

**HUMAN SUBJECTS**

**Detailed Description of Human Subjects:**

A total of 70 (35 CHD subjects and 35 healthy controls) will be recruited from the UCLA Medical Center and Children’s Hospital Los Angeles (CHLA) Pediatric Cardiology Clinics and studied at the UCLA MRI suite. Power analysis indicates a sample size of 59 subjects could detect a moderately large effect sizes of 0.47 on an ANCOVA with 2 covariates (age and gender) at an alpha level of 0.05, 2-tailed test with a power of 0.80. We will oversample by 10 subjects (~16%) to insure a final sample size of 60 subjects (30 CHD and 30 healthy controls), in case we have to delete subjects from the final analyses for excessive head movement that we cannot correct for in our procedures and which may not be visible during the initial data acquisition. Their age range will be 14 and 18 years of age, to minimize differences in brain maturation in younger subjects or age related disease etiology in older subjects.

Our past research experience in adolescent with CHD patients at UCLA Medical Center and CHLA has indicated that the ethnic breakdown of our subjects will be 60% White, 30% Hispanic, 8% African American and 1% Asian. Greater details on expected subject ethnic and racial information are listed in the “Targeted/Planned Enrollment Table” following this section. We expect the proportion of male and female subjects seen fairly equal from our past experience, at a ratio of 55% males and 45% females. However, there will be a conscious effort made by the investigators of this proposal to achieve an approximate 1:1 ratio of males: females (15 males: 15 females) with CHD. We will obtain this equal gender distribution by ceasing male CHD recruitment at 15, and then continuing to ask only females to be in the study. We do not expect to encounter problems with recruitment of female CHD patients, due to the accessible populations at both sites. All patients will have CHD and have completed surgical repair or palliation. Controls will be age- (to ± 1 year) and gender-matched at a 1:1 ratio to the CHD subjects.

**Identify Sources of Research Material:**

Research material for the study will consist of information from MRI equipment and medical records. Data to be collected exclusively for use on this research study include brain MRI images (structural MRI using SPGR techniques); non-invasive blood pressure, ECG, oxygen saturation via pulse oximetry (the blood pressure, ECG, and oxygen saturation will be closely monitored for early detection of any cardiovascular problems in this high risk patient population). MRI data will be digitally collected and transferred to the image analysis lab computers. Cognitive testing will be collected on paper and transferred to the data analysis computer.

Data from medical records will be collected from existing information on the patient’s hospital and clinic charts. This information, not collected exclusively for the study, will include age, sex, ethnicity, CHD diagnosis, number and type of surgeries, NYHA Functional Classification, LVFS / LVEF or qualitative RV function, AVVR, oxygen saturation, ECG, BMI, and medication use (particularly angiotensin-converting enzyme inhibitors, beta-blockers and diuretic dose and type).

**Recruitment Plans for Subjects:**

Prospective subjects will be recruited via study advertisement posters in the UCLA Medical Center (Pediatric Cardiology Clinic, Ahmanson-Adult CHD Clinic, and Transitional Program) and CHLA Pediatric Cardiology Clinic waiting rooms and around the UCLA campus. Recruitment will start approximately 2 months after the start of the study (first 2 months will be spent hiring and training project director and refining the data collection protocol) and end 6 months before the end of the study (to allow time for intensive analyses of MRI studies obtained in the first half of the study period). Prospective participants will call or e-mail the investigators to volunteer for the study or be referred by their cardiologist. The parent / adolescent of the CHD and healthy subjects will have the study briefly described and permission to contact their cardiologist (for CHD subjects only) for confirmation of study inclusion and exclusion criteria. After confirmation that prospective subjects meet the study inclusion and exclusion criteria, all study procedures will be explained in detail. If the prospective parent / adolescent expresses an interest in participating, an informed consent / assent form will be given to the subject to read as well as the telephone number of the principal investigator for further information and questions. After three business days, the prospective subject will be contacted to ascertain if they have any questions about the study and to obtain verbal consent for the study. If they consent, subjects will be scheduled for study procedures. On the day of the study procedure, subjects understanding of the research study will be confirmed (by having them verbally and accurately describe the study’s procedures and
risks to the principal investigator) and written informed consent will be obtained on the study’s informed consent form. A copy of the signed consent form, Human Subject Bill of Rights, summary of procedures, and study protocol will be given to the subject at that time.

