Prospective 4D Computed Tomography Angiography Of The Bicuspid Aortic Valve Apparatus: A Comparison Of Bicuspid Aortic Valves With And Without Aortic Insufficiency

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Study Summary

Title	Prospective 4D Computed Tomography Angiography Of The Bicuspid Aortic Valve Apparatus: A Comparison Of Bicuspid Aortic Valves With And Without Aortic Insufficiency
Short Title	Prospective 4D CTA of BAV Competence
IRB Number	
Protocol Number	
Methodology	Longitudinal observational study
Study Duration	9 years
Study Center(s)	Single-center study (University of Pennsylvania)
Objectives	Primary: • To use medical imaging to determine the anatomical parameters (e.g., aortic valve and aortic root dimensions and dynamics) of bicuspid aortic valve competence. Secondary: • To understand the natural history of BAV disease, including the development of aortic insufficiency and/or stenosis. • To determine the anatomical characteristics predictive of successful BAV repair.
Number of Subjects	60 subjects expected to enroll at Penn

Main Inclusion and Exclusion Criteria	Inclusion criteria: • At least 18 years of age • Documented bicuspid aortic valve identified via clinical imaging (e.g., CT, MRI, or echocardiogram) with minimal calcification at the time of enrollment • Participant must sign the informed consent form Exclusion criteria: • Pregnancy (determined by point of care urine pregnancy test) • Renal failure (estimated Glomerular Filtration Rate (eGFR) < 30), precluding them from receiving intravenous contrast) • Documentation of previous intravenous contrast allergy (unless they are having a CT with steroid preparation as part of routine clinical care) • Previous aortic valve replacement
Intervention	The study involves annual 4D CTA imaging of the bicuspid aortic valve for a period of 5 years. CTA is often standard of care for BAV patients, but patients in this study will receive a higher radiation dose with a 4D imaging protocol. There may also be patients enrolled in the study who have a 4D CTA for research purposes when a routine CTA is not required for clinical care.
Statistical Methodology	Patients will be stratified into "competent" and "incompetent" BAV groups based on the severity of aortic insufficiency on routine echocardiography at the time of study enrollment. Geometrical and functional measurements (e.g., coaptation area, coaptation height, cusp surface area, aortic root diameters, valve orifice area, localized cusp thickness, and aortic cusp and root velocities) will be extracted from each 4D CTA scan to quantify valve morphology and dynamics at each study time point, as well as longitudinally. Measurements from the competent and incompetent BAV groups will be reported and compared.
Data and Safety Monitoring Plan	The PI will be responsible for the data quality management and the ongoing safety of subjects.

Background and Study Rational

1 Introduction

The bicuspid aortic valve (BAV) is the most common congenital heart disease. The purpose of this study is to better understand the anatomy of physiologically "normal", or competent, BAVs without stenosis or insufficiency (AI) in order to support evidence-based standardization of BAV repair surgery. Men and women over 18 years of age with a diagnosis of BAV and minimal aortic valve calcification at baseline will undergo annual 4D computed tomography angiography (CTA) scans, transthoracic echocardiograms, and history and physical assessments over the course of the 5-year study period. Patients who are pregnant, have renal insufficiency (creatinine > 2 mg/dL), or who have a contraindication to intravenous contrast will be excluded. Patients will be stratified into study groups according to baseline AI: approximately half of patients will have no to mild AI at baseline and the other half will have moderate to severe AI at baseline. Anatomical measurements will be obtained from the 4D CTA scans and analyzed at each phase of the cardiac cycle, as well as longitudinally. The 4D CTA imaging and analysis will not

impact medical care of the study participants; the anatomical measurements will be used in the future as evidence-based standards for determining valve repair candidacy for BAV patients with AI.

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations. All episodes of noncompliance will be documented.

1.1 Background and Relevant Literature

The BAV is the most common congenital heart defect, reported to affect 0.5 – 2% of the population (Ward 2000). Since BAVs are typically imaged after a patient has developed symptoms of aortic insufficiency (AI) or aortic stenosis (AS), little is known about the geometric and dynamic anatomical features of the functionally "normal" or competent BAV, defined as a BAV without stenosis or insufficiency. Moreover, there are gaps in knowledge of the natural progression of BAV competence to BAV pathology, which most frequently manifests as AI and/or AS. There is limited data to predict if and when asymptomatic BAV patients will need to receive intervention to repair or replace their aortic valve.

