

6.1.3. Measure blood serum BNP.

6.2. Analysis:

6.2.1. Determine the feasibility of conducting these three tests on subjects.

6.3. Study Design (note: all study elements must be performed during the same visit):

6.3.1. Investigators will record baseline Demographic information (see Case Report Form).

6.3.2. Baseline blood flow 1: Investigators will place the Sensor on the fingertip of the right or left hand and record a **baseline** measurement of blood flow for 15 seconds.

6.3.3. Expiration blood flow 1: The subject will then perform forced **expiration** at 30mmHg or more, bearing down for 15 seconds.

6.3.4. A disposable mouthpiece will aid in achieving the proper expiration effort.

6.3.5. Recovery blood flow 1: After the expiration, the **recovery** blood flow will continue to be measured for 15 seconds.

6.3.6. The Subject will rest for at least 1 minute.

6.3.7. Baseline, Expiration and Recovery blood flow tests 2 and 3: Another 2 Measurements will be performed, including the Baseline, Expiration and Recovery, for a total of 3 Measurements.

6.3.8. Note: The Investigator will verify the outputs from the QuantaFlo Sensor are being recorded, but nothing will be displayed. The Subjects and Investigators will be blinded to the data.

6.3.9. A Cardiac Sonographer will obtain echocardiography images for analysis. (**Echo**) (see Case Report Form)

6.3.10. Subjects will not learn of the results of the blood flow test or Echocardiogram test.

6.3.11 After completion of the blood flow and Echocardiogram tests, the subject will have their blood drawn. Subjects may be informed of the result of the BNP blood test by the physician if desired or if results are abnormal.

6.4. Study Subjects

6.4.1. Inclusion Criteria:

6.4.1.1. All adult subjects 45 years of age or older will be eligible for enrollment.

6.4.1.2. The following groups will also be enrolled:

6.4.1.2.1. At least 50 Subjects from New York Heart Association (NYHA) Class 1 (One or more AHA Risk Factors, asymptomatic), ≤75% (36) Male, ≥25% (12) Female.

6.4.1.2.2. At least 50 Subjects from NYHA Class 2 (symptomatic), ≤75% (36) Male, ≥25% (12) Female

6.4.2. Exclusion Criteria:

6.4.2.1. Subjects on mechanical ventilation.

6.4.2.2. Subjects who require decisions by a medical power of attorney.

6.4.2.3. No more than 750 subjects will be enrolled.

6.4.2.4. Subjects unable to safely perform forced expiration.

6.4.2.5. Subjects with known technically difficult (TDS) trans-thoracic echocardiographic windows.

6.5. Data Collection:

6.5.1. Blood flow data will be collected in the data collection software.

6.5.2. Echocardiography images will be reviewed by the Sponsor.

6.5.2.1. All images submitted to the Sponsor shall have personal protected information removed and shall be identified only by the subject ID.

6.5.2.2. Images should be well optimized for assessment of LVEF following current American Society of Echocardiography (ASE) standards for trans-thoracic echocardiography.

6.5.3. Echocardiographic measures will be calculated by the Sponsor utilizing methods recommended by the ASE.

6.5.4. The blood serum BNP level will be analyzed by a third-party diagnostic laboratory.

6.5.5. All results will then be entered into spreadsheets for further analysis. Personal data will be de-identified by giving each subject a unique study code.

6.6. Feasibility and Time Frame:

6.6.1. Estimated recruitment of 20 subjects per week (at 3 Sites) is expected with an estimated time frame for completion of approximately 25 weeks.

6.6.2. The estimated completion date is December 2021.

6.7. Potential Risks:

6.7.1. The blood flow and echocardiography measurements are entirely non-invasive, presenting no known risks to the Subject.

6.7.2. The Subject will be asked to perform a forced expiration, which is routinely done in tests of pulmonary function. Forced expiration may cause lightheadedness and abnormal cardiac rhythm.

6.7.3. Blood will be drawn from the Subject. The Subject will experience pain where the needle enters the Subject's arm and may experience bruising and/or infection at the stick site. Some Subjects may also get lightheaded, nauseous, or faint.

6.8. Data Protection/Privacy:

6.8.1. All data will only be handled by the primary investigators listed. Paper copies of the data will be destroyed or locked in the respective investigator's offices. All data will be de-identified at the time of collection. The blood flow and echocardiography data will not be retained in the Subject's medical record. Blood BNP test results may be sent to the subject's medical record if requested by the subject, required by the site, or requested by the principal investigating physician.

7. **Human Subjects**
   7.1. Detailed Description:
      7.1.1. Enrolled subjects will have a brief non-invasive measure of blood flow and cardiac performance using commercially available devices (plethysmography and echocardiography), and performed by experienced, credentialed technicians.
      7.1.2. Enrolled subjects will have a routine blood draw using commercially available devices and performed by experienced, credentialed technicians.
      7.1.3. Subjects will be compensated for their participation in this study.

   7.2. Population:
      7.2.1. Some subjects may have heart failure, pulmonary hypertension or unexplained dyspnea. The average age will likely be ~60 years of age with an equal distribution of men and women.

   7.3. Recruitment of Subjects:
      7.3.1. Subjects will be recruited by the investigative center. Consent for the procedure shall be obtained and the investigative center will discuss the risks and benefits of each procedure. The subject will be asked to sign the attached HIPAA statement for usage of their medical information. Subjects will not be consented if they have received any sedating medications such as fentanyl, morphine, Versed or Ativan.
      7.3.2. Script for Verbal Consent (See 35-0173 QF+ Script for Verbal Consent, Multi-Lingual)

8. **Case Report Form** (See 35-0174 QF+ Case Report Form, Multi-Lingual)

9. **Subject Informed Consent Form**
   9.1. See 35-0175 QF+ Informed Consent Form, English
   9.2. See 35-0176 QF+ Informed Consent Form, Chinese, Traditional
   9.3. See 35-0177 QF+ Informed Consent Form, Spanish, Mexico
   9.4. See 35-0178 QF+ Informed Consent Form, Vietnamese
   9.5. See 35-0179 QF+ Informed Consent Form, Chinese, Simplified