Machine Learning-Assisted Pulse Wave Analysis for Heart Failure

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Jashanjeet Matharoo
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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Machine Learning-Assisted Pulse Wave Analysis for Heart Failure

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Abstract

Heart failure (HF) is a condition in which the cardiac muscle can no longer efficiently circulate blood to meet the body's needs. HF is a subset of cardiovascular disease (CVD), which accounts for 31% of the annual global death toll and costs the U.S. $200 billion annually in direct and indirect costs. Early detection of HF can lead to better outcomes and longitudinal quality of life, but there are currently minimal early detection techniques. Thus, this project aims to develop a novel diagnostic device for heart failure that is ergonomic, easy-to-use, and can be implemented for at-home screening. To develop this device, aortic waveform derivation and machine learning-assisted aortic waveform classification was conducted. We achieved a 49.96% waveform transformation accuracy as measured by augmentation index (AIx) accuracy and found statistically significant differences between mean AIx across all but one patient dataset. Additionally, we achieved a maximum classification accuracy of 77.8% using machine learning algorithms trained on native aortic waveforms. Future work should increase patient sample sizes to develop unique generalized transfer functions for the patient population of interest and to allow for more robust training of machine learning algorithms. The results shown here lay the framework for the application of the waveform transformation program and classification algorithm into a commercial diagnostic device that could lead to improved patient outcomes for millions of people each year.

Keywords: Heart Failure, Diagnostics, Machine Learning, Medical Device

Introduction

Cardiovascular Disease and Heart Failure

Cardiovascular disease (CVD) is the leading cause of death globally, accounting for 31% of the annual global death toll. Over 65% of this burden falls upon middle- and low-income countries.[1] Coronary artery disease (CAD) is a subset of CVD that accounts for over half of the annual U.S. death toll; it can also lead to heart failure (HF), which is a condition that occurs when the heart cannot efficiently pump blood throughout the body. The total costs due to cardiovascular diseases in the U.S. are reported to be over $200 billion annually - a figure resulting from both direct (hospitalization, medication, etc.) and indirect (lost productivity) costs.[2] There are many comorbid conditions that can result in CVD, CAD, and subsequently HF; these include hypertension, diabetes, past heart attack, cardiomyopathy, and sleep apnea. Early detection and treatment, however, can improve patient outcomes and longitudinal quality of life.[3]

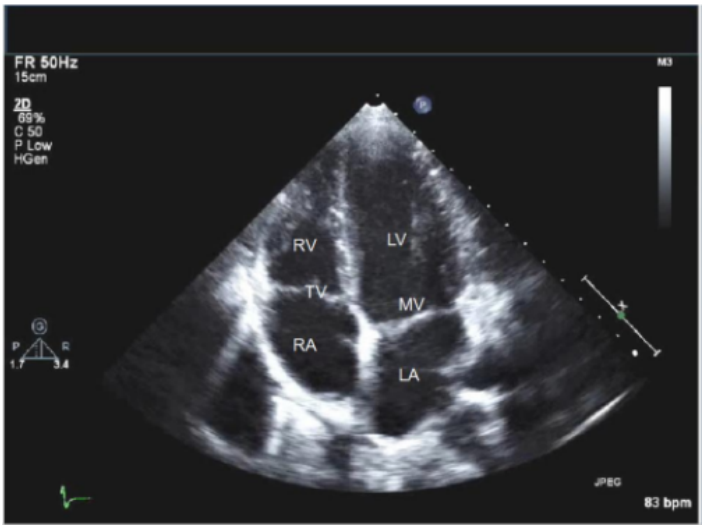

Fig. 1. The above figure displays findings from an echocardiogram study utilizing ultrasound to visualize the heart and its various chambers. Labelled in the above image are the left atrium (LA), the right atrium (RA), the left ventricle (LV), the right ventricle (RV), the tricuspid valve (TV), and the mitral valve (MV).