BAV patients who present with AI typically range in age from 20 to 50 years old and, based on age at presentation, will survive several decades after intervention (Boodwhani et al. 2010). While aortic valve replacement is the conventional treatment for AI, it is not an ideal intervention in younger patients with non-stenotic BAVs. Bioprosthetic valves have limited durability in this patient population and will require at least one additional valve replacement over the patient's lifetime (Aicher et al. 2011). Mechanical valves carry the risk of thromboembolic events and require life-long anti-coagulation, which limits quality of life in young patients (Salem et al. 2004). Therefore, BAV repair has become more widely adopted by surgeons in major cardiac centers in recent years, as early results have been satisfactory (Aicher et al. 2011, Svensson et al. 2014). However, repair strategies have not been standardized and are limited to single-center reports in relatively small patient series. Furthermore, techniques to determine repairability of a BAV have been adopted from normal trileaflet aortic valve studies (Schäfers et al. 2013) and there are no existing research studies of functionally normal BAV characteristics, such as coaptation height and cusp height. Such studies would help to standardize BAV repair procedures, as they would define the anatomical and dynamic valve characteristics that are needed to recreate BAV competence during valve repair surgery.

The goal of this research is to characterize the aortic valve and root geometry/dynamics of physiologically normal BAVs relative to BAVs with moderate to severe AI. While transesophageal echocardiography (TEE) is the most commonly used imaging modality to assess valve morphology and dynamics, it requires sedation and is not typically ordered for routine annual surveillance. In this study, 4D computed tomography angiography (CTA) imaging will be used to analyze aortic cusp motion and coaptation and to create four-dimensional BAV models to measure aortic root landmarks and valve characteristics over the cardiac cycle. The long-term goal of this research is to follow the natural history course of BAV syndrome and the development of AI or AS.

2 Study Objectives

2.1 Primary Objective

- To use medical imaging to determine the anatomical parameters (e.g., aortic valve and aortic root dimensions and dynamics) for BAV competence.

2.2 Secondary Objectives (if applicable)

- To understand the natural history of BAV disease, including the development of aortic insufficiency and/or stenosis.

- To determine the anatomical characteristics predictive of successful BAV repair.

3 Investigational Plan

3.1 General Design

This is a prospective observational study of patients with normally functioning (competent) and diseased (incompetent) BAVs. Patients will be stratified into two groups based on degree of baseline aortic insufficiency. Those patients with less than moderate (+2) AI will be in the "competent BAV" group, and those patients with greater than moderate (+2) AI will be in the "incompetent BAV" group. Each group will be limited to 30 patients. All patients will follow the same study time course and undergo the same study procedures, including an annual 4D CTA scan. The goal of this work is to describe differences in the anatomical and functional characteristics of BAVs in these two groups based on 4D CTA.

Overview of study procedures (described in Section 5):

- Screening for study eligibility and informed consent
- 4D CTA imaging at baseline and at 1-year intervals over a period of 5 years. (Annual CTA studies will be performed routinely in some or many of the patients, but the 4D protocol will be for research purposes.)
- Annual office visits and echocardiography studies over the 5-year study period (standard of care)

3.2 Study Measures

Image-derived measures of BAV morphology and dynamics

Features of BAV morphology and motion will be extracted from 4D CTA images acquired at baseline and at 1-year intervals over a period of 5 years. Manual and automated segmentation and deformable modeling algorithms similar to those presented in (Pouch et al., 2012) and (Pouch et al., 2015) will be used generate a 4D model of the BAV apparatus in each 4D CTA scan, which will depict BAV morphology and dynamics over one complete cardiac cycle. The measures extracted from each model will include, but are not limited, to the following:

- Cusp surface areas over the cardiac cycle
- Cusp height (geometric and effective)
- Cusp free margin length
- Cusp thickness (including raphe thickness, if applicable)
- Commissural height
- Characteristics of cusp fusion (e.g., symmetric cusp geometry or cusp fusion angle for asymmetric valves)
- Aortic root dimensions (e.g., sinotubular junction diameter/area, sinus of Valsalva diameter/area, aortic annular geometry, ventriculoaortic junction diameter/area, root volume)
- Coaptation height at diastole
- Cusp displacement over the cardiac cycle
- Cusp velocity/acceleration over the cardiac cycle
- Geometry of the ascending aorta (e.g., aortic size)

