Abstract

Every human or animal heart has a unique acoustic signature and this signature has a statistical norm for each species (i.e. human, dog, cat, horse, pig, etc.). Further, a deviation from this statistical signature norm, is an indication of a cardiac abnormality or disease. This biophysical model gives rise to a non-invasive diagnostic system by which a patient’s heart sound signature can be compared to known abnormal heart sound signatures to provide early detection of cardiac morbidity.

Introduction

A non-invasive technique, device, and associated central processing system (Motley, 2019)\(^1\) by which early heart abnormalities and disease are detected is henceforth referred to as Cardiometric Spectral Imaging (CSI). CSI is based on three dimensional contours (3DC) derived from time-frequency analysis of the heart sounds S1 thru S4 signatures individually and requires several disciplines to implement (Figure 1.0). The 3DC data is used as input to a correlation process that yields a feature set that is used as input to a Deep Learning Neural Network (DLNN) diagnostics process. The process is cognitively managed using Artificial Intelligence (AI) based pattern correlation searches and multiple-output supervised neural networks. Additionally, the system computes a cardiac severity rating which predicts the degree of advancement of the early diagnosed heart condition.
The CSI system is implemented using a special acoustic sensor, a sensor interface module, an associated SmartPhone or personal computer, a centralized server farm that executes the AI and DLNN algorithms, an updateable cardiac sounds contour template database, and advanced signal processing technology (Figure 2.0). The system operation involves placing a special acoustic sensor on the subject’s chest near the apex of the heart. The signals from the sensor are digitized and pre-processed by a sensor interface module (SIM). The interface module then connects to a SmartPhone, Personal Computer or Tablet where the data is packaged and sent to the Cardiometric Processing Center Server Farm where the time-frequency analysis, DLNN algorithms, Wavelet Transforms, and pattern correlation processes are executed. The diagnostic results and cardiac state are sent back to the SmartPhone, Personal Computer or Tablet for review by healthcare personnel. The CSI system emulates the auscultation performed by healthcare professionals using a stethoscope without the need for them to have perfect hearing at very low frequencies and expert acoustic recognition skills for identifying abnormal heart sound patterns. The CSI system is useable in a remote, home or clinical environment.

Additional problems solved by the CSI system include normalization of heart sound signature data for young children, women, older persons and DNA imposed heart signature parameters (i.e. tonal ranges, heart rates, gap signals between S1 thru S4 heart sounds, lung noise, and external noise or vibration). The CSI system includes a comprehensive data set of normal and abnormal heart sound signatures associated with all genders and ages. New and unknown heart sound signatures encountered by the CSI system are automatically included in the template database and are labeled once classical diagnosis procedures validate the newly observed abnormal heart condition.

![Figure 2.0 Cardiometric Spectral Imaging System Block Diagram](image-url)
Historical Background

The concept of using heart sound data, known as Phonocardiograms (PCG), as a medical diagnostic tool originated in 1924 which was essentially an electronically amplified stethoscope. The resulting sounds and graphical representations were so modified that physicians had to alter their listening techniques which distracted from the usefulness of the device. Various versions of the electronic stethoscope were created up to the 1980s when the centers for Medicare and Medicaid stopped paying for PCGs because they were outmoded and had very little diagnostic benefit. All insurance companies also stopped paying for the test. As a result, virtually all physicians stopped using PCGs as a part of diagnostic workups. To date PCGs have not provided the diagnostic effectiveness required to provide an early accurate diagnosis based on auscultation alone. Recent versions of automated stethoscopes include techniques to abstract cardiac features and reduce noise from the heart sound signal (Table 1.0). Additionally, the application of signal processing technology to access diagnostic data from the PCG data is also included in recent devices. Note that currently available heart monitoring/diagnostic devices do not include a complete system capable of identifying a plurality of abnormal heart conditions to an accuracy of at least 97% statistical significance. An Investigational Device Exemption (IDE) clinical trial is required to establish the CSI as an FDA approved heart diagnostic device/system.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Description</th>
<th>Category</th>
<th>Interface</th>
<th>Frequency Response</th>
<th>ECG</th>
</tr>
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<tbody>
<tr>
<td>DUO</td>
<td>Electronic Stethoscope + ECG</td>
<td>Sound Amplification (60X), Data Recording, Remote Data Sharing, &amp; Manual Control/Display</td>
<td>Bluetooth 4.0</td>
<td>20Hz – 2KHZ</td>
<td>Single Lead</td>
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<td>Electronic Stethoscope</td>
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<td>ADC Adscope 658</td>
<td>Electronic Stethoscope</td>
<td>Sound Amplification (18X), &amp; Manual Control/Display</td>
<td>None</td>
<td>Not Published</td>
<td>None</td>
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<td>ThinkLabs One</td>
<td>Electronic Stethoscope</td>
<td>Sound Amplification (100X), Data Recording, Remote Data Sharing, &amp; Manual Control/Display</td>
<td>E-mail using Smartphone</td>
<td>Not Published</td>
<td>None</td>
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<tr>
<td>Schiller 9.030100 Cardiovit CS-200</td>
<td>Electronic ECG Diagnostic System</td>
<td>Multi-Lead ECG, Diagnostic Software, Data Recording, Remote Data Sharing, &amp; Manual Control/Display</td>
<td>USB</td>
<td>Not Applicable</td>
<td>Multi-Lead</td>
</tr>
</tbody>
</table>
CSI Description

