Study Protocol
Title: Cardiology Database
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Specific Aim

The specific aim of this protocol is to create a cardiology database that can be used to address a variety of research questions in cardiovascular disease.

The database will include patients both with and without active cardiovascular disease, (approximately 12,000 patients consisting of cases and controls) from the following sites:
(1) Emory University Hospital
(2) Emory Clinic
(3) Crawford Long Hospital
(4) Grady Memorial Hospital
(5) Atlanta VA Medical Center (VA protocol specific elements are found on pages 11 – 18)
(6) Organized/Planned Community Events in the Atlanta Metropolitan area, held at
- Places of Worship
- Local Community Centers
- Shopping Malls
- Doctor's Offices and Health Clinics
- Any other miscellaneous locations, e.g. Parks, Leisure centers, Conference centers

The database will contain the following types of patient data:
(1) Medical record data, including imaging
(2) Patient questionnaire data
(3) DNA and other biochemical data obtained and/or generated from patient blood samples or cheek (buccal) swabs
(4) Non-invasive measurements of blood pressure, heart rate and studies relating to assessment of the health of arteries

Once the database is underway, it will support scientific investigations that will use information in the database to identify novel factors associated with the etiology, course, and treatment of various cardiovascular diseases. The database will be used primarily for research, and not for patient care.

Personnel & Facility Considerations

All personnel that are involved with this protocol or that will have access to the database have passed the IRB certifying examination. The personnel include faculty and staff employed at Emory University or at one of the recruitment sites. The list of IRB-approved individuals associated with this study is available upon request from the research coordinator or from the Emory IRB. Individuals involved with

recruiting, consenting, processing or in any way accessing VA subject identifiers will also have additional research (CITI) certification appropriate for VA research studies.

As noted above, this study is recruiting subjects from the following sites:
(1) Emory University Hospital
(2) Emory Clinic
(3) Crawford Long Hospital
(4) Grady Memorial Hospital
(5) Atlanta VA Medical Center (VA protocol specific elements are found on pages 11 – 18)
(6) Organized/Planned Community Events in the Atlanta Metropolitan area, held at
    Places of Worship
    Local Community Centers
    Shopping Malls
    Doctor's offices and Health Clinics
    Any other miscellaneous locations, e.g. Parks, Leisure centers, conference centers

Organized community events will include health fairs or planned community gatherings. We will only recruit subjects at these events after gaining explicit written consent from the event organizers and/or property managers. A table will be set up under the "Emory Cardiology Research" logo to discuss with interested subjects, ongoing cardiology research at Emory and offer participation in the database. A small seating area beside the table will be set up for blood draws (or buccal swabs if blood draw would be inappropriate in setting) and questionnaire completion

Experimental Design & Methods

1. Subject Selection/Recruitment*:*
Patients with and without active cardiovascular disease (Cardiovascular disease includes; Heart Failure and Cardiomyopathies, Ischemic Heart Disease, Peripheral Vascular Disease, Valve Disease, Adult Congenital Heart Disease, Electrophysiological Disorders and others generally accepted to be cardiac or vascular in origin) will be recruited. We will not attempt in any way to restrict the patient population in terms of gender, race or ethnicity. We expect that the patient population will be highly diverse.

Inclusion Criteria:
1. All hospital and clinic patients aged 18 years and older
2. Patients with active cardiovascular disease including but not limited to
    a. Ischemic Heart Disease
    b. Heart Failure and Cardiomyopathies
    c. Peripheral Vascular Disease
    d. Valve disease
    e. Adult Congenital Heart disease
    f. Electrophysiological Disorders
3. Any Atlanta metropolitan area resident aged 18 and above in satisfactory physical health and able to tolerate a blood draw or buccal swab.

Exclusion Criteria:
1. Significant Documented Anemia (Hemoglobin <8 g/dL)
2. Blood transfusions within past 3 weeks
3. Active Cancer (non-skin cancers)

4. Enrollment against doctor recommendation
5. Patient not able to provide consent including but not limited to:
    a. Intubated and critically unwell patients
    b. Dementia
    c. Alzheimer's disease
    d. Moderate to severe alcohol or drug abuse
    e. Against religious beliefs (e.g. Jehovah's witness

2. Procedures:
In order to carry out this protocol and establish the database, we will conduct the following procedures:

(1) Informed Consent: A trained research assistant/ cardiology fellow will ask the patient/subject whether he/she is willing to participate in the database. If the patient/subject answers in the affirmative, the assistant/fellow will explain the database project in greater detail and commence the informed consent process. Only IRB-approved staff will obtain consent from patients to be included in the database. Completed informed consent forms will be kept in a locked filing cabinet in the study coordinator's office, with VA consent forms stored only at the VA site.

(2) Collect Patient Questionnaire Data: After informed consent has been obtained, the research assistant/fellow will assist the patient/subject to complete a series of short relevant questionnaires. The questionnaire will be either in paper format or in electronic format (iPad© tablet) for non-VA Medical Center sites. We believe it will take the patient approximately 20 minutes to complete all of the questionnaires. The questionnaires will address a variety of factors such as patient medical history, family history of disease, medication usage, health behaviors, psychological factors, neuropsychological functioning etc. For women, additional questions regarding menstrual history will be taken. For those with no obstructive coronary arteries, additional detailed questionnaires related to symptoms, psychological factors, pain, and quality of life will be taken. Questionnaires from VA subjects will be stored only at the VA site with only de-identified questionnaire data uploaded onto a secure Emory database. If questionnaire is entered electronically, all data entered will be erased from the tablet computer once the patient presses the submit button. Submitted data will be uploaded onto a secure Emory database.