Measures from office visits, imaging studies, and interventions

Relevant measurements will be recorded from annual office visits, other routine cardiac imaging studies (e.g., echocardiography or MRI), and interventions such as cardiac surgeries performed during the study period. These will include, but are not limited, to the following (all are collected as standard of care):

- Physical exam measurements and vital signs (e.g., height, weight, pulse)
- Severity of AI or AS (assessed on routine echocardiography)
- Measurements from other routine images (e.g., echocardiography or MRI) complementary to the 4D CTA measures listed above
- Physical intraoperative measurements, such as cusp height (if an aortic surgery is performed during the study period)

- Additional relevant information, such as: cardiovascular symptoms, New York Heart Association Classification, information about cardiac procedures/surgeries performed (e.g., intraoperative exam findings, surgical approach, prosthetics used, factors motivating the surgical plan)

3.3 Study Endpoints

3.3.1 Primary Study Endpoint

The primary endpoint of this study is a set of 4D image-derived anatomical models of the BAV acquired at five one-year intervals. The anatomical and dynamic characteristics of the BAV will be analyzed over the cardiac cycle based on the 4D anatomical model generated from each 4D CTA study. The change in these characteristics (listed in Section 3.2) will be assessed over the 5-year period.

3.3.2 Secondary Study Endpoint

The secondary endpoint of this study is severity of AI and/or AS, as assessed by routine echocardiography.

4 Study Population and Duration of Participation

4.1 Duration of Study Participation

Estimated length of time to enroll all subjects: 2 years
Length of subject's participation in study: 5 years
Analysis and publication of results: 2 years
Projected overall duration of study: 9 years

4.2 Total Number of Subjects and Sites

We aim to have approximately 40 patients with adequate data to include in the final analysis. We believe enrollment of 60 patients into our study will account for potential error in obtaining adequate scans or loss of data due to patient withdrawal from study.

Penn is the only site at which patients will be enrolled.

4.3 Inclusion Criteria

- At least 18 years of age
- Documented bicuspid aortic valve identified via clinical imaging (e.g., CT, MRI, or echocardiogram)
- Participant must sign the informed consent form

4.4 Exclusion Criteria

- Pregnancy (determined from a point of care urine pregnancy test)
- Renal failure (estimated Glomerular Filtration Rate (eGFR) < 30), precluding them from receiving intravenous contrast)
- Documentation of previous intravenous contrast allergy (unless they are having a CT with steroid preparation as part of routine clinical care)
- Previous aortic valve replacement

4.5 Subject Recruitment

The Cardiology and Cardiovascular Surgical clinics at the University of Pennsylvania Health System see a high volume of patients with BAVs for both aortic surveillance and treatment. For reference, from July

2011 to June 2018, one surgeon at our center performed aortic valve replacement on 344 patients with BAV. Many more have undergone repair or have only been followed with routine echocardiogram and CT scans as they have not yet met the indications for surgery.

We will primarily using PennChart to identify patients scheduled in our cardiology and cardiac surgical clinics who have been diagnosed with BAV. Additionally, we will be identifying patients who receive an echocardiogram at Penn and are noted to have a BAV. After identification and screening via chart review, patients will be approached by a research coordinator, either in person (in clinic, heart and vascular testing center, or inpatient wards) or via telephone to gauge interest and, if interested, schedule them for a visit in our research clinic to sign consents. Finally, we will be identifying patients through the Penn Biobank to screen and, if they meet criteria, contact to gauge interest and schedule for a clinic visit. Privacy of individuals will be maintained by communicating only in private spaces within the hospital or by phone.

4.6 Vulnerable Populations:

We will not enroll patients who are unable to provide consent themselves. Pregnant women and children are excluded from this study. Monetary compensation will not be provided for participation.

Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged persons, and/or employees or students of the University of Pennsylvania will not be denied enrollment and any special protections and/or additional safeguards will be undertaken in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate.

5 Study Procedures

The procedures summarized in Section 3 are listed in Table 1.