The beating heart of a human or animal provides an excellent acoustic source, the properties of which are determined by its physical structure, the body structure of its host, and its beating rate. Essentially, the heart and host configuration is synonymous with an audio speaker enclosed in an associated speaker cabinet. Hence, the acoustic signal emitted is spectrally shaped by its physical source and surrounding structure. Sonar systems employed by the NAVY have used acoustic analysis to identify the presence and characteristics of underwater targets for many decades and their algorithms are well understood. The CSI system is an embellished adaptation of this technology for the purpose of identifying the properties of the beating heart acoustic signature. This signature is used to diagnose the current heart state as well as detect early signs of cardiac abnormality or disease.

Figure 3.0 illustrates the frequency range of sounds, murmurs, clicks, and gallops of the human heart. These acoustic signals are in the 3Hz to 1000Hz frequency range over a .1 to 3 second time window. Auscultation of these sounds is limited by a Physician’s or healthcare professional’s ability to hear in the 3Hz and 40Hz frequency range with a stethoscope where abnormal sounds and murmurs are easily identified. The auditability range for humans is in the 30Hz to 15 KHz range. Therefore detectability of many heart abnormalities that are manifested in sounds below 30 Hz are not detected using stethoscope auscultation.

![Figure 3.0 Heart Sounds Frequency Range](image)

Heart abnormalities and disease cause the heart to have specific sound time-frequency patterns that deviate from the statistical norm. Instead of relying on humans to hear and cognitively sort
out these patterns, a special vibration sensor and associated computers executing wavelet time-frequency analysis, digital signal processing and AI algorithms correctly detect heart sound components as low as 3 Hz using computer implementation. The resulting three dimensional time-frequency analysis contours (Figure 5) provide a visual image of S1 thru S4 heart sound patterns (Figures 4). Each heart sound component has a unique spectral contour for each human individual. The combination of the S1 thru S4 heart sound time-frequency contour is a unique signature for each individual. Although each individual has a unique set of CSI contours, there are common heart sound signatures that indicate when an abnormal or diseased condition is present. CSI exploits the deviation from these common norms in the CSI Three Dimensional Contours to identify the presence of an abnormal or diseased heart state. This detection process is executed using deep learning semantic networks manifested as goal trees and neural nets. An additional benefit of this type analysis is the ability to rate the severity of the heart state on a cardiac severity rating scale, “CSR”, which is easily interpreted for clinical applications.

The low frequency detectability challenge is completely eliminated by processing the heart sounds in the digital domain. The use of high speed computers and a special acoustic sensor, removes the human hearing limitations while expanding the analytical processing range.

Figure 4.0 Heart Sounds Physiological Relationships
With reference to Figure 6, the CSI remote system includes a plurality of portable heart sound monitoring apparatus that consists of special acoustic sensors, a SIM and associated SmartPhone or PC. A Central Processing Server farm at a remote location is linked to the SmartPhone or PC through a local or wide area network (public or private) to provide the signal processing functions required to create the 3D contours. Additionally, the Central Processing Center is the location of the reference diagnostic contours database as well as patient Cardiometric data. The entire process is managed by AI algorithms.

Figure 5.0 3D Spectral Contour of the S2 Heart Sound

Figure 6.0 Cardiometric Spectral Imaging System Block Diagram
CSI uses the public internet cloud for the link between the plurality of remote SmartPhones and the Cardiometric Processing Center. A second alternative CSI configuration uses a local area network (LAN) of a hospital, diagnostic center, or medical care facility to link the plurality of remote SmartPhones to the Cardiometric Processing Center. A third CSI configuration uses a private network (WAN) to link the SmartPhones to the Cardiometric Processing Center server farm. For each network configuration, the results from the Cardiometric Processing Center are sent back to the remote Smartphone or PC through the Cloud, LAN, or WAN. Optionally, reports are e-mailed from the server farm directly to the patient’s physician or associated healthcare professional. A forth network configuration uses only localized resources to collect the heart sound signal, perform the CSI 3DC analysis, perform pattern recognition, and AI based computer assisted diagnosis. In this structure, the heart sound collection and high performance server processing equipment are co-located. This forth configuration is consistent with a centralized clinical imaging facility where the procedure is performed by radiologist or healthcare professionals.