(3) Collect Medical Record Data if patient/subject is recruited from a clinical or hospital site: After the questionnaire has been completed, a trained research assistant will then access the patient's medical records and collect pertinent medical record-information to be entered into the database, such as medical history, family history of disease, medication usage, health behaviors, laboratory results, angiographic results, procedure results etc. Data will also be merged with records from the Cardiac Data Bank and any other relevant Emory medical database to obtain additional clinical data on the patients.

Subjects recruited from the VA site will have their identifiable information stored on site only. Only de-identified data necessary to complete the study aims will be shared and merged with the primary database at Emory.

Subjects recruited from the community will provide questionnaire data and we will request access to their primary care or hospital medical records.

(4) Collect and Analyze Blood Samples: We will collect up to 50 mls of blood to be used in connection with this database. For patients less than 60 years of age, an additional 10 mls of blood will be drawn. This additional blood will allow us to evaluate T-cell response in young patients with heart disease. In most cases, the blood sample will be obtained as part of other blood draws the patient undergoes as part of their visit/procedure. However, for certain patients/subjects (those who are not having blood tests as part of their clinical care), the blood draw will be initiated specifically for this study by placing a needle in an arm vein. Blood draws will be obtained by a nurse or physician who is administering to the patient/subject. The blood draw will be done in the appropriate clinical setting where the patient is receiving clinical care or in a controlled environment if blood draw is taking place in a community setting. Blood draws in the community will be performed by research assistants, nurses or physicians with appropriate credentialing and certification. Once the blood has been obtained, it will be transported to the Emory Clinical Research Center with de-identified labeling. Various biochemical tests will be run on these blood samples to assess factors such as lipids, inflammatory and oxidative stress markers, blood glucose levels, etc. The information from these tests will be included in the database. Additionally, each blood sample will be assessed for DNA (genetic) content, and this information will be entered into the database. Lymphoblast cell lines may also be created from the blood cells. During the informed consent process, the subjects will have given permission for the DNA/cell lines to be duplicated indefinitely for future research. Neither the subjects nor the subjects' families will be contacted about this future use of their information. The research investigators involved in this study and in future studies and any other individual who may have access to the blood sample and its derivatives are not authorized to and are forever prohibited from using the material for any attempt at cloning a human being.

For locations unsuitable for blood draws we will instead obtain from subjects a cheek (buccal) swab using a simple spatula designed for collection of a small quantity of cells from the inside of the cheek. This is a very safe and non-harmful way of collecting DNA.

For VA subjects, blood samples will initially be transported to Emory for processing, but will be returned for long term storage at the VA site. All samples will only be identified by a study number with no visible patient identifiers. (VA protocol specific elements are found on pages 11 – 18.)

Samples for biomarker/genomic testing may be sent de-identified to collaborating institutions or laboratories after completion of required material transfer agreements. Examples of these tests include high-sensitivity troponin, galectin-3, soluble urokinase plasminogen activator, and genotyping among others.

(5a) Measurement of autonomic balance using Simband: Heart rate variability (HRV), a measure of fluctuations in beat to beat intervals of the sinus node, is a non-invasive index of cardiac autonomic nervous system control. We will obtain HRV data using photoplethysmography data from the Samsung Simband. We will explore the possibility of detecting heart failure and ischemia through HRV during rest and valsalva based on short-term heart rate variability change with Valsalva using the Samsung Simband, which measures HRV using electrocardiographic and photoplethysmography data. The signals (de-identified) will be processed in MATLAB, and using their algorithms, diagnoses heart failure, and coronary artery disease will be ascertained. These will then be reconciled against the clinical data in univariate and multivariate models that include other medical history, cardiac diagnostics data, demographics, and labs by study team. The clinical data may also be used to inform future enhanced algorithms.

We will ask subjects to wear a multisensor wristband, the Samsung Simband after consent is obtained until angiography is performed. Valsalva Maneuver will be performed for 1 minute, 5 minutes after onset of recording. Subjects may continue to wear the device until the start of the catheterization. After use, the device will be cleaned and disinfected with SaniWipes (55% alcohol), which are germicidal, using hospital-grade disinfectant.

(5b) Measurement of long-term autonomic balance using ECG Patch: We may obtain electrocardiographic data for up to 72 hours to measure cardiac electrical activity non-invasively using an ECG patch, the MC10 BioStamp nPoint or the VivaLNK Vital Scout. All data will be de-identified and stored on Emory servers for processing. If discharged before monitoring is complete, participants may be given pre-paid envelopes to mail back the patch from home. If lost, they will not be financially responsible for the patch.

(6) Collect wire heads and sheath samples at the time of left heart catheterization. After left heart catheterization is completed, 2-3 cm of the J-end of the wire will be cut and will be transferred to a tube containing collection solution (Qiazol). Collection tube will then be transferred and kept at -80˚C. Endothelial Cells attached to these wires and sheaths will be used for DNA (genetic) and mRNA (gene expression) analysis.

(7) Measures of arterial health (Vascular function studies)
We may also offer participants one or more simple tests of vascular function to measure arterial health. These tests are non-invasive and carry minimal risk. Studies requiring subjects to lay supine will only be performed where suitable beds are available. Studies requiring seating only will be performed in any suitable location. One of these tests, which will only be selectively offered, requires wearing a simple device for 24 hours.

Measurement of endothelial function by brachial artery flow-mediated vasodilation (FMD)

We will determine endothelium-dependent, FMD of the brachial arteries from two-dimensional ultrasound images according to established and validated methodologies. Images will be obtained with a 10 mHz linear array transducer and an Acuson ultrasound system. We will perform imaging with the subject resting supine for at least 10 minutes on a bed in a quiet setting. For each subject, optimal brachial artery images will be obtained between 2 and 10 cm above the antecubital crease. After baseline measurements a blood pressure cuff is inflated to 200 mm Hg over the proximal portion of the right arm for 5 minutes. Endothelial dependent function will be determined during the first two minutes of release. This test will take approximately 20 minutes. Images are analyzed by a line tracking software program (MIA, Iowa).