Table 1: Schedule of Study Procedures

Study Phase	**Screening**	**Observation Study Visits**				
Visit Number		1 (Baseline)	2	3	4	5
Years from Baseline Study		0	1	2	3	4
Review Inclusion/Exclusion Criteria	X	X	X	X	X	X
Medical Record Review (routine office visits, imaging and laboratory studies, cardiac procedures)	X	X	X	X	X	X
Informed Consent	X					
4D CTA		X	X	X	X	X
Pregnancy Test		X	X	X	X	X
Adverse Event / Unanticipated Problems Assessment		X	X	X	X	X

Does your study use MRI? (CAMRIS is the appropriate contact for all studies involving MRIs)

☐ Yes **X** No (If No, no CAMRIS review needed)

Does your study include pregnant women?

☐ Yes **X** No

Does your study involve the exposure to radiation, radiotracers and/or radiological imaging modalities?

X Yes ☐ No (If No, no RRSC review is needed)

Will any of the radiation exposure result from procedures that are or could be performed solely as a result of a subject's participation in the research protocol?

X Yes ☐ No

Ultrasound

☐ Yes **X** No (routine echocardiography only)

Will your study be using CT Scans? (CACTIS is the appropriate contact for studies involving CT scans)

X Yes ☐ No

Studies involving Nuclear Medicine: Will subjects be undergoing any of the following procedures specific to research:

☐ MUGA
(See Nuclear Medicine-Muga Scan)
☐ PET/CT Scan
(See PET/CT Scan)
☐ Bone /DXA
(See Bone Scan)
X None of the above apply

Check off all of the following procedures that will be performed in your research- each option you select will link to the template language document:

☐ Apheresis/plasma exchange
☐ Leukapheresis
☐ Bone Marrow Biopsy or Aspirate
☐ Use of AP clinical specimens
☐ Biopsies- check those which apply
☐ Blood draw
X None of the above apply

5.1 Screening

The screening visit for eligibility assessment will include:

- Medical record review to verify documentation of a BAV, previous aortic interventions, presence of renal failure, contraindications to contrast agents, and pregnancy status. (Note: a pregnancy test will be performed prior to each 4D CTA study.) Pregnant women will be excluded from the study if they confirm pregnancy at the time of screening or if the pregnancy test prior to baseline imaging is positive.
- Informed consent

5.2 Study Intervention or Observational Phase (Give this section a name that is relevant to the design of your study)

5.2.1 Baseline Imaging

After being identified, screened, and have provided informed consent, all patients will undergo a baseline 4D CTA imaging study. A pregnancy test will be performed in women prior to the 4D CTA study. Each 4D CTA scan will be performed according to established TAVR imaging protocols with modifications to limit radiation dose to approximately 5 mSv.

Additional baseline information may be collected (standard of care):

- Other routine imaging studies (e.g., echocardiography or MRI)
- Physical exam
- Vital signs
- Laboratory tests, including creatinine level
- Quality of life assessments

5.2.2 Annual follow-up imaging and visits

After baseline imaging, patients will have annual routine clinic follow up visits (1 year ± 90 days) that will consist of the following:

- Medical history and physical (standard of care)
- Transthoracic echocardiogram (standard of care)
- Laboratory studies, including creatinine level (standard of care)
- 4D CTA (research). As annual CT scans are often standard of care in these patients, the research component will be the additional 4D imaging protocol, performed according to established TAVR imaging protocols with modifications to limit radiation dose to approximately 5 mSv.

5.3 Unscheduled Visits and Surgeries

Medical information and image data collected as standard-of-care at visits other than the scheduled annual follow-up may be included in the patient's research record. For example, relevant information from cardiac imaging studies or office visits other than the annual follow-up will be documented, especially as it relates to the development of AI and/or AS and associated symptoms. If a patient requires aortic valve repair or replacement during the 5-year study period, information that is routinely acquired during the operation will be recorded (e.g., procedures performed, prosthetic devices used, pre- and post-operative imaging and exam measurements, etc.).

5.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study procedures or visit schedules. Patients will be followed for any safety events. If a patient meets the indications for valve surgery during their participation in the study, they will remain in the study on their original study timeline, unless they require an aortic valve replacement, at which point they will end their study participation. It will be documented whether or not each subject completes the study.

