

Use of a Computerized Body Auscultation
Device (©VoqX) for the Diagnosis of Structural
Cardiac Pathologies

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Study Title

Use of a Computerized Body Auscultation Device (VoqX) for the
Diagnosis of Structural Cardiac Pathologies

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Sponsor

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AIMS and OBJECTIVES

Patients presenting to the echocardiogram laboratory for routine clinically indicated echocardiography or to the cardiac catheterization laboratory for routine clinically indicated catheterization procedures will undergo a computerized auscultation using the VoqX stethoscope and will have their heart sounds auscultated and recorded.

Thus, our aims will include the following:

- i) To prospectively determine the accuracy of the VoqX device as a tool to non-invasively validate in patients for structural cardiac pathologies, by comparing the results in terms of structural cardiac pathologies ascertained from using the VoqX device with those derived from echocardiography or cardiac catheterization testing. This will be undertaken after the VoqX device has been trained in identifying a variety of cardiac pathologies, including normal heart sounds, aortic stenosis, and mitral valve disease, using this pilot validation study.

HYPOTHESES

We hypothesize the following:

- i) The clinical findings in terms of suspected structural cardiac pathologies ascertained using the VoqX device strongly agree with structural cardiac diagnoses, including normal heart, aortic stenosis as well as its severity, and mitral valve regurgitation and its severity, diagnosed using echocardiography or cardiac catheterization testing. This would suggest that the VoqX device could be an accurate tool to non-invasively screen for cardiac structural pathologies, such as the severity of aortic valve stenosis, and the severity of mitral valve regurgitation.

INTRODUCTION

The acoustic stethoscope is the most basic and yet most iconic diagnostic instrument used by clinicians when performing physical examinations in patients, and has been in use for more than 200 years¹. It is used to listen to the sounds of the body; most typically those generated in the lungs, heart, abdomen, and blood vessels, and can facilitate quick and non-invasive diagnoses allowing for prompt treatment or referral for further testing.

Technological developments in recent decades have enabled the integration of electronic and digital components into the stethoscope design, but to date have failed to improve auditory performance and user's diagnostic accuracy². The ability to accurately diagnose and properly

interpret the information acquired by auscultation of a variety of body sounds depends on user experience and skills and may therefore vary significantly between users. In addition, a significant proportion of the body's sounds are produced at frequencies below the threshold for detection of the human ear and may therefore be ignored by health-care providers for diagnostic purposes. Further, the increasingly widespread availability of advanced imaging modalities has dramatically decreased our reliance upon simple auscultation to diagnose cardiovascular pathologies. However, such advanced imaging modalities, including echocardiography and cardiac magnetic resonance imaging, are not ubiquitous, and their overuse can lead to increased costs, overburdened healthcare systems, and delayed treatment^{3, 4}. Integrating computerized digital technologies, and artificial intelligence capabilities with deep learning-based algorithms into a stethoscope holds the potential to enhance the accuracy and reliability of findings derived from simple bedside auscultation. This in turn could help mitigate existing issues surrounding stethoscope diagnostic accuracy, and user-dependence, as well as the separate issue of overreliance on expensive, and less accessible, specialized imaging modalities.

In recent years, we have witnessed tremendous technological advancements in the fields of software and electronics, which is reflected in the incorporation of various sensors and computerized tools based on artificial intelligence into medical devices^{5, 6}. We believe that these technologies can be used to significantly improve the diagnostic performance of simple bedside auscultation as a physical examination maneuver by way of a novel stethoscope that enables auscultation and acquisition of sounds and signals typically found in the infrasound frequency level⁷. These infrasonic sounds can be transformed into the auditory sound range and can then be processed into characteristic sound patterns using artificial intelligence and machine learning

algorithms. The processed sound data could then be used to differentiate between normal and abnormal auscultation findings and could therefore be used to accurately identify specific pathologies, in a quick, inexpensive, and non-invasive way at the bedside of the patient. Thus, the current study aim is to pilot and validate a computerized infrasound body auscultation device (VoqX) to characterize and identify the unique auscultated sounds that correspond with the normal heart as well as various structural cardiac pathologies, severity grading of aortic stenosis, and mitral regurgitation, diagnosed using gold standard testing such as echocardiography and invasive cardiac catheterization. After validation of the device, we aim to determine if the VoqX device can be successfully used to accurately screen subjects with normal heart, and screen for various cardiac structural pathologies, such as aortic stenosis, and mitral regurgitation, that it has been validated to identify, as compared to gold-standard testing using echocardiography and invasive cardiac catheterization. This in turn holds the potential to facilitate the accurate, rapid, and cheap bedside screening of structural cardiac pathologies.