Endothelial function assessment using pulsatile arterial tonometry

Pulsatile arterial tonometry (PAT, Itamar Medical Ltd.) is performed with a device that measures reactive hyperemia of the finger and the magnitude of hyperemia correlates with coronary microvascular endothelial function, peripheral vascular endothelial function measured as brachial reactivity, and can be inhibited by LN^G monomethyl arginine, indicating that it is NO-dependent. We are employing this technique currently in ongoing studies and have found it to be easy to use and reproducible.

Technique: Briefly, this system comprises a finger probe to assess digital volume changes accompanying pulse-waves. The patients will be studied in the supine position on a bed with both

hands at the same level. Baseline blood pressure of both hands is measured and PAT probes, one on each hand (fingers 2, 3 or 4) will be placed. The blood pressure cuff will remain on one hand (the study arm) and the other arm will serve as a control. Following a 10-minute equilibration period, the blood pressure cuff is inflated to 60 mmHg above systolic pressure for 5 minutes followed by deflation of the cuff and continuous recording from both arms for 10 minutes. This test will take approximately 25 minutes. The reactive hyperemic ratio RH-PAT is calculated by the computer as the ratio of the area under the hyperemic curve to the resting.

Arterial compliance

Vascular function will be assessed as pulse wave velocity and radial pulse wave analysis measured noninvasively using the SphygmoCor® Pulse Wave Velocity system (PWV Medical, NSW, Australia). In brief, peripheral pressure waveforms are recorded from the radial artery at the wrist, using applanation tonometry with a high-fidelity micromanometer. After 20 sequential waveforms have been acquired, a validated generalized transfer function will be used to generate the corresponding central aortic pressure waveform. All pulse wave analyses will be taken in the sitting position in a quiet room after a brief period (at least 5 minutes) of rest. Pulse wave analysis. The pulse wave velocity (PWV) system measures the velocity of the blood pressure waveform between any two superficial artery sites. Carotid-femoral artery PWV will be determined by measuring transcutaneous Doppler flow velocity; recordings are carried out simultaneously at the base of the neck over the common carotid artery and the femoral artery in the groin with the PWV system attached to a laptop computer. The time delay (t) will be measured between the feet of the flow waves recorded at these points. The distance (d) traveled by the pulse wave is measured over the body surface as the distance between the two recording sites minus that from the suprasternal notch to the carotid artery recording site. PWV is calculated as PWV=d/t. This test will take approximately 10 minutes. Reproducibility and experience: Dr. Quyyumi is currently conducting an NIH funded study in a multi-ethnic community population of 1000 subjects who are all having arterial compliance assessed in this manner. Three technicians have been trained to conduct these measurements reliably and reproducibly. Previous studies have demonstrated mean differences between consecutive AIx and AP measurements performed on 2 different days of 1.37% and 1.2 mm Hg, respectively; 95% limits of agreement for AIx and AP were 10.1% and 9.6 mm Hg, respectively.

Endothelial function assessment during sleep and wakeful states: Watch-PAT (Itamar Medical) is a portable sleep diagnostic unit that consists of a wrist watch like device, a finger pulse oximeter, and snoring and position sensors. The peripheral arterial tone (PAT) signal is obtained via a finger probe with a pneumatic sensor. The signal varies during sleep and wake cycles. It also provides recognizable patterns in various pathologic states during sleep, including sleep disordered breathing and periodic limb movements. PAT technology measures the time course of pulsatile arterial volume as a surrogate for changes in the autonomic tone during sleep and wakeful states, and differentiates between NREM and REM sleep stages. We are currently using a similar technology from the same company for assessment of vascular function, with the difference that this would measure similar parameters but for longer time period correlating with changes in sleep cycle.

Technique: The Watch-PAT is a self-contained device that is worn on the wrist and uses a non-invasive finger mounted pneumo-optical probe to measure the PAT signal. The recorded signals are stored in a removable memory card in the device to be downloaded to a computer for automatic analysis utilizing proprietary algorithms. In addition to the PAT Signal, the Watch-PAT records oxygen saturation and actigraphy. A fourth channel, pulse rate, is derived from the PAT Signal. A probe which detects patient motion is attached to the skin above the sternum bone. The participant is required to wear

the device continuously for a period of 24 hours. This device is light weight, well-padded for patient comfort and non-invasive. After a period of 24 hours the participant returns to the study site for removal of the device.

Carotid Ultrasound

Carotid Intima-Media Thickness (IMT), the distance between detection of the lumen and intima and that of the media and adventitia, will be measured by means of B-mode and color flow Doppler ultrasound of the carotid arteries. The combination of B-Mode and Color Flow Mode allows to more fully distinguish between plaque-mimicking motion artifacts and the actual presence or absence of plaques. Additionally, the proprietary technology allows for multi-angle image acquisition and selects the image with the thickest build-up of the arterial IMT. Our analysis will focus on the overall mean IMT index of the left and right common carotid artery, which represents the most common approach in previous studies.

Technique: The ultrasound probe will be placed on the lateral aspect of the participant's neck, while supine, that corresponds to the area overlying the carotid artery. Ultrasound gel or water will be applied to the probe prior to application. Gentle pressure will be placed on the neck using the probe to acquire the proper image. The procedure will take approximately 15 minutes to perform. Proper carotid images used for analyses are selected and captured by the imaging software thereby minimizing inter-technician error. Mean carotid IMT indices are then automatically produced by the imaging software as output.