1.0 Special Acoustic Sensor

The CSI system special acoustic sensor is a highly sensitive vibration sensor with a flat frequency response in the 3Hz to 1000Hz range. The CSI system uses a G.R.A.S. 47AD earthquake sensor unit (Figure 7) with the following general specifications:

Frequency Range : 3.15 Hz to 10Khz
Dynamic Range : 18dB(A) to 138 dB
Preamplifier : Built-in CCP
Sensitivity : 50 mV/Pa

The acoustic sensor is a pre-polarized unit with a built in low noise constant current powered preamplifier and an automatic transducer identification circuit.

Figure 7.0 Special Low Frequency Acoustic Sensor
2. Sensor Interface Module

The CSI Special Acoustic Sensor SIM block diagram is shown in Figure 8. This module provides the pre-processing of the heart sound signals for transport to the Cardiometric Processing Center by the Smartphone or PC. The CSI SIM uses a very low frequency low noise differential amplifier to increase the heart sound signal from the acoustic sensor to at least 5 volts peak-to-peak. The signal is then filtered with a 10 KHz low pass filter to prevent aliasing by the sample and hold and the high resolution analog-to-digital conversion process. The process of separating the individual S1 through S4 sound component is performed using a Quad-Port First in First out (FIFO) buffer. The FIFO provides the facility to detect and separate the signal windows (signal + gap) associated with each of the S1 through S4 sound components. The peak detector array locates the S1 through S4 repeat pattern and separates each component into a separate window which is packed into separate files and transferred to a memory array that emulates a USB memory device compatible with the Smartphone or PC.

3.0 Deep Learning Artificial Intelligence

CSI employs DLNN Artificial Intelligence (Figure 9) to manage the Wavelet Time-Frequency Analysis parameters, the 3DC correlation process, the DLNN Tree and the 3DC database updates. CSI AI involves the algorithms that process the individual S1 thru S4 data and emulate an improvement in the cognitive acoustic analysis normally done by healthcare personnel using a stethoscope. The goal of the AI algorithms is to determine which known heart sound pattern best fits the target patient heart state regardless of the age, gender, or genetic predispositions.

The DLNN based diagnostics is a three stage process. The first stage of the AI process involves converting the acoustic heart sound signal into an image map that is manageable by DLNN algorithms. CSI uses a Continuous Wavelet Transform (CWT) Equation (1) to analyze the acoustic heart signal frequency content as a function of time to create a 3D time-frequency image.
of the signal. This approach provides a multiresolution analysis (MRA) where the signal is analyzed at different frequencies with different resolutions. The MRA is designed to give good time resolution and poor frequency resolution at higher frequencies and good frequency resolution and poor time resolution at low frequencies where abnormalities are most detectable.

\[ a_0^{(1)} = \sigma (\omega_{0,0} a_0^{(0)} + \omega_{0,1} a_1^{(0)} + \ldots + \omega_{0,n} a_n^{(0)} + b_0) \]

or

\[
\begin{bmatrix}
    a_0^{(1)} \\
    a_0^{(2)} \\
    \vdots \\
    a_0^{(n)}
\end{bmatrix} = \sigma
\begin{bmatrix}
    \omega_{0,0} & \omega_{0,1} & \omega_{0,2} & \ldots & \omega_{0,n} \\
    \omega_{1,0} & \omega_{1,1} & \omega_{1,2} & \ldots & \omega_{1,n} \\
    \vdots & \vdots & \vdots & \ddots & \vdots \\
    \omega_{k,0} & \omega_{k,1} & \omega_{k,2} & \ldots & \omega_{k,n}
\end{bmatrix}
\begin{bmatrix}
    a_0^{(0)} \\
    a_1^{(0)} \\
    \vdots \\
    a_n^{(0)}
\end{bmatrix} +
\begin{bmatrix}
    b_0 \\
    b_1 \\
    \vdots \\
    b_n
\end{bmatrix}
\]

Equation (1)

Where:
- \( \omega \) - is the path weight
- \( a \) - is node value
- \( \sigma \) - is activation function (worm_1)
- \( b \) - is bias

This approach is consistent with heart sound signals. By way of example, an isolated S2 cardiac time-frequency 3DC mapping is illustrated in Figure 5.
Figure 9.0 Deep Learning Neural Network Flow Diagram

With reference to Figures 10 the S1 thru S4 signals including the information in the gaps between the signals provide the input data to the CWT. CSI separates the S1 thru S4 signals into four separate data sets with the goal of reducing the processing capacity required to correctly identify a particular heart abnormality or disease. The CWT performs the MRA process on each heart S-signal individually. This is the 3DC mapping process that is used in the correlation process where the patient input data is compared to the known abnormality contours. These contours form the root nodes of the identification process. Ideal models of heart sounds of known heart abnormalities or disease are processed using MRA and make up the image template data base used in the DLNN training data and actual patient diagnostic process. The template categories are normal, murmur, clicks, and gallop which reflect types of heuristic sounds observed by health care professionals using a stethoscope and form the second node level in the identification process. Training data from 500 human subjects with known heart abnormalities or disease are used to calibrate the system.
The second stage of the process (Figure 11) involves computing the correlation values between patient cardiac sound data and the template database. The output of this process is a vector of numbers that reflect how well each of the patients' S-sounds compares to the S-sounds of known abnormalities or disease. This vector of numbers provides the input nodes to the DLNN.