DEVICE DESCRIPTION

The ©CompuSteth stethoscope detects both infrasound and audible sounds and is capable of amplifying auscultated sounds by a factor of thirty. *Sanolla* has developed artificial intelligence-based technology, which uses the full spectrum of sound including sounds within the infrasound range, to identify specific clinical conditions through its unique proprietary sound signature images. These offer the potential to facilitate the early and at-the-bedside diagnosis of structural cardiac pathologies, whose associated murmurs and added heart sounds may otherwise be unclear, inaudible, or inaccurately and unreliably characterized by different users. The VoqX stethoscope is an updated version of the ©CompuSteth stethoscope and as such it detects the

same range of sounds and has the same capabilities of amplifying auscultated sounds as the ©CompuSteth. The table below summarized the changes between the Compusteth stethoscope and the VoqX stethoscope:

Item	VoqX	Compusteth
Software	Audio Control application: 01.02.00	- Audio Control application: Beta 2.00.00 - Audio Process: Beta 1.05.00
Usability	- Touch screen 3 Button – 2 volume, 1 on/off - Multifunction LED - Ear tips - Tubes - Back Cover - Rubber Cover - Front cover - Replaceable membrane	- Touch screen 3 Button – 2 volume, 1 on/off - Multifunction LED - Ear tips - Tubes - Back Cover - Rubber Cover - Front cover - Replaceable membrane
Front Unit		
Sound	Improved sound clarity	Clear sound



Figure 1: VoqX devices stethoscope

MATERIALS and METHODS

Target accrual

We seek to recruit 600 study participants for this study.

Participant Population

We will recruit individuals referred to the echocardiogram laboratory for routine clinically indicated echocardiography, or to the cardiac catheterization laboratory for routine clinically indicated catheterization procedures. Study participants will be consented for participation in the

study and will have bedside cardiac auscultation performed at baseline prior to their index echocardiogram or cardiac catheterization procedure.

Inclusion Criteria

1. Aged 18 years of age or older.
2. Referred to the echocardiogram laboratory for routine clinically indicated echocardiography, or to the cardiac catheterization laboratory for routine clinically indicated catheterization procedures
3. Individuals with normal heart sounds, isolated aortic stenosis (any degree of severity), or isolated mitral regurgitation (any degree of severity)

Exclusion Criteria

1. Patients with unstable cardiovascular or pulmonary disease
2. Patients with mixed valvular heart disease, (i.e. any patient with greater than mild stenosis or regurgitation in another valve).

Patient Flow

In the current study we plan to recruit 600 patients who have been referred to the echocardiogram laboratory for routine clinically indicated echocardiography, or to the cardiac catheterization laboratory for routine clinically indicated catheterization procedures. We plan to include individuals with normal heart structure and sounds, isolated aortic stenosis (of varying severity), and isolated mitral regurgitation (of varying severity), while excluding individuals who have multiple valve involvements or combined valve pathologies. Each patient will have baseline

testing using the VoqX device, which will be used to auscultate and record each patient's heart sounds at the bedside prior to the index echocardiogram or cardiac catheterization procedure. This process will take less than 10 minutes and is outlined below. Patients will then proceed with their clinically indicated echocardiograms or cardiac catheterization procedures.

Amongst the first 200 study participants, the results of the echocardiograms and invasive cardiac catheterization procedures will be used to train the VoqX device to identify normal heart and to screen and grade for various cardiac structural pathologies, aortic stenosis, and mitral regurgitation, diagnosed by gold-standard testing. Subsequently, after we have validated that the VoqX device knows how to characterize and identify sounds that correspond to various structural cardiac pathologies, we will then prospectively 'test' how well the VoqX device is able to screen normal heart from cardiac pathologies, such as aortic stenosis, and mitral regurgitation, and identify the severity of the valve disorder in the subsequent 200 participants of the study. We will do this by comparing the results obtained from auscultation with the VoqX device against the results obtained from gold-standard testing with echocardiography or invasive cardiac catheterization.