Nailfold Capillaroscopy

Subjects who are enrolled in this registry may be contacted for nailfold capillaroscopy which is a non-invasive, minimal risk evaluation of finger nailfold under the microscope to examine the capillary bed. Microvascular structural abnormalities such as reduced capillary density (rarefaction) may contribute to ischemic heart disease. Nailfold capillaroscopy can be used to evaluate capillary flow, rarefaction and other morphological changes. In subjects with hypertrophic cardiomyopathy and hypertension, capillary rarefaction has been shown.

Technique: Patient will have to remove fingernail polish and wash hands with warm water and soap (clean hands) prior to examining the fingernail under the capillaroscope. One to two drops of vegetable oil will be placed on the fingers of the right and left hand (not thumbs), and the nailfold microcirculation will be examined under a microscope (Optillia Instruments, Sweden). Exclusions to this procedure are (1) patient refusal; (2) finger/hand deformity that precludes testing; (3) condition that precludes accurate or safe testing. A blood pressure cuff may be placed around the forearm and inflated to a comfortable, low level of pressure to increase blood flow to the hand during microscopic imaging. Images will be processed and measurements of capillary loops will be made digitally via Optillia Instruments software.

Optical coherence tomography angiography

Optical coherence tomography angiography (OCTA) is a novel retinal imaging modality that permits noninvasive depth-resolved imaging of the retinal microvasculature. The technology leverages existing optical coherence tomography technology with novel image acquisition and analysis algorithms to detect retinal vascular flow. This technology has led to novel insights into retinal microvascular abnormalities not previously detectable with conventional examination and imaging techniques.

Technique: Images can be acquired without contrast through an un-dilated pupil in <5 seconds. Subjects will undergo OCTA imaging with an FDA-approved clinical OCTA device (AngioPlex, Carl Zeiss Meditec, Dublin, CA) at the Emory Eye Center. Imaging will be obtained on one eye with 3 x 3 mm and 6 x 6 mm scan patterns centered on the fovea. Angiograms will be segmented into three slabs to resolve the superficial retinal capillary plexus, middle capillary plexus, and the deep capillary plexus. Images will be thresholded to generate a binary vascular map. The microvasculature will be assessed quantitatively for each vascular map, assessing both the size of the foveal avascular zone and parafoveal vessel density.

(8) Cognitive Testing

We may ask participants to complete cognitive tests to assess their memory and thinking abilities. These tests might include but are not limited to the Montreal Cognitive Assessment (MoCA) which is a 30-point scale that assesses multiple domains and is equivalent to the Mini-Mental Status Examination in detecting cognitive deficits and Trails A and B which are neuropsychological tests of visual attention and task changing.

(9) Collection of Follow-up data: Patients enrolled at Emory University Hospital will be asked to return for a follow-up visit in 1 month, 3 months, and 1 year after their enrollment. This visit will be brief and will include an additional 50 cc of blood draw this time from a peripheral vein. The main purpose of these follow-up visits is to re-measure biomarkers and progenitor cells to evaluate effects of medications such as statins on these factors.

Patients who are unable to return for follow-up but who have consented to electronic follow-up will receive an e-mail at designated times providing information to complete questionnaires online using REDCap Anonymous Survey Data Collection. The email and questionnaires do not contain any personally identifying information nor questions asking the participants for identifying data.

Patients will also be contacted at certain times after the baseline contact so that the database can obtain follow-up information on patients. Such follow-up information will include cardiovascular events, quality of life, and other relevant follow-up information. Patients may also be contacted in order to determine if they wish to participate in additional studies. (IRB approval will be obtained beforehand for any additional studies.)

Follow up data may also be obtained from patients' Emory Healthcare, Grady, or outside hospital/health system medical records if available. Data from public records or databases such as the National Death Index (NDI) will also be used for follow-up analysis.

(10) Linking of Database Information: After a patient is enrolled, he/she will be assigned a study ID number. This ID number, and not the subject's name, will be used as the research identifier for each subject.

(11) Restricted Data Collection on Persons Who Refuse to Participate in All of the Study or Part of the Study: If a patient declines to participate in all portions of the study, the patient will not be assigned a study ID number and the study coordinators/data collectors will refrain from collecting any data on the patient. If a patient agrees to participate in some portions of the study but not others, the patient will be assigned a study ID and the study coordinators/data collectors will be instructed to collect data only on those aspects of the study to which the patient has agreed to participate. These procedures will help prevent unauthorized inclusion of a patient's data in the database.

3. Statistical Considerations:

As a general matter, we believe that the projected sample size of the database (at least 12,000 patients) will allow a wide variety of scientific questions to be addressed with an adequate amount of statistical power.

Potential Risks, Discomforts, and Benefits

For some of the patients, we will initiate the blood draw by placing a needle into an arm vein. The risk from blood drawing is very small, but may include discomfort, bruising, infection and a chance of dizziness/fainting. Using sterile precautions will minimize risk of infection. A bruise may develop at the site of the puncture, but this will go away in two to three days.

Another risk from participating in the database is the potential for the release of confidential information and associated problems, such as insurance and employment discrimination. Some patients may also be made somewhat uncomfortable by some of the questions in the questionnaires.

There are minimal risks from the non-invasive vascular function studies:
Flow mediated dilatation – subjects may experience transient discomfort from the blood pressure cuff, which will be deflated if very uncomfortable. Transient discomfort may also arise from the ultrasound probe being placed on the patient's skin which will be relieved with removal of the probe.

Reactive Hyperemia – subjects may experience transient discomfort from the blood pressure probe on the upper arm which will be relieved with deflation of the cuff.