The third stage of the process involves training, validating and testing the DLNN (Figure 9). CSI uses a 10 layer DLNN with a 23 node output layer. The DLNN inputs data from the four correlation processes (96 feature data set).

Figure 10.0 CSI Processing System Block Diagram

Figure 11.0 CSI Correlation Process Block Diagram
In procedural English, the overall process is as follows:

- **Step 1:** Individually digitize S1 thru S2 heart sounds are mapped into digital image contours using a multiresolution CWT with a “Morlet” mother wavelet.

- **Step 2:** The CWT contours are normalized to a standard form by dilation or compression which involves adjusting the CWT parameters (scale and translation).

- **Step 3:** Execute training process (**Figure 12**) using heart sound signature training data contour sets into a (10 to 100) layer Deep Learning Neural Network to select the weights and biases that provide minimum loss (i.e. closeness of match between the data set and diagnostic classification). Steepest Gradient and Backpropagation are used to fine tune the weights and biases.

- **Step 4:** Perform correlation computations between the patient heart sound signatures and the reference contour templates.
  
  - Group Correlation computations into four categories.
    
    - Normal Signatures – N
    - Murmur Signatures – M
    - Click Signatures – C
    - Gallop Signatures – G
  
  - Each correlation computation produces a number between 0 and 1.
  
  - Form reference template correlation value vectors reference database.
  
  - Input the correlation numbers into the Deep Learning Neural Net Tree.
  
  - Node functions are given by **Equation (1)** and the activity function is described in (**Figure 13**), and henceforth referred to as *Worm_1*. This function is specifically designed to optimize the threshold process between the neural net hidden layer nodes.

- **Step 5:** Use the DLNN tree to determine which diagnosis best fits the patient’s heart sound signature pattern with at least 97% certainty. The DLNN process emulates cognitive adaptive consideration with regards to the age and gender of the patient undergoing diagnosis.
- Step 6: Compute the CSR, a value between 0 and 1, based on correlation data and resulting diagnosis \textbf{Equation (4)}. Early onset of abnormal conditions is manifested by progressively higher CSR numbers.

- Step 7: Update the contour database for the cases where no high degree of diagnostic certainty can be determined for the patient input data set. The new condition entry is later titled after validation by other diagnostic procedures.

- Step 8: Create a report which contains all related diagnostic data.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure12.png}
\caption{CSI Training Process}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure13.png}
\caption{DLNN Activity Function}
\end{figure}

CSI is capable of identifying abnormal heart sound patterns in men, women or children of any age by adjusting the scale dilation or compression of the CWT. CSI is also capable of identifying patterns not in the CSI contour database and auto classifying them based on other diagnostic procedures.

\subsection*{4.0 CSI Preprocessing and Training Data Preparation}

CSI uses synthetically produced Training Data of the heart sound patterns for the DLNN. This data henceforth referred to as \texttt{Cbad\_1} and \texttt{Ctest\_1} is created by digital emulation of the
aforementioned heart sounds resulting from normal, abnormal, and diseased heart states. The training data is used to initialize the DLNN prior to imputing hundreds of diagnosed heart abnormality data sets. These data sets correspond to known diagnosed cardiac conditions and are primarily used to tune the weights and bias in the neural network tree. The data sets are divided into training data, validation data, and test data.

5.0 CWT and Correlation Computations

With reference to Figure 11, CSI uses a CWT to map the heart sounds S1 thru S4 plus gaps into individual 3DCs. A correlation process is used to prepare the DLNN input data. This process compares the cardiac sound contour library templates with patient S1 thru S4 heart sounds data. This preprocessing architecture greatly reduces the number of input data points required by the system without sacrificing identification accuracy. CSI uses ninety two (92) contour templates which are compared to the patient contour data (i.e. four sets of twenty three (23) which corresponds to the 23 diagnosable cardiac abnormalities in the contour library).

The mathematical expression for the CWT is provided in Equation 2 where s is the scale, t is translation and the value of the CWT is a magnitude between 0 and 1. A “Morlet” Wavelet (Figure 16) is used in the CWT due to its close relationship with human perception, both hearing and vision. A discretized version of the CWT calculations allows execution by a digital computer. The CWT calculations are used to form the contours used in the first stage of the identification process. The dimensions of the contours are Scale, Translation and Magnitude. These contours represent spectral properties of the heart sounds, which are unique for each beating heart. A library of synthetically implemented heart sound contours is used as templates for comparison with real patient data.

\[
X(s,\tau) = \frac{1}{|s|^{1/2}} \int_{-\infty}^{\infty} x(t) \psi\left(\frac{t - \tau}{s}\right) d(t)
\]

Equation (2)

Where:
- s – is scale
- x – is input data
- \(\psi\) – is mother wavelet
- \(\tau\) – is translation
- \(X\) – is the Wavelet