Auscultation Procedure

Each patient will undergo auscultation of cardiac heart sounds using the VoqX device by a trained study coordinator, who will be performing the recording using the stethoscope. This will be done at the patient's bedside or in an examining office. All participants will be asked to remove shirts and undergarments, though female participants will be permitted to wear bras, so

that the auscultating sensor of the stethoscope can be placed on bare skin. The patient will be reassured that the VoqX device feels like any “normal stethoscope” on the skin.

The computerized auscultation will be done immediately prior to the echocardiogram or cardiac catheterization procedure. The VoqX Stethoscope sensor will be placed on the patient's chest, with the patient reclining at 45 degrees in an examining chair/bed, and heart sounds will be auscultated and recorded from up to 6 pre-specified locations:

A – Aortic Region: 2nd right parasternal intercostal space

P – Pulmonic Region: 2nd left parasternal intercostal space

T – Tricuspid Region: 4th left parasternal intercostal space

M – Mitral Region: 5th left intercostal space midclavicular line (apical region)

In addition, each subject with the diagnosis of aortic valve stenosis may have both sides of their neck auscultated in the region of the carotid artery.

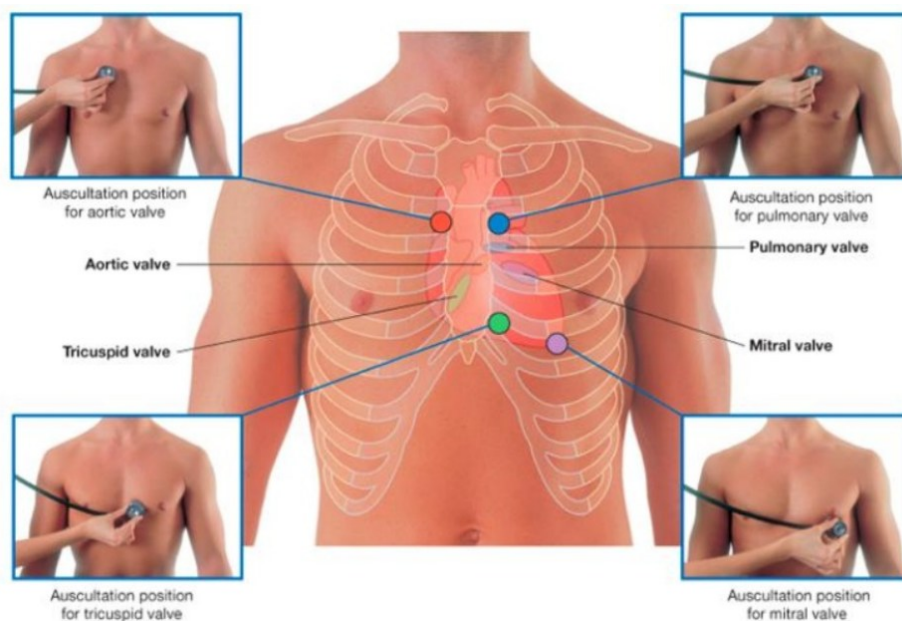


Figure 2: Sites of auscultation for the physical examination using the VoqX Stethoscope

The stethoscope sensor will be placed on each of the four required points for 30 seconds each.

The patient will be asked to remain silent but breathe normally during the auscultation and recording of heart sounds. After auscultation and recording of heart sounds is completed at each of the required points, the participants will proceed for their clinical studies.

The study coordinator will wash and dry their hands between seeing and examining different study participants. Similarly, the sensor of the VoqX device will be cleaned using anti-microbial sanitary wipes between its use in different participants.

VoqX device Data

Auscultated and recorded information collected by the VoqX device will then be transferred to a computer using dedicated software provided by *Sanolla* and will be added to each participant's data form in a de-identified manner using participant codes. The recorded data and sound signals will then be transferred to an external computer and will be processed by machine learning algorithms developed by *Sanolla* to identify pathology specific features and to generate suspected diagnoses (with severity grading).

Patient Safety

All patients enrolled in the study must provide written consent prior to entering the study. All participant information will be recorded in a de-identified manner. Study participants wishing to discontinue participation can do so at any time without any impact to their clinical care. The

findings derived from the VoqX device will not impact patient care or clinical management decisions, which will continue to be made based on clinically indicated testing and evaluation by each participant's treating physician.