Pulse wave Analysis and Pulse Wave Velocity – subjects may experience transient discomfort from the probe being placed on the skin which will be relieved immediately on lifting the probe from the skin.

WatchPAT - This device is light weight, well-padded for patient comfort and non-invasive. It is very well tolerated and does not disturb patient activity during the day and is not reported to disrupt sleep. Some subjects may experience mild discomfort from the finger or skin probes, which can be relieved immediately upon removal.

Carotid Ultrasound- The ultrasound probe may cause some temporary discomfort. If there is a plaque present in the participant's carotid artery, there is a small but rare chance that the motion and pressure placed by the ultrasound probe may mobilize the plaque upwards to the brain, possibly causing a stroke.

Nailfold Capillaroscopy – This procedure is of minimal risk to the patient, well tolerated, and there are no long-term risks. Some subjects may experience mild transient discomfort when blood pressure cuff is inflated in the forearm to a low level to increase blood flow. Some subjects may experience minimal transient discomfort from the manual pressure of the microscope probe on the finger.

OCTA-this test is a safe and requires neither dilation of the eyes nor use of a contrast agent. Subjects with an acute eye problem will be rescheduled after addressing the complaint.

Simband: The device is non-invasive, easy to wear, generally well tolerated. Some subjects may experience light temporary discomfort with wristband or may report fatigue and discomfort from Valsalva maneuver.

ECG Patch Recordings – subjects may experience temporary discomfort from extended use of the adhesive (which resembles a standard clinical electrode) or from the process of preparing the skin (may require shaving and cleaning of the skin).

There may be no direct benefit to the subjects. However, the information obtained may help to advance the understanding of cardiovascular disease and may thus be of future benefit to patients with these disorders or to at-risk members-of-society. The subjects incur no cost from participating in this study. However, they are also not paid for their participation. If they are patients at one of the study sites, they are still responsible for the costs of the clinic visit and any clinical labs ordered by their doctors.

Safeguards to Protect Patient Confidentiality

All information will be kept private. No current or future research results will go into the medical record. If scientific reports, publications, or educational materials are written using information from the database, patients within the database will not be identified by name.

Agencies that make rules and policy about how research is done have the right to review information within the database. Agencies that pay for the study also have this right. The Emory University IRB may also review such information. All efforts will be made to use only the study ID number, not the subjects' names, when these agencies are reviewing information within the database.

All VA identifiable data will be stored in a secure database at the VA site. Only de-identified data will be shared with the Emory database in order to complete the aims of the study. Only VA certified research personnel will have access to identifiable VA subject data

Access to this database will be restricted by a database manager and will be password protected. The only individuals who will be able to see patient identifiers, like name, address, and social security number, will be the Principal Investigator, research coordinators, recruiters and the database managers. Other investigators will have different passwords that will provide restricted access to the database. Those with restricted access will be able to query the database for scientific information/variables, but will not be able to view information on patient identifiers such as name, address, and social security number. If investigators with restricted access want to conduct studies which require them to obtain patient identifiers so that patients can be contacted for follow-up information/follow-up visits, these investigators will have to submit a separate protocol to IRB to get permission to obtain patient identifiers and contact patients.

Collaborations

The information in the database will be shared with Emory and non-Emory investigators to help them study cardiovascular diseases. These studies will require authorization by the Principal Investigator. Any approved study run by an investigator at any institution must be approved by an Institutional Review Board.

Studies that might be approved to use the information in the database will be those designed to understand factors associated with the etiology, course, and treatment of various cardiovascular diseases, and perhaps other types of diseases as well. The research investigators involved in this study and in future studies and any other individual who may have access to the blood sample and its derivatives are not authorized to and are forever prohibited from using this material for any attempt at cloning a human being.

Information that may be released to researchers may include, but is not limited to: medical information, age, gender, ethnic background, family history, imaging data, blood samples and blood sample products. Identifiers, like names, addresses, and social security numbers, will not be released, except if patients need to be contacted again for specific purposes in new studies. All efforts will be made to keep true identities confidential.

This study will be conducted at the Atlanta VA under the following protocol specifications:

VA Specific Aim :

The specific aim of this protocol is to create a cardiology database that can be used to address a variety of research questions in cardiovascular disease.

The database will include patients both with and without active cardiovascular disease, from the Atlanta VAMC.

The database will contain the following types of patient data:
(1) Medical record data
(2) Patient questionnaire data
(3) DNA and other biochemical data obtained and/or generated from patient blood samples or cheek (buccal) swabs or other biological samples
(4) Non-invasive measurements of blood pressure, heart rate and studies relating to assessment of the health of arteries

Once the database is underway, it will support scientific investigations that will use information in the database to identify novel factors associated with the etiology, course, and treatment of various cardiovascular diseases. The database will be used primarily for research, and not for patient care.

VA Personnel & Facility Considerations:

All personnel will be credentialed to work in research at the Atlanta VAMC.

VA Experimental Design & Methods:

1. Subject Selection/Recruitment*:*
Patients with and without active cardiovascular disease (Cardiovascular disease includes; Heart Failure and Cardiomyopathies, Ischemic Heart Disease, Peripheral Vascular Disease, Valve Disease, Adult Congenital Heart Disease, Electrophysiological Disorders and others generally accepted to be cardiac or vascular in origin) will be recruited. We will not attempt in any way to restrict the patient population in terms of gender, race or ethnicity. We expect that the patient population will be highly diverse.

Inclusion Criteria:

4. All hospital and clinic patients aged 18 years and older, OR
5. Patients with active cardiovascular disease including but not limited to
    a. Ischemic Heart Disease
    b. Heart Failure and Cardiomyopathies
    c. Peripheral Vascular Disease
    d. Valve disease
    e. Adult Congenital Heart disease
    f. Electrophysiological Disorders

,OR…

6. Any Atlanta metropolitan area resident aged 18 and above in satisfactory physical health and able to tolerate a blood draw or buccal swab.