The mathematical expression for the correlation process is provided in Equation 3. Correlation between the patient data set and each of the 92 heart sound templates is computed. The resulting
92 correlation values form the input nodes of the neural network and are indicative of how well the patient heart sound contours match each of the 23 heart conditions. Once a high probability diagnosis match is determined by the neural network, the cardiac severity rating (CSR) is computed as the maximum correlation values from each of the sounds (S1 thru S4) averaged (Equation 4).

\[
S = f \ast g = \int_{-\infty}^{\infty} f(\tau)g(t-\tau)d(\tau)
\]

Equation (3)

Where:

\(\tau\) – is independent variable

\(t\) - is time shift

\[CSR = \max (S_{1\text{cor}} + S_{2\text{cor}} + S_{3\text{cor}} + S_{4\text{cor}})\]

Equation (4)

Where:

- \(CSR\) is the Cardiac Severity Rating
- \(S_{1\text{cor}}\) is the correlation vector for the S1 heart sound signature
- \(S_{2\text{cor}}\) is the correlation vector for the S2 heart sound signature
- \(S_{3\text{cor}}\) is the correlation vector for the S3 heart sound signature
- \(S_{4\text{cor}}\) is the correlation vector for the S4 heart sound signature

6.0 CSI Processing Center

The implementation of this invention is primarily possible due to the recent availability of super computers, Terabyte storage, and high bandwidth online connectivity. A diagnostic DLNN that has a 97% confidence interval requires processing neural trees with hundreds of nodes and branches. With the availability of 3.00 GHz twelve core twelve thread processors, 30 Megabyte on chip cache, and Terabyte high speed memory, it is possible to easily process neural trees with \(10^6\) nodes and \(10^2\) hidden layers.

With reference to Figure 14 the Cardiometric Processing Center performs the following task:

- Ethernet Interface (multiple routing servers);
- Account User Validation process using encrypted patient data (dual redundant secure accounting servers);
- Unpacking of S1 thru S4 acoustic heart data (multi-port high speed servers),
- Converting S1 thru S4 acoustic heart data to an image map using a continuous wavelet transform (server bank of supercomputers);
- Multi-dimensional correlation between patient heart sound image contours and the CSI reference contours (server bank of supercomputers);
- Deep Learning Neural Net determines which diagnostic template best matches the reference templates of abnormal or diseased heart function (server bank of supercomputers);
- Database management of account information, diagnostic contour templates, heart sound data, and time-frequency patient data (multiple banks of supercomputer database servers);
- Webpage User interface server accessible by Smartphone (multiple high speed web servers);
- Report generator providing diagnostic data to webpage interface (supercomputer); and
- A cardiologist manual control interface providing access to computational parameters and patient data.

The CSI processing center provides simultaneous processing of heart sound data from a plurality of remote sites, allowing delivery of DLNN access from any Smartphone with online access. The hosted web sites allow viewing the patient input heart sound contour and the resulting match to a heart condition identified from comparison with the CSI contour database. Additionally a CSR number is provided for easy indication of the severity of a diagnosed condition, thus alleviating the need for a health care professional to read the heart sound contours.
7.0 Cardiac Acoustic Training and Test Data Sets

The learning process associated with the CSI Deep Learning Neural Network is illustrated by the two layer example in Figure 13. In one embodiment of this invention, a training data set consisting of acoustic heart data in the form of time series vectors (Cbad_1) for the 23 normal and abnormal heart conditions were created. Additionally, an independent acoustic heart test data set (Ctest_1) was created to validate the performance of the deep learning neural net. These data sets are Python and Matlab compatible.

The output of the example two layer neural net is given in Equation 5. The weights $W$ and biases $b$ are the only variables that effect the output $y^\wedge$. The loss function is given in Equation 6. Each iteration of the training process consists of the following steps:

- Calculating the predicted output $y^\wedge$, known as Feedforward
- Updating the weights and biases, known as Backpropagation

Updates of the weights and biases are done by increasing or decreasing their values using a gradient descent method. Two thousand iterations are used to train the CSI neural net.

$$y^\wedge = (W_2\sigma(W_1x + b_1) + b_2)\quad \text{Equation (5)}$$

Where:

- $W$ is the path weight
- $\sigma$ is the activation function
- $b$ is the bias
- $y^\wedge$ is the output
- $x$ is the input
Sum-of-Squares Error = $\sum_{l=1}^{L} (y - y^\wedge)^2$ \hspace{1cm} \text{Equation (6)}

Where:

- $y$ is the labeled output
- $y^\wedge$ is the neural net output layer

Current Clinical Trials

Table 2.0 list current clinical trial status associated with devices that use electronically collected heart sound data for diagnostics of specific abnormalities or diseases. In 2005, in collaboration with the Johns Hopkins University School of Medicine, Zargis, the manufacturer of the AI stethoscope, conducted a study to assess the impact of the Cardioscan R System on referral decisions made by primary care physicians regarding heart murmurs. The results of the retrospective study, published in Clinical Cardiology in 2008, showed that Cardioscan R led to a 41% reduction of unnecessary and costly cardiac referrals by physicians. The study also credits Cardioscan R with aiding physicians in improving detection of murmurs associated with potentially harmful heart disease by 46%. The purpose of the study was to characterize the accuracy of a commercially available artificially-intelligent stethoscope in determining which childhood murmurs suggest underlying congenital structural heart disease and therefore warrant diagnostic echocardiograms.

