OFFICIAL TITLE: NONINVASIVE, SUBHARMONIC INTRA-CARDIAC PRESSURE MEASUREMENT

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PROPOSED RESEARCH PLAN

The primary objectives of this trial are:

1. To study cardiac pressure changes in patients scheduled for a left and/or right heart catheterization using subharmonic aided pressure estimation (SHAPE) and correlate results to Swan-Ganz catheter based pressure measurements and to establish if the errors in pressure measurements for clinically important ventricular systolic and diastolic pressures obtained using SHAPE are within 5 mmHg of the catheter pressure data.
2. To compare the left ventricular relaxation rate (peak isovolumic –dP/dt) and relaxation time constant (tau or τ) in addition to the clinically important left ventricular systolic and diastolic pressures obtained using SHAPE and high fidelity micromanometer-tipped Millar pressure catheters.

**Trial Design:** This is an open-label, non-randomized trial that will be conducted at Thomas Jefferson University. Enrolled patients undergoing cardiac catheterization will receive a continuous infusion of Sonazoid® (GE Healthcare, Oslo, Norway) co-infused with 0.9% NaCl solution over a 5-10 minute time period using the setup and infusion rates described by GE Healthcare's (GEHC) Protocol Supplement. Ultrasound imaging will be performed using a SonixTablet scanner with a SA 4-2 transducer (Analogic Corporation, Peabody, MA) and the SHAPE algorithm will be used to measure pressure values in the heart. Peripheral pressure measurements will be acquired using a cuff-based SphygmoCor system. Data will be stored on a PC and compared to pressure-catheter measurements.

**Trial Population:** This trial will consist of up to 80 adults (21 years of age or older) undergoing cardiac catheterization at Thomas Jefferson University (TJU).

**Trial Procedures:** Subjects eligible for trial enrollment will be identified by the co-investigators, Drs. Savage, Cohen and Mehrotra (at TJU) from their patient population of subjects scheduled for cardiac catheterization. The research coordinators for this study will explain the study to the patients. The patient will be given time to consider the risks and benefits of the study and ask questions about participation. The coordinator will review the consent form with the patient and then the patient will be given the form to review. The patient, coordinator, and a study investigator will all sign the consent form. The patient will be given a copy of the signed consent form for their records.

After consenting to participate in this study, a full demographic profile, known drug allergies or intolerances, and review of the subject's medical/surgical history will be recorded. Patients with known cardiac shunts will be excluded from the study. If the subject is a woman of childbearing potential, she will have a urine pregnancy test (the results of which will be made available to the subject prior to study initiation).

Whenever a subject undergoes a cardiac catheterization as part of their standard clinical care and agrees to participate in the study, we will perform the corresponding SHAPE measurements during the catheterization procedures to synchronously acquire SHAPE measurements and catheter based pressure measurements. Administration of Sonazoid will be performed under direct supervision of a medical doctor. Additionally, resuscitation equipment will be in immediate proximity to the patient during Sonazoid infusion. Three vials (6 ml) of Sonazoid microbubbles (16 µl per vial when reconstituted) will be prepared for each subject by resuspending each vial in 2 ml of water for injection, supplied by GEHC, as described in the instructions provided by GEHC. Infusions will be performed as described. All materials and supplies used for the infusion procedure will be identical to those described in GE Healthcare's current Sonazoid IND. Briefly, an intravenous cannula will be placed in a vein in the subject's arm. A 0.9% NaCl solution will be started and used to fill up the connecting tubes before being connected to a 3-way stopcock. The

stopcock will then be connected to the extension tubing leading to the cannula. All three vials of suspended Sonazoid will be drawn into a 10 ml syringe, placed in a syringe pump at the same level or below the patient, and connected directly to the stopcock. After the stopcock to the 0.9% NaCl solution has been opened, the saline solution will be infused at a rate of at least 2 ml/min. Then, Sonazoid will be co-infused at the target rate of 0.024 µl/kg body weight/minute (suspension infusion rate of 0.18 ml/kg/hour), but the rate may be reduced if necessary to achieve optimal levels of contrast. This infusion rate was selected based on our group's previous experiences with Sonazoid infusion in human subjects in general [Halpern et al. 2002; Landmark et al. 2008] and in SHAPE portal hypertension subjects in particular [Eisenbrey et al. 2013]. This dosing scheme is designed to avoid (or limit) the number of cases that has to be discarded due to insignificant enhancement (as in our pilot study; Eisenbrey et al. 2013). The dosage is based off the GEHC provided, study specific resuspension and infusion instructions and the total Sonazoid dose given over a maximum of 15 minutes (0.36 µl/kg) will be well below the maximal tested dose which was still found safe in Phase I clinical trials (2.7 µl of microbubbles/kg in PBI 0001 as detailed in the Sonazoid Investigator's Brochure). The duration of contrast agent infusion will range from 5 to 10 minutes.