Exclusion Criteria:

6. Significant Documented Anemia (Hemoglobin <9 g/dL; Hematocrit <30%)
7. Blood transfusions within past 3 weeks
8. Active Cancer (non-skin cancers)

(Exclusion criteria excludes patients from blood sampling, but not from the rest of the protocol.)

2. Procedures:

In order to carry out this protocol and establish the database, we will conduct the following procedures:

(1) Informed Consent: A VA credentialed, trained research assistant/ cardiology fellow will ask the patient/subject whether he/she is willing to participate in the database. If the patient/subject answers in the affirmative, the assistant/fellow will explain the database project in greater detail and commence the informed consent process. Only IRB-approved staff will obtain consent from patients to be included in the database. Completed informed consent forms will be kept in a locked filing cabinet in the study coordinator's office at the AVAMC.

(2) Collect Patient Questionnaire Data: After informed consent has been obtained, the research assistant/fellow will assist the patient/subject to complete a series of short relevant questionnaires. We believe it will take the patient approximately 20 minutes to complete all of the questionnaires. The questionnaires will address a variety of factors such as patient medical history, family history of disease, medication usage, health behaviors, psychological factors, neuropsychological functioning etc. For women, additional questions regarding menstrual history will be taken. Questionnaires from VA subjects will be stored only at the VA.

(3) Collect Medical Record Data if patient/subject is recruited from a clinical or hospital site: After the questionnaire has been completed, a trained research assistant will then access the patient's medical records and collect pertinent medical record-information to be entered into the database, such as medical history, family history of disease, medication usage, health behaviors, laboratory results, angiographic results, procedure results etc.

Subjects recruited from the VA site will have their identifiable information stored at the VA site. A copy of this data, including PHI, will be shared with Emory through an approved informed consent document and HIPAA authorization.

(4) Collect and Analyze Blood Samples: We will collect up to 50 mls of blood to be used in connection with this database. For patients less than 60 years of age, an additional 10 mls of blood may be drawn. This additional blood will allow us to evaluate T-cell response in young patients with heart disease. In most cases, the blood sample will be obtained as part of other blood draws the patient undergoes as part of their visit/procedure. However, for certain patients/subjects (those who are not having blood tests as part of their clinical care), the blood draw will be initiated specifically for this study by placing a needle in an arm vein. Blood draws will be obtained by a physician member of the study team who is administering to the patient/subject. The blood draw will be done in the appropriate clinical setting where the patient is receiving clinical care or in a controlled environment if blood draw

is taking place in a community setting. Once the blood has been obtained, it will be either processed at the VA or transported to the Emory Clinical Research Center with de-identified labeling. Various biochemical tests will be run on these blood samples to assess factors such as lipids, inflammatory and oxidative stress markers, blood glucose levels, etc. The information from these tests will be included in the database. Additionally, each blood sample may be assessed for DNA (genetic) content, and this information will be entered into the database. Lymphoblast cell lines may also be created from the blood cells. During the informed consent process, the subjects will have given permission for the DNA/cell lines to be duplicated indefinitely for future research. Neither the subjects nor the subjects' families will be contacted about this future use of their information. The research investigators involved in this study and in future studies and any other individual who may have access to the blood sample and its derivatives are not authorized to and are forever prohibited from using the material for any attempt at cloning a human being.

VA Blood samples will be either processed at the VA and/or transported to Emory for processing, and long term storage per the VA off site tissue banking waiver. All samples will only be identified by a study number with no visible patient identifiers. The first 125 of blood samples taken at the VA will be stored onsite and will never be transferred to Emory.

(5) Measures of arterial health (Vascular function studies)
We may also offer participants one or more simple tests of vascular function to measure arterial health. These tests are non invasive and carry minimal risk. Studies requiring subjects to lay supine will only be performed where suitable beds are available. Studies requiring seating only will be performed in any suitable location. One of these tests, which will only be selectively offered, requires wearing a simple device for 24 hours.

Measurement of endothelial function by brachial artery flow-mediated vasodilation (FMD): We will determine endothelium-dependent, FMD of the brachial arteries from two-dimensional ultrasound images according to established and validated methodologies. Images will be obtained with a 10 mHz linear array transducer and an Acuson ultrasound system. We will perform imaging with the subject resting supine for at least 10 minutes on a bed in a quiet setting. For each subject, optimal brachial artery images will be obtained between 2 and 10 cm above the antecubital crease. After baseline measurements a blood pressure cuff is inflated to 200 mm Hg over the proximal portion of the right arm for 5 minutes. Endothelial dependent function will be determined during the first two minutes of release. This test will take approximately 20 minutes. Images are analyzed by a line tracking software program (MIA, Iowa).

Endothelial function assessment using pulsatile arterial tonometry, PAT**:** Pulsatile arterial tonometry (PAT, Itamar Medical Ltd.) is performed with a device that measures reactive hyperemia of the finger and the magnitude of hyperemia correlates with coronary microvascular endothelial function, peripheral vascular endothelial function measured as brachial reactivity, and can be inhibited by LN^G monomethyl arginine, indicating that it is NO-dependent. We are employing this technique currently in ongoing studies and have found it to be easy to use and reproducible.