<table>
<thead>
<tr>
<th>Clinical Trials Description</th>
<th>Condition or Disease</th>
<th>Interventions</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Accuracy of an Artificially-Intelligence Stethoscope</td>
<td>Heart Murmurs, Congenital Heart Disease, Structural Heart Disease</td>
<td>Device: AI Stethoscope</td>
<td>Complete</td>
</tr>
<tr>
<td>Phono-and-Electrocardiogram Assisted Detection of Valvular Disease</td>
<td>Aortic Value Stenosis, Mitral Regurgitation, Heart Murmurs, Valvular Heart Disease</td>
<td>Diagnostic Test: AS Algorithm 1 &amp; 2, MR Algorithm 1 &amp; 2</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Vivo-AS (Aortic Stenosis) Detection Study</td>
<td>Aortic Stenosis</td>
<td>Device: Vivo System</td>
<td>Complete</td>
</tr>
<tr>
<td>Rapid Non-invasive Detection of Aortic Stenosis</td>
<td>Heart Valve Diseases, Aortic Valve Disease, Heart Murmurs</td>
<td>Device: Vivo System</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Confirm Rx vs Reveal LINQ Which is More Reliable in Data Transmission Randomized Clinical Study</td>
<td>Cardiac Arrhythmias, Syncope, Atrial Fibrillation, Atrial Flutter, Tachycardia, Stroke</td>
<td>Device: Abbott, Inc, Confirm Rx versus Medtronic Reveal LINQTM</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

CSI is a fully comprehensive heart murmur, gallop, click and normal heart sound diagnostic system which is a major embellishment of a Cardioscan R type system. Other devices currently in clinical trials are primarily acoustically enhanced electronic stethoscopes or ECG systems and do not include AI assisted diagnosis for a comprehensive suite of heart abnormalities and disease.
Future Clinical Trials

A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against control in human beings (Friedman, 1996). Section 201(h) of the Food, Drugs and Cosmetics Act defines a medical device as any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized. CSI is such a device and is intended as a primary heart abnormality or disease diagnostic aid device in a remote, home, or clinical environment and therefore requires a PMA and associated Investigational New Drug (IND) clinical trials. Misdiagnosis or failure to detect critical heart conditions using CSI may cause loss of life. The use of the CSI device/system in such an application requires FDA approval and coding designation for insurance re-imbursement purposes.

A CSI device clinical trial will involve validating to a statistical significance the accuracy of correctly diagnosing heart abnormalities or disease based on acoustic heart data. Table 3.0 lists the conditions that CSI claims to diagnose with a 97% level of confidence.

Table 3.0 CSI Diagnostic Suite

<table>
<thead>
<tr>
<th>Heart Sound Title</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Single S1 S2</td>
<td>Normal</td>
</tr>
<tr>
<td>2 Split S1</td>
<td>Normal</td>
</tr>
<tr>
<td>3 Mid Systolic Click</td>
<td>Mitral Valve Prolapse</td>
</tr>
<tr>
<td>4 Early Systolic Murmur</td>
<td>Acute Mitral Regurgitation</td>
</tr>
<tr>
<td>5 Mid Systolic Murmur</td>
<td>Mitral Regurgitation (Coronary Artery Disease)</td>
</tr>
<tr>
<td>6 Late Systolic Murmur</td>
<td>Mitral Regurgitation (Mitral Valve Prolapse)</td>
</tr>
<tr>
<td>7 Holosystolic Murmur</td>
<td>Mitral Valve Prolapse with Regurgitation</td>
</tr>
<tr>
<td>8 S4 Gallop</td>
<td>Left Ventricular Hypertrophy</td>
</tr>
<tr>
<td>9 S3 Gallop</td>
<td>Both Normal and Cardiomyopathy</td>
</tr>
<tr>
<td>10 Systolic Click + Late Murmur</td>
<td>Mitral Valve Prolapse with Mitral Regurgitation</td>
</tr>
<tr>
<td>11 S4 and Mid Systolic Murmur</td>
<td>Ischemic Cardiomyopathy + Mitral Regurgitation</td>
</tr>
<tr>
<td>12 S3 and Holosystolic Murmur</td>
<td>Dilated Cardiomyopathy with Regurgitation</td>
</tr>
<tr>
<td>13 Mitral Snap Diastolic Murmur</td>
<td>Mitral Stenosis</td>
</tr>
<tr>
<td>14 Normal S1 S2</td>
<td>Supine Normal</td>
</tr>
<tr>
<td>15 Systolic Murmur with Absent S2</td>
<td>Severe Aortic Stenosis</td>
</tr>
<tr>
<td>16 Early Diastolic Murmur</td>
<td>Aortic Regurgitation</td>
</tr>
<tr>
<td>17 Systolic and Diastolic Murmurs</td>
<td>Combined Aortic Stenosis and Regurgitation</td>
</tr>
<tr>
<td>18 Single S2</td>
<td>Normal in Elderly</td>
</tr>
<tr>
<td>19 Split S2 Persistent</td>
<td>Complete Right Bundle Branch Block</td>
</tr>
<tr>
<td>20 Split S2 Persistent</td>
<td>Normal</td>
</tr>
<tr>
<td>21 Ejection Systolic Murmur</td>
<td>Innocent Murmur</td>
</tr>
<tr>
<td>22 Ejection Systolic Murmur Split S2</td>
<td>Arterial Septal Defect</td>
</tr>
<tr>
<td>23 Ejection Systolic Murmur + Click</td>
<td>Pulmonary Valve Stenosis</td>
</tr>
</tbody>
</table>

