Study Title: Phono- and Electrocardiogram Assisted Detection of Valvular Disease

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Study Protocol and Statistical Analysis Plan

Phono- and Electrocardiogram Assisted Detection of Valvular Disease (PEA-Valve Study)

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Abstract

The diagnosis of valvular heart disease (VHD), or its absence, invariably requires cardiac imaging. A familiar and inexpensive tool to assist in the diagnosis or exclusion of significant VHD could both expedite access to life-saving therapies and reduce the need for costly testing. The FDA-approved Eko Duo device consists of a digital stethoscope and a single-lead electrocardiogram (ECG), which wirelessly pairs with the Eko Mobile application to allow for simultaneous recording and visualization of phono- and electrocardiograms. These features uniquely situate this device to accumulate large sets of auscultatory data on patients both with and without VHD.

In this study, we seek to develop an automated system to identify VHD by phono- and electrocardiogram. Specifically, we will ask whether we can develop machine learning algorithms to learn the phonocardiograms of patients with clinically important aortic stenosis (AS) or mitral regurgitation (MR), and then task the algorithms to identify subjects with clinically important VHD, as identified by a gold standard, from naïve phonocardiograms. We anticipate that our study has the potential to revolutionize the diagnosis of VHD by providing a more accurate substitute to traditional auscultation.

Specific aim(s)

Aim 1: Can a machine learning algorithm derived from simultaneous phono- and electrocardiogram recordings reliably diagnose clinically important aortic stenosis?

Aim 2: Can a machine learning algorithm derived from simultaneous phono- and electrocardiogram recordings reliably diagnose clinically important mitral regurgitation?

Significance

Valvular heart disease (VHD) is a common global health problem, with population-based studies showing a prevalence of 10% for aortic stenosis (AS) and 20% for mitral regurgitation (MR).[1,2] New surgical and interventional advances allow us to treat patients at an older age or whose risk of intervention would previously have been untenable.[3] Given that the incidence of both MR and AS increases with increasing age, there is a growing need to identify these conditions so as to offer disease-altering therapies.

In current clinical practice, the diagnosis of VHD relies heavily on echocardiography.[4] This, in turn, requires both a referral from a provider with a clinical suspicion for VHD, typically from an abnormality on auscultation, as well as access to the echocardiogram itself. MR and AS both result in reliably reproducible auscultatory findings: holosystolic and systolic crescendo-decrescendo murmurs, respectively.[5] Yet despite this, auscultation as a diagnostic tool is notoriously poor: its accuracy to detect MR and AS ranges only from 5-40%.[6,7] These factors all lead to concerns for underdiagnosis of these increasingly treatable conditions.

Here, we will address the needs for both greater access to and improved diagnostic accuracy of testing for VHD. We will utilize a combination of phonocardiogram (PCG) and single-lead electrocardiogram (ECG) recordings, synced in real-time to a secure cloud-based server, using the Eko Duo electronic stethoscope. With these data, we will develop and validate a machine learning algorithm to diagnose clinically important AS or MR. As the Eko Duo is essentially similar to a traditional stethoscope, an iconic tool widely accepted by patients and providers alike, its use to drive an automated detection algorithm is both feasible and attractive as a substitute for traditional auscultation. Furthermore, by shifting the burden of test interpretation away from the clinician and onto the algorithm, we hypothesize that we will improve overall diagnostic accuracy.

Methods

Overview of design: Cross-sectional study of all subjects undergoing clinical echocardiograms at the UCSF adult echocardiography laboratory

Study subjects

Overview: We will enroll adult subjects undergoing clinical echocardiograms at the UCSF Parnassus campus. These subjects will be grouped into derivation and validation cohorts sequentially, stratified by case status, so as to reach the expected sample size. Such grouping will occur after subject enrollment and data collection.

Target Population: Adults with either moderate-to-severe to severe AS or moderate-to-severe to severe MR (cases) and adults with structurally normal hearts with minimal VHD (controls). In a more-stringent, parallel analysis, a target population of controls will be defined as having any degree of AS or MR less than moderate-to-severe.

Accessible Population: Adults meeting the entry criteria undergoing clinical echocardiograms at the UCSF echocardiography laboratory amenable to participation.

Inclusion Criteria:

- Adults > 18 years of age
- Able to provide consent
- Undergoing complete (i.e. not limited) echocardiogram studies

Exclusion Criteria:

- Refusal to participate

Sampling Scheme: We will approach subjects presenting to the adult echocardiography laboratory at UCSF Parnassus consecutively. Additionally, we will pre-screen subjects for a high likelihood of having AS or MR (based on indication for study and prior diagnoses in the APEX medical record) and selectively their enrollment during situations where the enrollment capacity of the study coordinator is saturated.