Technique: Briefly, this system comprises a finger probe to assess digital volume changes accompanying pulse-waves. The patients will be studied in the supine position on a bed with both hands at the same level. Baseline blood pressure of both hands is measured and PAT probes, one on each hand (fingers 2, 3 or 4) will be placed. The blood pressure cuff will remain on one hand (the study arm) and the other arm will serve as a control. Following a 10-minute equilibration period, the blood pressure cuff is inflated to 60 mmHg above systolic pressure for 5 minutes followed by deflation of the

cuff and continuous recording from both arms for 10 minutes. This test will take approximately 25 minutes. The reactive hyperemic ratio RH-PAT is calculated by the computer as the ratio of the area under the hyperemic curve to the resting.

Arterial compliance: Vascular function will be assessed as pulse wave velocity and radial pulse wave analysis measured noninvasively using the SphygmoCor® Pulse Wave Velocity system (PWV Medical, NSW, Australia). In brief, peripheral pressure waveforms are recorded from the radial artery at the wrist, using applanation tonometry with a high-fidelity micromanometer. After 20 sequential waveforms have been acquired, a validated generalized transfer function will be used to generate the corresponding central aortic pressure waveform. All pulse wave analyses will be taken in the sitting position in a quiet room after a brief period (at least 5 minutes) of rest. Pulse wave analysis. The pulse wave velocity (PWV) system measures the velocity of the blood pressure waveform between any two superficial artery sites. Carotid-femoral artery PWV will be determined by measuring transcutaneous Doppler flow velocity; recordings are carried out simultaneously at the base of the neck over the common carotid artery and the femoral artery in the groin with the PWV system attached to a laptop computer. The time delay (t) will be measured between the feet of the flow waves recorded at these points. The distance (d) traveled by the pulse wave is measured over the body surface as the distance between the two recording sites minus that from the suprasternal notch to the carotid artery recording site. PWV is calculated as PWV=d/t. This test will take approximately 10 minutes. Reproducibility and experience: Dr. Quyyumi is currently conducting an NIH funded study in a multi-ethnic community population of 1000 subjects who are all having arterial compliance assessed in this manner. Three technicians have been trained to conduct these measurements reliably and reproducibly. Previous studies have demonstrated mean differences between consecutive AIx and AP measurements performed on 2 different days of 1.37% and 1.2 mm Hg, respectively; 95% limits of agreement for AIx and AP were 10.1% and 9.6 mm Hg, respectively.

Endothelial function assessment during sleep and wakeful states:. Watch-PAT (Itamar Medical) is a portable sleep diagnostic unit that consists of a wrist watch like device, a finger pulse oximeter, and snoring and position sensors. The peripheral arterial tone (PAT) signal is obtained via a finger probe with a pneumatic sensor. The signal varies during sleep and wake cycles. It also provides recognizable patterns in various pathologic states during sleep, including sleep disordered breathing and periodic limb movements. PAT technology measures the time course of pulsatile arterial volume as a surrogate for changes in the autonomic tone during sleep and wakeful states, and differentiates between NREM and REM sleep stages. We are currently using a similar technology from the same company for assessment of vascular function, with the difference that this would measure similar parameters but for longer time period correlating with changes in sleep cycle.

Technique: The Watch-PAT is a self-contained device that is worn on the wrist and uses a non-invasive finger mounted pneumo-optical probe to measure the PAT signal. The recorded signals are stored in a removable memory card in the device to be downloaded to a computer for automatic analysis utilizing proprietary algorithms. In addition to the PAT Signal, the Watch-PAT records oxygen saturation and actigraphy. A fourth channel, pulse rate, is derived from the PAT Signal. A probe which detects patient motion is attached to the skin above the sternum bone. The participant is required to wear the device continuously for a period of 24 hours. This device is light weight, well padded for patient comfort and non invasive. After a period of 24 hours the participant returns to the study site for removal of the device.

Carotid Ultrasound:

Carotid Intima-Media Thickness (IMT), the distance between detection of the lumen and intima and that of the media and adventitia, will be measured by means of B-mode and color flow Doppler ultrasound of the carotid arteries. The combination of B-Mode and Color Flow Mode allows to more fully distinguish between plaque-mimicking motion artifacts and the actual presence or absence of plaques. Additionally, the proprietary technology allows for multi-angle image acquisition and selects the image with the thickest build-up of the arterial IMT. Our analysis will focus on the overall mean IMT index of the left and right common carotid artery, which represents the most common approach in previous studies.

Technique: The ultrasound probe will be placed on the lateral aspect of the participant's neck, while supine, that corresponds to the area overlying the carotid artery. Ultrasound gel or water will be applied to the probe prior to application. Gentle pressure will be placed on the neck using the probe to acquire the proper image. The procedure will take approximately 15 minutes to perform. Proper carotid images used for analyses are selected and captured by the imaging software thereby minimizing inter-technician error. Mean carotid IMT indices are then automatically produced by the imaging software as output.

Patients will also be contacted at certain times after the baseline contact so that the database can obtain follow-up information on patients. Such follow-up information will include cardiovascular events, quality of life, and other relevant follow-up information. Patients may also be contacted in order to determine if they wish to participate in additional studies. (IRB approval will be obtained beforehand for any additional studies)

Ankle Brachial Index:

The Ankle Brachial Index (ABI) is a standard, non-invasive method to assess peripheral artery disease. Blood pressures in the arm, leg and foot on both sides of the subject are recorded. The ABI is then calculated for each leg by a ratio of the leg blood pressure over the highest arm blood pressure.

Technique: We will utilize the Dopplex Ability (Huntleigh Diagnostics) to measure the ABI. The participant will be placed in the supine position. Blood pressure cuffs will be placed on their upper arm, lower arm, lower leg, and foot on both sides. All blood pressure cuffs connect to the machine and will simultaneously measure blood pressures in each extremity. The ABI result is then automatically calculated by the machine. The entire procedure will take approximately 10 minutes to perform.

Exercise Treadmill Test.