An IND clinical study is generally intended as the primary support for a marketing application. The study is designed to demonstrate a “reasonable assurance of safety and effectiveness”.
endpoints and sample size are statistically driven and designed to assess both safety and effectiveness. A device IND and associated FDA review is much more complex than the usual IND type clinical trials due to the need to understand the internal operations of the device. In the CSI case, the details of the hardware element (i.e. sensor interface module) and the AI software will be rigorously reviewed by the FDA.

An important part of the execution of an IND clinical trial designed to prove the efficacy of CSI in diagnosing heart abnormalities and disease, is the participant inclusion and exclusion criteria. The participant screening process de-complicates efficacy interpretations due to other illnesses or abnormalities.

Inclusion criteria

A patient is eligible for the clinical trial if all of the following apply:

1.0 Aged Infant to 80 years (inclusive).
2.0 Male or Female.
3.0 All Races.
4.0 The patient must present to a cardiologist for a total cardiac evaluation.
5.0 The patient must have a diagnosed heart abnormality or disease.
6.0 Willing to sign a consent form.

Exclusion criteria

A patient is not eligible for the clinical trials if any of the following apply:

1.0 Unwilling to sign consent form.
2.0 Non English speaking.
3.0 Moderately agitated or disruptive patients.
4.0 Currently diagnosed diabetes.
5.0 Currently diagnosed liver disease.
6.0 Any pulmonary conditions that would create abnormal physical findings that would interfere with the fidelity of the cardiac sound sensor (e.g., obstructive pulmonary disease, such as asthma or COPD, with audible wheezing)
7.0 Use of intravenous vasodilators.
8.0 History of prior myocardial infarction, percutaneous coronary intervention (i.e. stents) or coronary artery bypass graft surgery.
9.0 Any chest wall configuration preventing adequate contact between the CSI acoustic sensor and the precordium.
10.0 Artery calcification resulting in non-diagnostic CT angiographic images.
11.0 Subjects who have conditions which the researcher feels may limit the ability to sense the heart sounds or the accuracy of the CSI system.
Of particular interest in the CSI IND clinical trial is the methodology for testing the claim that CSI is an effective heart diagnostic device to a statistical significance required for a life risk application. The applied statistical analysis methodology for validating the efficacy of the CSI device/system employs a multi-step process. With reference to Figures 9 and 11, CSI is based on a correlation process followed by a deep learning neural network to identify the abnormal or disease condition of the patient’s heart based on its acoustic signature. The computational output of each of these processes is used to determine to a statistical significance the accuracy of the CSI system.

In procedural language the analytics used to test the accuracy claim of the CSI system are as follows:

Step 1  - For each participant the CSI system diagnosis is recorded based on patient acoustic signature compared to diagnostic suite library listed in Table 3.0.

Step 2 The corresponding correlation coefficients for S1 thru S4 are used to calculate the CSR (Equation 4) for the identified diagnosis.

Step 3 A test of hypothesis of the statistical significance of the correlation coefficients to a confidence level of 97% performed using a sample population of 100 participants and a two tail t-distribution method (Figure 16). This test is done for independently clinically verified diagnosis. The null hypothesis is \( H_0: \sigma = 0 \) and the alternate hypothesis is \( H_a: \sigma \neq 0 \).

![Figure 16.0 t-distribution Two Tail Test](image)

The test statistic is given by

\[
t = r / \sqrt{(1 - r^2) / (n - 2)}
\]
Where: \( r \) is the sample correlation coefficient (CSR)  
\( n \) is the sample size  

Step 4 If \( t \) is in the rejection region, the diagnosis validity is at a 97% confidence level.