6 Statistical Plan

6.1 Sample Size Determination

The sample size for this study is based on our previous work on automated heart valve analytics in 3D transesophageal echocardiography, wherein a minimum of 20 patients was needed to develop and evaluate the accuracy of semi-automated methods for reconstructing the mitral valve and tricuspid aortic valve apparatus in 3D images and to derive anatomical valve features similar to those described in Section 3.2 (Pouch et al. MedIA 2014; Pouch et al. MedIA 2015). Similar to the 4D CTA analysis proposed in this study, we used those image analysis techniques to carry out a statistical shape analysis of physiologically normal mitral annular geometry (Pouch et al., ATS 2014), as well as a comparison of normal vs. myxomatous valve morphology (Pouch et al., 2016), also with ~20 subjects per group. In this protocol, we propose to enroll 30 subjects in both the "competent BAV" and "incompetent BAV" groups; we anticipate this is the number needed to ensure that we obtain adequate image data from at least 20 subjects in each group given the potential for suboptimal image quality or patient withdrawal. Based on our previous work, 20 patients per group is likely the minimum necessary as a starting point to demonstrate feasibility of BAV modeling in 4D CTA data.

6.2 Data Analysis

6.2.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

6.2.2 Analysis of Primary Outcome of Interest

Post-processing of each 4D CTA data set will involve manual or semi-automatic image segmentation (labeling) and geometrical modeling of the BAV at each cardiac phase. Geometrical and functional measurements (e.g., coaptation area, coaptation height, cusp surface area, aortic root diameters, valve orifice area, localized cusp thickness, and aortic cusp and root velocities) will be extracted from the 4D CTA image segmentations to quantify valve morphology and dynamics at each study time point, as well as longitudinally. Measurements from the competent and incompetent BAV groups will be reported with standard descriptive statistics, including group means and standard deviations time-normalized with respect to the cardiac cycle at each study time point. Comparison of valve measurements in the two groups will be carried out with independent Student t-tests at multiple phases of the cardiac cycle with false discovery rate adjustment to account for multiple comparisons. We will perform additional statistics on longitudinal data. Comparable measurements will be made on standard-of-care echocardiography and/or MR image data when available.

7 Safety and Adverse Events

Potential safety issues in this study are related to radiation and contrast for the 4D CT exam. An internal safety committee, including representation from Radiology and Cardiothoracic Surgery, will monitor for adverse events. All CTs will be reviewed on a quarterly basis concerning radiation dose. Moderate to severe contrast reactions will be reported to the IRB as severe adverse events and evaluated individually by the safety committee. Patients who have severe adverse events will be withdrawn from the study. Mild reactions to contrast will be reviewed quarterly to evaluate whether the participant should continue in the trial.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

All image data and non-image patient information will be associated with a study-specific subject ID. The link between the subject ID and patient identity will be maintained in a RedCap form that will only be accessible to the PI and designees. The data files (medical images and patient characteristics) used for offline analysis will be de-identified and associated with the study-specific patient ID, not a patient name or other PHI. These data files will be stored on a password protected NAS server, stored in a locked Penn clinical research facility, accessible only to authorized personnel only through the UPHS network and will be independent of the RedCap form. Date-shifting will be used to ensure confidentiality, and the date shifting scheme will be stored only in the RedCap form. Any data shared with other investigators will be de-identified and void of both direct and indirect identifiers. If data transport is necessary, only UPHS-approved devices will be used.

8.2 Data Collection and Management

A link between the patient's medical record, name, and study-specific subject ID will be recorded in a RedCap form to which only the PI and designees will have access during the study. Images and electronic data forms containing PHI will be stored on computers or servers managed by the University of Pennsylvania Health System. When saving raw image data from the CT scanners, hospital-approved encrypted hard drives will be used for data transport. All papers with patient related study data (such as inclusion/exclusion forms, ICFs, imaging reports) will be stored in a locked binder closet within the Thoracic Aortic Surgery Program offices located at 5000 Ravdin Courtyard.

All PHI will be stored in RedCap. The PHI will include name, medical record number, date of birth, encounter dates, and the randomly generated number by which all that patient's dates in the database are shifted. Images will be anonymized and stored on a password protected NAS server, stored in a locked Penn clinical research facility, accessible only to authorized personnel only through the UPHS network. Any image data exported from the NAS server will be de-identified. Patient factors exported from the RedCap database for analysis will not include patient identifiers, such as patient name or MRN. The patient's date of birth and all encounter dates will be time-shifted by the same number of days in a range between -60 and -5. The date-shift value will be randomly generated and stored in the RedCap form that will link the patient's PHI to their study-specific ID. No published or presented materials will identify subjects by names or initials.