Recruitment Strategy: Introduction of study at time of registering for echocardiogram with a brochure or flyer, followed by in-person approaching of potential subjects while awaiting the clinical echocardiogram.

Retention Strategy: None. We will retain a master file of the medical record numbers to identify contact information in the future if deemed necessary.

Measurements

Overview: Our study will focus on two measurements: 1) the gold standard assessment of VHD by echocardiogram, as reported by the UCSF echocardiography laboratory. 2) 10 second simultaneous PCG and single-lead ECG recordings by the Eko Duo device at each of the four standard cardiac auscultatory positions. Our study takes advantage of the fact that all clinical echocardiogram reports include these valvular assessments.

Gold Standard: The echocardiogram is accepted as the gold standard for diagnosis of VHD severity by the cardiology community.[4] To minimize the burden on the investigators, as well as reduce costs, we will take advantage of that all clinical echocardiogram reports include assessments of VHD, which will serve as our gold standard. These reports follow American Society for Echocardiography (ASE) guidelines,[8,9] which allow grading of VHD as follows: none, mild, moderate, or severe. The UCSF echocardiography laboratory includes additional categories of trace, mild-to-moderate, moderate-to-severe, and critical, allowing for interpretations where individual parameters within the study conflict. Our primary measurement will be the final conclusion of severity of VHD for MR or AS, as reported by a board-certified cardiologist. We will define "clinically important" VHD as that graded moderate-to-severe or worse, as this would encompass all levels of disease which could require direct intervention. In addition, we will extract the entire echocardiography report, as well as the images of the echocardiogram files, so as to save the data for future use as new research questions arise.

Device Measurements: Recordings of the simultaneous PCG and single-lead ECG will be performed for each subject in a standardized manner. Each subject will undergo 10 second recordings using the Eko Duo device at the four standard auscultation positions. Observers will be trained on the systematic method of obtaining measurements. Time and patient permitting, we will also obtain the same recordings using the Eko Core device, which uses the same software but does not include ECG recording. As the device will allow visualization of the PCG during recording, the observer will get real-time feedback on positioning of the device to maximize the quality of the recording at each position. We will plan for periodic review of recordings to ensure adequate data quality. We anticipate that this flexibility and real-time feedback will improve the generalizability of the use of the device to a real-world (i.e. non-study) clinical situation.

Primary Outcome: Our primary outcome will be the identification of either clinically important MR or AS (either present or absent) by the algorithm on the device measurements from subjects in the validation set. For the primary outcome, we will define our controls as patients with VHD no greater than mild severity as per the gold standard. As our algorithm will provide a score comparing similarity of the learned characteristics with test (validation set) data, we will plot our results as a receiver operating characteristic (ROC) curve at each score. In addition, we will plan to calculate

the likelihood ratios (both positive and negative) of the test at sensitivity cutoffs of 0.9, 0.95, and 0.99.

Secondary Outcome: Our secondary outcome will be substantially the same as our primary outcome, but in this case, we will define our controls as all subjects with less than moderate-to-severe or greater disease of the valvular condition (MR or AS) in question. This will necessitate the generation of a separate algorithm with the derivation set, which we will perform in parallel.

Confounders and Bias: The derivation and validation of our algorithms will occur remotely, after the clinical echocardiogram has been performed, and therefore with no effect on the outcome of the gold standard. Our test may be influenced by the presence of other conditions causing systolic murmurs (including VHD other than AS or MR, or congenital heart disease). We will include these measures from the echocardiogram report to compare test performance in those with and without these other conditions.

Statistical issues
Null Hypothesis: A machine learning algorithm cannot predict the presence of clinically important AS or MR.

Sample Size Justification:

- Sensitivity of Algorithm: 90%
- Specificity of Algorithm: 90%
- Target Likelihood Ratio (+) of Algorithm [LR(R)]: 9 (derived from Sn / [1 – Sp])
- Minimum Likelihood Ratio (+) of Algorithm [LR(R)]: 5
- Confidence Level = 0.95 (alpha = 0.05)
- Confidence Interval [LR(R)]: 5.120-15.820
- Sample Size = 110 per group; 330 per cohort (control, AS case, MR case); 660 overall (training and validation cohorts)
- Summary: Assuming the sensitivity and specificity of the machine learning algorithm for detection of clinically important AS or MR are both 0.9, a total sample size of 660 is not expected to go below the threshold likelihood ratio of 5.0 in the 95% confidence interval in either the derivation or validation cohorts.
- Justification of Critical Assumptions: We assume that our algorithm can produce a sensitivity and specificity of 90% in detecting aortic stenosis or mitral regurgitation compared to hearts with no valvular disease, based upon prior published reports using neural networks, using sample sizes of under 100 cases.[10] Furthermore, we estimate a minimum likelihood ratio of 5 would be necessary for the test to be clinically useful. While this estimate works well for our validation set, the number needed for our derivation set is less clear; the estimates above are a conservative number. We anticipate training the algorithm after enrollment of every 20 cases using a bootstrapping approach; this will provide interim test characteristics and help determine the true number needed for the derivation set. As this is, in part, a pilot study, identification of the true sensitivity and specificity of the test is in itself a valuable result.