**Potential Risks:**

The primary risks for the MRI-related study procedures include feelings of claustrophobia and hearing loss secondary to the high noise levels generated by the MRI scanner. While we ask subjects if they are nervous or anxious in small/enclosed spaces (claustrophobic), there is a risk that the subject may not be aware of being claustrophobic. Therefore, before we initiate any MRI study, we always orient subjects to the MRI scanner setup and allow them to examine the layout in the MRI scanner before data collection. Risk of hearing loss is dramatically reduced through the use of ear protection. Because these patients are at increased risk for cardiac dysrhythmias due to the nature of their disease, we always have an investigator trained in advanced cardiac life support in the MRI scanner room at all times with the patient during the MRI scans. In our research teams previous studies of 84 OSA adults, 30 congenital central hypoventilation children, 80 advanced heart failure, 13 congenital heart disease adolescents, and 120 adult and pediatric healthy controls, we have not had any adverse events (syncope, nausea, dysrhythmias, or chest pain during or after any of the MRI procedures proposed for this grant). While these adverse events would not be associated solely with MRI scanning, the fact that these patients have a high incidence of dysrhythmias that can lead to death make it very important for us to monitor them closely. Thus we remain extremely vigilant about early detection and prevention in this high risk patient group. Because of these potential risks (not from the MRI procedure, but because of the high risk nature of the patient population), we will continuously monitoring the electrocardiogram and arterial oxygen saturation during the study. All subjects will be watched continuously while in the MRI machine via closed circuit television (viewed by the MRI staff), continuous monitoring of ECG and oxygen saturation, and in person (a nurse or physician trained in advanced cardiac life support will be present in the MRI room with all subjects during the study). Oxygen and ambu bags are available in the same MRI scanner room as the subjects, as well as a crash cart (equipped with defibrillator, intubation and advanced cardiac life support drugs) just outside the doorway of the MRI scanner room (15 feet from the subject). Also, subjects can speak with us at any time during the MRI scan via a microphone in the MRI tube.

Frustration or distress may occur if the subject is having difficulty remembering items on the cognitive tests. If a subject shows signs of distress (head in hands, crying, hitting their head, verbalizing frustration or anger at themselves for not remembering), Dr. Pike or research assistant will stop the testing, provide the correct answer, and offer assistance (emotional support and reassurance). If distress continues, they will refer the patient to their primary care provider or closest emergency room depending on the level of distress.

**Procedures to Protect or Minimize Potential Risks:**

To minimize risks to the subject, standard tests ordered for routine UCLA and CHLA care will be used to assess cardiac functional status (echocardiogram and cardiac catheterization hemodynamic data). Confidentiality of subjects will be preserved by coding each patient data sheet with a unique subject number, and the patient-code number key stored in a locked file cabinet in the principal investigator’s office. In all of the research experience of the principal investigator and co-investigators, such procedures have been completely successful at maintaining patient confidentiality. As the CHD subjects have the potential for life threatening events at any given time, precautions have been taken regarding the sites of patient study. For example, subjects will be studied only in UCLA Medical Center MRI facility, with constant nursing and medical supervision, crash cart and emergency medical supplies within 15 feet of each patient study area, and physicians (pediatric cardiologist) and nurses trained in emergency resuscitative procedures. To minimize the chances of an adverse event occurring during the study, CHD patients will be carefully screened for inclusion and exclusion criteria (both at the time of recruitment and immediately before the initiation of study data collection procedures) and their participation in the study will be based not only on the CHD patient agreement but also must include their UCLA or CHLA cardiologist’s clearance (note: all UCLA and CHLA Cardiologists will review this proposal and will be given a copy of the study specific aims and procedures prior to the initiation of subject recruitment). Subject participation in the study will be immediately stopped and their cardiologist and co-investigator physician (Dr. Nancy Halnon) notified for evaluation of the subject if any of the following should occur: ventricular tachycardia (more than 3 ventricular beats in a row), bradycardia (sudden decrease in HR to less than 50 beats/minute and mean blood pressure decrease of > 15%), oxygen desaturation (> 15% drop from baseline O2 saturation on pulse oximeter), nausea, or syncope. Monitoring of
data for patient safety will be performed every 3 months and as needed. See the Data Safety Monitoring Plan below if an adverse event, such as syncope or ventricular dysrhythmia should occur during the study procedures.

Furthermore, in the unlikely event that frustration and distress from memory / cognitive testing occurs, the PI will stop the test, provide the correct answer and offer assistance (emotional support and reassurance). If distress continues, the PI will refer the patient to the neurodevelopmental psychologist, primary care provider or closest emergency room depending on the level of distress.

**Discussion of Risks and Anticipated Benefits of Study:**

As the possible risks to subjects are either small or unlikely to occur, and the potential increase in general knowledge regarding the relationships of memory and brain structure in CHD patients is important, we feel that the study is justified. Moreover, the study could provide important information regarding CHD pathophysiology and suggest alternative treatment strategies. Other than the patient participation compensation ($50 for completion the memory testing; $150 for MRI study; total of $200), parking covered and copy of structural MRI, there are no immediate benefits to participating subjects. The structural MRI could be of some clinical benefit to each subject's physician.