Exercise treadmill testing with ECG monitoring using the Bruce or other standardized protocol will be performed on patients who are ambulatory and stable per American College of Cardiology guidelines in order to 1) judge exercise capacity, 2) ischemia burden, 3) BP and/or heart rate response,

Echocardiogram.

Echocardiography may be performed to assess myocardial and valve function and morphology.

(6) Linking of Database Information: After a patient is enrolled, he/she will be assigned a study ID number. This ID number, and not the subject's name, will be used as the research identifier for each subject.

(7) Restricted Data Collection on Persons Who Refuse to Participate in All of the Study or Part of the Study: If a patient declines to participate in all portions of the study, the patient will not be assigned a study ID number and the study coordinators/data collectors will refrain from collecting any data on the patient. If a patient agrees to participate in some portions of the study but not others, the patient will be assigned a study ID and the study coordinators/data collectors will be instructed to collect data only on those aspects of the study to which the patient has agreed to participate. These procedures will help prevent unauthorized inclusion of a patient's data in the database.

(8) Visual Paired Comparison (VPC) testing: a method that combines infrared eye-tracking with a behavioral task of recognition memory involving imagery on a computer has recently been shown to be a sensitive early predictor of cognitive decline. VPC assesses memory function by determining whether a participant exhibits preference for a novel picture compared to a previously viewed picture assessed by viewing time, and it has been shown a sensitive predictor of the development of mild cognitive impairment (MCI) and Alzheimer's disease in recent studies. This early technology may provide valuable prognostic information regarding self-management behaviors and may be useful in predicting the rate of hospitalization in CHF patients.

3. Statistical Considerations:
As a general matter, we believe that the projected sample size of the database (at least 12,000 patients) will allow a wide variety of scientific questions to be addressed with an adequate amount of statistical power.

VA Potential Risks, Discomforts, and Benefits:

For some of the patients, we will initiate the blood draw by placing a needle into an arm vein. The risk from blood drawing is very small, but may include discomfort, bruising, infection and a chance of dizziness/fainting. Using sterile precautions will minimize risk of infection. A bruise may develop at the site of the puncture, but this will go away in two to three days.

Another risk from participating in the database is the potential for the release of confidential information and associated problems, such as insurance and employment discrimination. Some patients may also be made somewhat uncomfortable by some of the questions in the questionnaires.

Blood flow measurements: The blood pressure inflation lasts for 5 minutes and can result in temporary feelings of numbness and pins and needles in the arm that last for one or two minutes. However, this is generally well tolerated and causes no long-term side effects. The blood flow measurement device worn for 24 hours is very well tolerated. The device is light weight and padded and does not disturb sleep or any other daily activities.

Carotid Ultrasound- The ultrasound probe may cause some temporary discomfort. If there is a plaque present in the participant's carotid artery, there is a small but rare chance that the motion and pressure placed by the ultrasound probe may mobilize the plaque upwards to the brain, possibly causing a stroke.

Peripheral vein blood draw- This procedure is usually quick and safe. There might be a slight discomfort associated with needle insertion or tourniquet placement. A small bruise might develop at

the site of needle insertion that usually disappears in a few days. To minimize the risk of infection, alcohol will be rubbed against your skin using alcohol pads.

Exercise Treadmill Testing-Exercise treadmill testing has a 1/10,000 risk of cardiac arrest or death.

There are minimal risks from the non-invasive vascular function studies:

WatchPAT - This device is light weight, well-padded for patient comfort and non-invasive. It is very well tolerated and does not disturb patient activity during the day and is not reported to disrupt sleep. Some subjects may experience mild discomfort from the finger or skin probes, which can be relieved immediately upon removal.

VPC Testing: Participants may experience mild discomfort from starting at the screen for 10 minutes.

There may be no direct benefit to the subjects. However, the information obtained may help to advance the understanding of cardiovascular disease and may thus be of future benefit to patients with these disorders or to at-risk members-of-society. The subjects incur no cost from participating in this study. However, they are also not paid for their participation. If they are patients at one of the study sites, they are still responsible for the costs of the clinic visit and any clinical labs ordered by their doctors.

VA Safeguards to Protect Patient Confidentiality:

All information will be kept private. No current or future research results will go into the medical record. If scientific reports, publications, or educational materials are written using information from the database, patients within the database will not be identified by name.

Agencies that make rules and policy about how research is done have the right to review information within the database. Agencies that pay for the study also have this right. The Emory University IRB may also review such information. All efforts will be made to use only the study ID number, not the subjects' names, when these agencies are reviewing information within the database.

All VA data that is remaining at the Atlanta VAMC will be stored in a secure database. Access to this database will be restricted by a database manager and will be password protected to be accessed by authorized research study team members. The only individuals who will be able to see patient identifiers, like name, address, and social security number, will be the Principal Investigator, research coordinators, recruiters and the database managers. If investigators want to conduct research activities beyond those specified in this protocol using data from this database, these investigators will have to submit a separate protocol to IRB and R&D for approval.

VA Collaborations:

The information in the database will be shared with other investigators to help them study cardiovascular diseases. These studies will require authorization by the Principal Investigator. Any approved study run by an investigator at any institution must be approved by an Institutional Review Board.

Studies that might be approved to use the information in the database will be those designed to understand factors associated with the etiology, course, and treatment of various cardiovascular diseases, and perhaps other types of diseases as well. The research investigators involved in this study and in future studies and any other individual who may have access to the blood sample and its derivatives are not authorized to and are forever prohibited from using this material for any attempt at cloning a human being.

VA Future Studies:

When this study is approved, approval will not extend beyond the creation of the database. Any future studies that wish to make use of the database must therefore get approval from IRB and R&D by submitting separate protocols.