Analysis approach: We will generate ROC curves (plotting Sn vs. 1-Sp) for algorithm scores for the validation set. Ultimately we will generate 4 curves: two each for MR and AS, using algorithms generated by our primary (defining controls as having no greater than mild VHD) and secondary (defining controls as not having moderate-to-severe or greater VHD) approaches. Additionally, we anticipate performing exploratory, descriptive analyses of the algorithm itself, by identifying clinical correlates to the characteristics most heavily weighted in detecting AS or MR.

Miscellaneous

Ethical considerations: No major concerns. Data will be securely stored on HIPAA compliant platforms. The study qualifies as minimal risk by UCSF CHR criteria.

Pretest plans: Prior to study recruitment, study staff will collect data on themselves and providers to test the data collection system. During initial subject recruitment, study staff will review the process after each day to discuss roadblocks or concerns.

Data Management Plan: Data from our study will come from two sources. Reports of echocardiograms, extracted from the electronic medical record (APEX), will be reviewed by study staff to generate our main database of disease characteristics. A master file linking subject identifiers with identifiable information, as well as extracted and de-identified echocardiogram reports and de-identified raw echocardiogram images will be stored on a secure research server used by the Division of Cardiology. Recorded PCG and ECG data (the actual study measurements) will be synced in real-time to a secure, HIPAA-compliant, cloud-based server managed by Eko Devices. At pre-specified times of algorithm training, the machine learning team (coordinated by Eko Devices) will be provided keys to the assignment of subject identifier to VHD category.

Quality control measures: Periodic review of the recorded data will be performed by the study PI to ensure appropriate data quality.

Timetable:

Contract/Logistics												
	Subject Enrollment											
				Algorithm Development								
							Analysis					
										Publication		
Overall Timetable: 9 Months												

Budget:

Item	**Estimated Cost**	**Notes**
Research Coordinator	$88000	Costs not included: Eko Duo & Eko Core Device Salary support for machine learning (headed by John Maidens)
PI (10% FTE)	$25000	
Statistician (10% FTE)	$20000	
Division Research Overhead	$14000	
Indirect Costs (58.5%)	$79000	
Total	*$226000*	

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Appendix: Data Dictionary for Echocardiography Report Abstraction

Data Dictionary

#	Name	Type	Label	Values	Notes
1	Rec	Binary	Device Recordings	0 – No 1 – Yes	
2	Ind	Text	Indications for Study	Free Text	May need to include some common sample indications (i.e. murmur)
3	AS	Integer	Aortic Stenosis	0 – None 1 – Trace 2 – Mild 3 – Mild/Moderate 4 – Moderate 5 – Moderate/Severe 6 – Severe 7 – Critical	
4	MR	Integer	Mitral Regurgitation	Same as 1	
5	TR	Integer	Tricuspid Regurgitation	Same as 1	
6	AR	Integer	Aortic Regurgitation	Same as 1	
7	PR	Integer	Pulmonic Regurgitation	Same as 1	
8	TS	Integer	Tricuspid Stenosis	Same as 1	
9	MS	Integer	Mitral Stenosis	Same as 1	
8	PS	Integer	Pulmonic Stenosis	Same as 1	
9	VR	Binary	Valve Replacement	0 – No 1 – Yes	
9a	Loc	Integer	Valve Replacement Location	1 – Aortic 2 – Pulmonic 3 – Tricuspid 4 – Mitral	
9b	VType	Integer	Valve Replacement Type	0 – Annular Ring 1 – Bioprosthetic 2 – Mechanical	
10	PDA	Binary	Patent Ductus Arteriosus	0 – No 1 – Yes	
11	VSD	Binary	Ventricular Septal Defect	0 – No 1 – Yes	
12	ASD	Binary	Atrial Septal Defect	0 – No 1 – Yes	
13	Cong	Binary	Congenital Heart Disease	0 – No 1 – Yes	
14	Other	Text	Other – Free Text	Free Text	Free text required given complexity