8.3 Records Retention

The link between the patient's medical record and subject ID will remain accessible in RedCap only to the PI and designees after completion of the study. The purpose of maintaining this link is if additional examination of the record is necessary to complete data entry, or if in a future follow-up study additional

information from the medical record may be needed to test future hypotheses. The PI will not access identifiable data for a future research study without prior IRB approval.

The RedCap form and anonymized images will be stored indefinitely to support future follow-up studies. PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study PI will be responsible for ensuring the ongoing quality and integrity of the research study.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Ethical Considerations

10.1 Risks

It is expected that at least half of the patients enrolled in this study will undergo annual CTA as standard of care as many BAV patients have dilatation of the ascending aorta. For research purposes, this group would receive a higher radiation dose for a 4D CTA of the aortic valve. There will also be study participants who would not require an annual CTA as part of their routine medical care. The latter group will receive a radiation dose for research purposes only. For all patients in the study, a standard transcatheter aortic valve replacement (TAVR) 4D CTA imaging protocol will be used with modifications to limit the radiation dose as close to 5 mSv as possible. Such modifications include restricting the scan such that only the necessary BAV anatomy is imaged with 4D CTA. (A 4D CTA of the entire chest is not necessary for this study, since the study focuses on a characterization of the BAV cusps and root.) The risks associated with ionizing radiation, IV contrast, and incidental findings are described below.

Risks: CT imaging and ionizing radiation
This research study involves exposure to radiation during the 4DCTA scan. Therefore, the patient will receive a radiation dose. This radiation dose is not necessary for their medical care and will occur only as a result of their participation in the study. At doses much higher than they will receive, radiation is known to increase the risk of developing cancer after many years. At the doses they will receive, it is very likely that they will see no effects at all.

Risk of pregnancy and ionizing radiation
Pregnant women will be excluded from having CT scan due to the possibility of unforeseen side effects to the fetus. All female subjects that are capable of becoming pregnant must take a pregnancy test within 24 hours prior to the CT exam to rule out pregnancy. A point of care pregnancy test (urine screening) will be carried out prior to each CT exam.
CT scans produce x-rays. If there is a chance of pregnancy the patient should inform the study staff and the CT exam should be postponed.

CT contrast agent: ISOVUE 370 (non-ionic)
Risk of IV contrast agents used in CT imaging
Approximately 95% of CT contrast reactions are mild to moderate in degree and most resolve without treatment. However, life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. People with heart disease, kidney disease, or allergies are more likely to have a severe reaction to contrast agents. The patient will be instructed to inform the study staff if the patient has a history of heart disease, kidney disease, or allergies.
Common effects of iodinated IV contrast agents are:

- Feelings of overall warmth, especially in the bladder area after injection
- A metallic taste during the injection
- Warmth, burning sensation or momentary pain at the injection site during contrast injection
- Less common are nausea, vomiting, headache, hives and itching
- Rare, but serious reactions are rapid heartbeat, changes in blood pressure, heart attack, kidney failure, pulmonary edema, serious life-threatening allergic reaction.

Risk of IV Placement:
There is a possibility that multiple needle sticks will be necessary to ensure proper intravenous line placement. A small amount of pain or bruising may occur with intravenous catheter (IV) placement and there is a small risk of infection at the injection site.

Risks: CT Imaging and Incidental Findings
It is possible that during the course of the research study, the research staff (and/or radiologist that reviews the CT scan) may notice an unexpected finding(s). Should this occur, the finding (s) will be considered by the appropriate medical personnel and the study principal investigator will inform them, if necessary. These finding(s) may or may not be significant, and may lead to further testing (such as additional imaging studies, or biopsy). This may result in anxiety or harm to the patient due to the additional testing. The costs of such additional testing will not be covered as part of this research study.

10.2 Benefits

There is no direct benefit to study participants. *The 4D CTA acquired in this study will not be used for clinical care or surgical decision-making for the participants but will likely benefit future BAV patients*. The following paragraphs describe the ways in which the study may benefit patients in the future.