Initially, ultrasound imaging will be performed with the SA 4-2 phased array to locate the tip of the Swan-Ganz catheter as it progresses through the cardiac chambers and guide the spectral Doppler sample volume placement (for SHAPE measurements). At this time, peripheral pressures will be acquired using a SphygmoCor system (in about 10 s). Based on the measured peripheral pressures, the SphygmoCor system will estimate the central aortic pressures (in another 10 s). This pressure value will be recorded and entered into the SHAPE software. Then the Sonazoid infusion will be initiated (dosage as indicated above) and once a constant concentration of contrast has been reached, the SHAPE algorithm to select the optimal incident acoustic pressure will be activated [Dave et al. 2013]. Ultrasound scanning will be first performed in the aorta. After the optimal incident acoustic pressure is determined, the data from the aorta will be obtained using the optimum incident acoustic pressure. Based on the aortic pressure (in mmHg, obtained from the SphygomoCor system) entered into the SHAPE software, and the acquired ultrasound data from the aorta (in dB), the SHAPE software will compute a calibration factor for each subject in units of mmHg/dB. The field of view will then be adjusted to acquire the data from the left or right ventricles. For each chamber, subsequent SHAPE data will be acquired simultaneously with the Swan-Ganz catheter data (as part of the patient's standard-of-care) using the optimal incident acoustic pressure. During the data acquisition from the right and left ventricles, the SHAPE software will use the calibration factor (in mmHg/dB) obtained from the aorta, to translate the subharmonic amplitude (in dB) to pressure values (in mmHg) and display these pressure values in real-time. Ultrasound data will be acquired from the left and right ventricles in 10 s segments. These measurements will be repeated as mentioned before. All the pressure values obtained using the SHAPE software will be stored on the SonixTablet. After acquiring the ultrasound imaging data the remainder of the heart catheterization will be completed by the attending cardiologist according to the patients' standard of care.

The proposed agent for the study, Sonazoid (GE Healthcare,), is a sterile non-pyrogenic suspension of lipid stabilized perfluorobutane microbubbles for contrast-enhancement, with a median diameter between 2.4 and 3.5 µm [Forsberg et al. 2008]. Previous in vitro results have shown Sonazoid to be superior for SHAPE measurements relative to other ultrasound contrast agents [Halldorsdottir et al. 2011]. It should be pointed out that the safety of Sonazoid has already been established in numerous animal studies and in human studies for the evaluation of the liver and heart both in this country and in Europe [Landmark et al. 2008]. Sonazoid has been approved for use in patients with liver lesions in Japan (for more than 8 years) and it has since been approved for imaging use in South Korea, Taiwan, China and Norway [Bouakaz et al. 2007; Jang et al. 2013]. Finally, we have previously obtained investigator initiated IND (investigational new drug) for Sonazoid use in patients in USA and no adverse events were reported in this study no

adverse reactions attributable to contrast agent infusions were observed in our pilot study [Eisenbrey et al. 2013].

All examinations will be recorded. During the examination, the subharmonic pressure estimates will be displayed on the SonixTablet scanner, these estimates will be noted down and the data will be stored on a PC. Data will be compared to the catheter based measurements. Emergency services (e.g., a crash cart) will be available within the hospital in case of any acute adverse reactions. Patients will be monitored for a minimum of one hour post Sonazoid administration. During this time a trained CPR personnel and resuscitation equipment will be available. SHAPE data will later be compared to all clinical variables obtained from the patient to determine potential correlations.

**Statistical Methodology:** This is a study to prove the feasibility of real-time, in vivo SHAPE in human cardiac applications. Our statistical analysis will address the following major questions:

1. For the human studies, do subharmonic pressure estimates correlate (i.e., $r > 0.8$) with invasively-determined blood pressure measurements in patients scheduled for a left and/or right heart catheterization and will the errors in pressure measurements for clinically important ventricular systolic and diastolic pressures obtained using SHAPE be within 5 mmHg of the catheter-based pressure data (i.e., is real-time clinical SHAPE feasible)?
2. Will SHAPE measurements accurately predict other pressure contour-derived indices i.e., ventricular relaxation rate (peak isovolumic –dP/dt) and relaxation time constant (tau or $\tau$) with errors less than 5%?

All of the statistical analyses proposed for the human clinical trial will be repeated split by racial and ethnic groups to determine if clinically important race/ethnicity differences exist in the ability of SHAPE to monitor cardiac pressures. All analyses and computations will be performed using IBM SPSS Statistics.

**Key References:**


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