**Data and Safety Monitoring Plan**

This study is minimal risks for the participants in this non-clinical trial study. However, as we take research subject safety very seriously, we attached a detailed Data Safety Monitoring Plan which we use for all of our MRI research projects. The PI(s) have primary responsibility for the overall conduct of the study and for the safety of participating human subjects. The PI(s) will ensure that 1) the informed consent process is conducted appropriately and that informed consent is obtained prior to proceeding with any study procedures; 2) only eligible subjects, per protocol eligibility criteria, are enrolled in the study; 3) data are collected and analyzed per protocol requirements; 4) procedures are implemented to ensure that the project is consistently monitored for possible adverse events; 5) adverse events are reviewed promptly and reported as required to the UCLA IRB; 6) the privacy and confidentiality of study participants is maintained. The PI(s) will discuss with the research team the following issues on a regular basis: subject recruitment, issues related to implementation of the study protocol, any adverse events, and any complaints or problems emanating from participants. The following data safety and monitoring plan will be implemented:

a) The PI(s) have primary responsibility for monitoring data integrity and patient safety during all study procedures for the duration of the study. Dr. Pike is a nurse practitioner trained in pediatric and adult advanced life support. Dr. Kumar is an expert in running the MRI machine and well trained in patient safety issues while in use. We will work as a team during all data acquisition to assure patient and investigator safety.

b) The PI(s) and research team will monitor the data quarterly (every 3 months) and as needed to discuss study progress, any safety issues, protocol violations (i.e. participate not completing all required tests) or adverse events (i.e. cardiac dysrhythmias, syncope, or chest pain / pressure, breech in privacy or confidentiality, unknown claustrophobia in MRI scan and any unanticipated problems). To ensure confidentiality of participant data, all personal identification will be separated from the data, except on the master file which will be kept in a locked cabinet (which is NOT in the same location as the data files) where only the PI(s) has access.

c) Unanticipated problems (such as bradycardia, syncope, or skin discomfort from ECG electrodes) will be reported by the PI(s) within 24 hours to the UCLA IRB and NINR. A detailed description of the adverse event and the response of the research team will be included in the report. Adverse events for this study will include: cardiac dysrhythmias, syncope, or chest pain / pressure, breech in privacy or confidentiality, unrecognized claustrophobia (subjects are asked during informed consent and a tour of the scanner is given to reduce this occurrence) in MRI scan will be reported in 24 hours to UCLA IRB. In the unlikely event that 2 subjects develop an adverse event, unanticipated problem or 1 subject with a serious unexpected adverse event (such as cardiac arrest), accrual will stop, and a review of eligibility and possible revisions will be assessed. If revisions to eligibility are made, an amendment will be sent to the NINR and UCLA/CHLA IRB. Recruitment will resume pending NINR and UCLA / CHLA IRB approval and/or additional recommendations from these organizations. In addition to a detailed description the adverse event, the following information will also be included in the report:

a. Number of subjects approached for study since the last report period
b. Number of subjects who were successfully recruited since the last report period
c. Total number of subjects approached for recruitment since study began
d. Total number of subjects successfully recruited since study began
d) All study procedures will be performed at UCLA. Recruitment of subjects into the study will take place at UCLA and CHLA.
e) While it is unlikely, if there are any new developments in the literature that would impact patient safety or ethics of the proposed study, enrollment will stop; modifications to the study will be made, and approval of these modifications will be obtained from the NINR and UCLA / CHLA IRB before resumption of study activities. Enrolled subjects will be notified if deemed necessary by the UCLA / CHLA IRB and PI(s).
f) This study is not a clinical trial and will not require an interim and/or futility analysis

**Human Research Subject Protection Training of Key Personnel on Grant:**
In accordance with NIH policy, UCLA / CHLA has implemented an educational program on the protection of human subjects. Following are the names of all key personnel who are responsible for design and conduct of this project:

- Nancy Pike, PhD, RN
- Rajesh Kumar, PhD
- Danny JJ Wang PhD
- Nancy Halnon, MD, MS
- Alan B. Lewis MD
- “To Be Named”

Each person identified as key personnel have completed the CITI UCLA or CHLA training entitled “Human Research-Biomedical Researchers”. The program is comprised of nine modules: (1) Introduction, (2) Ethical Principles, (3) IRB Regulations and Review Process, (4) Informed Consent, (5) Records-Based Research, (6) Research with Protected Populations, (7) FDA Regulated Research, (8) Conflict of Interest Involving Human Subjects, and (9) UCLA/CHLA. In addition, all key personnel have completed the CITI UCLA or CHLA HIPAA training. Key Personnel have completed an online course. Certificates of completion of the training are on file through CITI UCLA/CHLA training.

In addition, the “To Be Named” personnel on the grant (project director) will undergo both Human Research Biomedical training and HIPAA certification before starting their work on the study.