This study may benefit BAV patients in the future since it will provide information that can help standardize the approach to BAV repair. For example, the thresholds on cusp height that are used to intraoperatively determine whether a BAV is repairable are based on tricuspid aortic valve data rather than physiologically normal BAVs. This study will produce a much-needed data set on physiologically normal BAV morphology that will provide quantitative evidence for cusp height thresholds and other measurements that drive intraoperative decision making. Thus, the knowledge gained from this study will help to determine whether a future patient is best suited for valve repair or valve replacement based on their pre-operative BAV morphological and dynamic characteristics. By providing descriptive information on how a pathological BAV should look and function after a successful valve repair, this research could make repair a viable and more accessible alternative treatment in BAV patients for whom valve replacement is not a suitable option.

An additional benefit of the study is that it provides insight into the development of BAV pathology through longitudinal imaging. It is likely that many of the patients who are enrolled as part of the “incompetent BAV” group and some who are enrolled as part of the “competent BAV” group will need to undergo surgical intervention within 5 years of the baseline scan. By imaging participants with 4D CTA on an annual basis, the study will provide information on the detailed morphological and dynamic changes that the BAV apparatus undergoes as patients develop worsening symptoms that necessitate surgical intervention. To the best of our knowledge, longitudinal 4D images have not before been acquired in this clinical context and can provide new insights into the timing of surgical intervention for future patients.

The first-line imaging modality used for surgical planning is TEE, which requires sedation and is therefore conventionally performed in the operating room immediately before surgery. As a result, important decisions regarding the surgical plan (such as risk stratification for valve repair vs. replacement) are often made rapidly in the operating room. This study may demonstrate that in the future, 4D CTA could be an alternative image strategy that provides the surgeon and patient with information earlier in the surgical decision-making process (i.e., before the patient enters the operating room), which could decrease time under cardiopulmonary bypass.

10.3 Risk Benefit Assessment

The risks involved in the study are minimal since the 4D CTA protocol will be modified to give the lowest necessary radiation dose (a target of 5 mSv, which is consistent with many routine diagnostic CT scans). While there are no direct benefits to the study participants, the information gained from the study could potentially have a significant impact on surgical management of BAV patients with AI. In the young BAV patient population with AI, BAV repair is preferable to the conventional treatment (BAV replacement) when the likelihood of a durable repair is high. However, image data on physiologically normal BAVs is not currently available to guide standardization of the procedure and develop better evidence-based criteria for predicting repair durability. Without such data, heart valve repair surgeries can go through decades of trial and error before a standardized approach is optimized, as was the case with mitral valve repair surgery. An additional benefit of this study is that it could potentially show that 4D CTA has BAV characterization capabilities that are not feasible with routine intraoperative echocardiography. Such a finding could lead to enhanced pre-operative planning abilities, which could reduce the time needed for intra-operative decision making and would provide the surgeon and the patient with more information about the likelihood of a durable BAV repair before they enter the operating room.

10.4 Informed Consent Process / HIPAA Authorization

Study personnel will approach patients in clinic or via telephone after diagnosis of a BAV has been made, screening for inclusion and exclusion criteria has been performed, and the physician has spoken to the patient about research and feels it is appropriate for the study team to approach the patient. Patients will be interacting with an investigator in the outpatient clinic to gain informed consent and follow up information and via telephone to schedule visits. Only study personnel will be permitted to contact patients regarding their participation in this study. If at any point prior to signing informed consent a patient expresses a lack of interest in the study the patient will not be contacted again. If at any point after signing informed consent a patient expresses in writing a desire to withdraw from the study, the patient will be withdrawn from the study and will not be contacted about this study in the future.

All subjects for this study will be provided a consent form describing this study providing sufficient information for subjects to make an informed decision about their participation in this study. Please see protocol attachments for a copy of the Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The subject must sign the consent form, and the investigator-designated research professional obtaining the consent. Subjects will be consented by the study Principal Investigator or appropriate designee. Potential subjects will review the consent form in detail with the person designated to consent and have the ability to take the consent home for further review.

11 Study Finances

11.1 Funding Source

This study is funded through a pilot grant awarded by the Institute for Translational Medicine and Therapeutics. The original proposal is attached.

11.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Stipends or Payments

There are no subject payments or stipends.

12 Publication Plan

Publication will adhere to the policies of the University of Pennsylvania and the Perelman School of Medicine.

13 References

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14 Attachments

The following documents are attached:

- Informed consent form
- Research proposal funded by the Translational Biomedical Imaging Center (TBIC) of the Institute for Translational Medicine and Therapeutics at Penn.