For a 100 participant clinical trial, the threshold that must be exceeded to reject the null hypothesis (i.e. \( H_0: \) there is very little correlation between patient acoustic signature and a reference signature in the CSI database), is a \( t_{\alpha/2} \), of 2.748 for a 0.015 level of significance. If for example the CSR is .75 (i.e. typical average correlation coefficient for S1 thru S4), the test statistic \( t \) is 168.01 for a two tail \( t \)-distribution. Since \( t \) is much greater than \( t_{\alpha/2} \) the null hypothesis is rejected. This means there is a 97% certainty that the correct diagnosis has been achieved.

**Future Research**

Recently, the advent of noninvasive imaging modalities has dwarfed the importance of cardiac auscultation in clinical practice (Frishman, Banks)\(^3,4\). Devices such as the handheld ultrasound have enabled detailed on-site visualization of the cardiac anatomy and are further threatening the role of the stethoscope as a bedside examination tool (Liebo, Mehta)\(^5,6\). In this way, there has been a decrease in the appreciation of the importance of cardiac auscultation, and physicians are decreasingly proficient and confident in their examination skills (Vukanovic, Mangione)\(^7,8,9\). Studies have also suggested a low level of inter-observer agreement regarding cardiac murmurs (Lok)\(^10\).

The smartphone has become a popular device. As of 2015, 64% of Americans and 88% of South Koreans were reported to own a smartphone (Poushter)\(^11\). Smartphones are frequently used for health purposes, such as counseling or information searches (Smith)\(^12\). The modern smartphone has excellent processing capability and is equipped with multiple high-quality components, such as microphones, display screens, and sound speakers. There have been efforts to use smartphone health apps for self-diagnosis (Lupton)\(^13\). However, some of these software apps have shown poor credibility, and their role in health care is not yet established (Armstrong)\(^14\).

A smartphone app for cardiac auscultation that could be used by non–medical expert users is currently being developed. Although the importance of cardiac auscultation is declining in the hospital setting, it could serve as a screening tool at the prehospital stage if it can be performed easily by smartphone users themselves. A pilot study to test the feasibility of cardiac auscultation using the built-in microphones of smartphones without any add-on devices was performed. The study tested (1) whether heart sound recording using a smartphone is feasible, and (2) whether an automated diagnostic algorithm can classify heart sounds with acceptable accuracy. Heart sounds were recorded using the smartphone microphones and processed electronically. Diagnostic algorithms were developed by applying convolutional neural networks, which we used for the
diagnosis of the recorded heart sounds. In the study, diagnostic accuracy of the algorithms were assessed.

The app described in the study requires further development. An all-in-one system is crucial, comprising recording, audio processing, and a diagnostic algorithm. Instructions that help users record their heart sound by themselves are also needed. Improvements in the ability of the app to acquire interpretable heart sounds and to provide an accurate diagnosis, is the goal of future development. Another potential application is the use of a diagnostic algorithm with commercialized electronic stethoscopes performed by medical personnel (Leng)\textsuperscript{15}. This may improve the quality of clinical practice by assisting early-career doctors or nurses to assess patients.

In the app used in the study, heart sounds were recorded by placing the phone on the skin of the chest, using the built-in microphone. In most smartphones, microphones are located on the lower border of the device (Figure 17). Heart sounds can be best heard in the intercostal spaces. The instructions for this app indicated the anatomical landmarks and auscultation areas. While maintaining the contact of the lower margin of the smartphone with the chest wall, users are required to manipulate the device to start and stop recording. Users can see on the screen whether their heart sounds are properly being captured.

![Figure 17.0 Heart Sound Recording Using a Smartphone App](image)

The concept of cardiac auscultation using smartphones is feasible. Indeed, diagnosis using convolutional neural networks yielded a high diagnostic accuracy. However, use of the built-in microphones alone is limited in terms of reproducible acquisition of interpretable heart sounds.
Summary and Conclusions

In simple terms, CSI is a non-invasive diagnostic procedure that converts acoustic heart sounds into 3D images. These patient 3D images are compared to 3D images of known heart abnormalities and diseases and if there is a high degree of certainty (i.e. **statistical significance**), the resulting computer aided diagnosis is reported to the healthcare professional. This procedure is available in a remote, clinical, or home environment.

In analytical terms, CSI converts the acoustic signal processing of S1 thru S4 heart sounds into a visual time-frequency spectrum picture. Mathematical cross correlation between the patient’s time-spectrum image and a reference library is performed that yields correlation coefficients between 0 and 1. The challenge is to convert the correlation analysis process into **statistically significant** verification that CSI correctly diagnoses early to late heart abnormalities or disease. CSI uses AI to make this decision mathematically rather than a simple observation (“yes or no”) of whether the diagnosis is correct.

Therefore, based on the aforementioned description of CSI and the claim to diagnose a comprehensive suite of heart conditions, an IND clinical study should be pursued with an expected outcome of full FDA approval and associated billing coding.

References:

2. Evans C, Ildstad S. Small Clinical Trials. 2001
11. Poushter J. Smartphone ownership and Internet usage continues to climb in emerging economies but advanced economies still have higher rates of technology use. Washington, DC: Pew Research Center; 2016. Feb 22, [2018-02-09].