The VoqX device is passively acquiring body acoustic sounds and thus applies no radiation to the study participant. The device is battery operated and is not connected to a high-power source.

The device has been tested and approved by the Israeli Standard Institute for the following:

Safety Testing according to IEC 60601-1:2005, and EMC Test according to IEC 60601-1-2.

Therefore, the device is safe and is highly unlikely to cause hazard to patients or users.

Any adverse events observed during the procedure or study will be recorded in each participant's data form. All adverse events, regardless of severity or relationship to the investigational device, will be recorded in accordance with Good Clinical Practice (GCP) guidelines, ISO14155. We however do not anticipate any side effects since the VoqX device passively acquires body acoustic sounds without applying any radiation.

Echocardiography and Cardiac Cauterization

After having their heart sounds auscultated, study participants referred for echocardiography or cardiac cauterization will undergo their respective tests. The findings of the echocardiogram and cardiac catheterization will then be ascertained by review of each patient's procedural report.

The following pieces of information will be derived, where available:

- Presence of any valvular (specifically aortic, pulmonic, tricuspid or mitral valve) disease
- Severity of any valvular disease (trivial, mild, moderate, severe)

- Presence of pulmonary hypertension
- Presence of left ventricular hypertrophy
- Presence of left ventricular enlargement/dilatation
- Presence of right ventricular hypertrophy
- Presence of right ventricular enlargement/dilatation
- RVSP (mmHg)
- Mean and maximal pulmonary arterial pressure
- Pulmonary vascular resistance
- PCWP
- Cardiac Index
- Ejection Fraction
- Left ventricular end-diastolic volume
- Left ventricular end-diastolic pressure
- Right ventricular end-diastolic volume
- Right ventricular end-diastolic pressure

Comparisons will then be made to see if the diagnoses derived from the VoqX device are like the diagnoses derived using echocardiography or cardiac catheterization, and if so to what extent.

For the purposes of the current study we will include individuals with normal heart sounds, isolated aortic stenosis (any degree of severity), and isolated mitral regurgitation (any degree of severity). Subjects with involvement of more than 1 valve or combined valvular disease will be excluded.

Other Clinical Information to be collected

Additional patient information that will be collected and entered into the patient's data form includes the following:

- Demographic information including age, sex, and ethnicity
- Height, weight and BMI
- Smoking history including never, former or current smoker
- Relevant medical history, including diabetes mellitus, hypertension, hyperlipidemia, history of angina, previous myocardial infarction, previous transient ischemic attack or stroke, history of peripheral vascular disease, history of ischemic limb, history of chronic obstructive pulmonary disease
- Family history of ischemic heart disease
- Current medications, including ACE-inhibitors/angiotensin receptor blockers, beta-blockers, calcium channel blockers (dihydropyridines or diltiazem or verapamil), thiazide diuretics, loop diuretics, long or short acting nitrates, aspirin clopidogrel, warfarin, other anticoagulants, statins, fibrates
- Main presenting complaint for which testing was recommended, including asymptomatic screening, chest pain, shortness of breath, lightheadedness/dizziness, syncope, palpitations, peripheral edema
- Current heart failure or acute coronary syndrome

Each study participant will receive a unique de-identified numeric code, and clinical information will be stored for each patient under this code. Further, information recorded from the VoqX device will be transferred to *Sanolla* for application of their artificial intelligence algorithm and to generate their putative diagnoses, again in a de-identified fashion.

Statistical Analysis

We will summarize the baseline clinical profile of all study participants undergoing echocardiography or cardiac catheterization. Categorical data will be summarized with frequencies and percentages. Continuous data will be summarized with medians and interquartile ranges.

The presence or absence of various structural cardiac pathologies are predicted using the VoqX device will be compared as binary data with the actual presence or absence of the same diagnoses made using gold-standard testing with echocardiogram or cardiac catheterization also as binary data. McNemar's test will be used to compare the diagnostic findings from the VoqX device with those from echocardiogram or catheterization, Cohen's kappa coefficient will be used to determine the degree of agreement between both sets of diagnostic findings.

For all the above, the type 1 error rate will be 0.05 in a two-sided test and p-values and confidence intervals will be calculated at the 95% confidence level. All analyses will be performed using SAS version 9 (Cary, NC).

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