Diagnostic tools used to identify cardiovascular diseases currently include electrocardiograms,

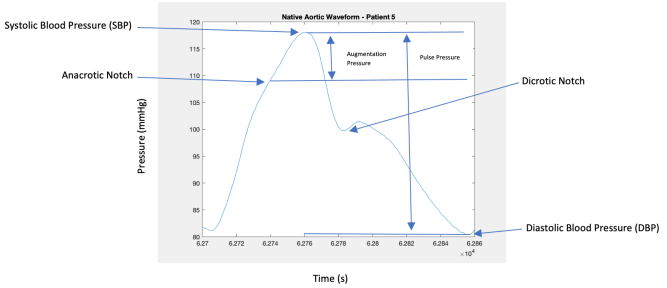

Fig. 2. The above figure displays a representative aortic pressure waveform with the pressure in mmHg along the y-axis and time along the x-axis. Labelled are physiologic features such as systolic blood pressure, diastolic blood pressure, anacrotic notch, and dicrotic notch. Additionally, compound measurements such as augmentation and pulse pressure are also shown.

echocardiograms, exercise and nuclear stress tests, angiograms, cardiac CTs, and pulse wave velocity measures.[4] These tools allow clinicians to quantify cardiovascular function by measuring or calculating various characteristics such as heart rate, cardiac output, ejection fraction, arterial elasticity, and many others. Figure 1 shows partial findings from an echocardiogram displaying various heart chambers and vessels from which physiological indicators of CVD and HF can be determined.[5] Analysis of diagnostic findings in the context of the patient's history and the results of any other tests performed then allow clinicians to determine whether or not a patient has developed a cardiovascular disease. However, there are currently minimal early detection techniques for HF, even fewer of which can be implemented for at-home screening.[6]

Pulse Waveform Analysis

Pulse waveform analysis (PWA) has the potential to address this gap of accessible early diagnostics for CVD and HF. PWA is the analysis of the pressure waveform created by blood of various pressures flowing through the vasculature and can be measured directly (catheterization) or indirectly (plethysmography). From the pulse waveform, many physiological characteristics can be measured; for example, Figure 2 shows measurements of systolic, diastolic, anacrotic notch, dicrotic notch, and mean arterial pressures. From these characteristics, compound measurements and prognostic information can be derived by clinicians and aid decision-making.[7]

A clinically relevant compound measurement is the Augmentation Index (AIx), which is derived from dividing the difference between the systolic pressure and the anacrotic notch pressure by the pulse pressure.[8] Physiologically, AIx is a measure of arterial stiffness as it offers a standardized measure of the location of the anacrotic notch relative to the systolic and diastolic pressures. More specifically, AIx indicates the interference to the current pulse wave by the reflection wave from an earlier bolus of blood traversing the artery.[9] Studies have shown AIx to be significantly correlated with clinical indicators of cardiovascular disease risk, indicating the index's potential to provide clinically relevant diagnostic information.[10] A follow-on study further supported the aforementioned findings and elaborated on the usefulness of AIx in predicting CVD in various contexts. Specifically, pulsatile arterial hemodynamics, which included measures of wave reflection, were found to be predictive of CVD in conditions of essential hypertension, renal failure, diabetes, and aging.[11]

In addition to AIx, characteristics of the anacrotic and dicrotic notches can also offer diagnostic insight. A clinical study of septic shock patients revealed that the dicrotic notch location could be used to determine the etiology of tachycardia in this patient population. Specifically, the distance between the dicrotic notch and the systolic peak could determine whether the tachycardia was compensatory or non-compensatory.[12] A separate analysis of severe aortic stenosis showed the presence of a pronounced anacrotic notch could indicate stenosis severity. The study predicted that this waveform finding would be due to a drop in pressure due to turbulence in the aortic vessel indicative of the aforementioned pathology.[13] The analysis of the aforementioned waveform features, including AIx, anacrotic notch, and dicrotic notch, would serve as essential components of a diagnostic device for CVD and HF.

Central Waveform Derivation Techniques

Although catheterization is the most accurate approach to recording aortic pulse waveforms for analysis, prior work has shown that these central waveforms can be derived from peripheral (radial and brachial) waveforms that can be measured noninvasively. The seminal work in this area defined transfer functions to derive central pressure waveforms from measurements at both the brachial and radial arteries. They also demonstrated that these generalized transfer functions could be applied to human subjects under various circumstances with acceptable accuracy.[14] Subsequent studies adopted this method and validated the accuracy of generalized transfer functions by comparing measured and derived values for features such as systolic and mean arterial pressures; specifically, researchers found a correlation between measured and derived values of $r = 0.995$ with $p < 0.001$.[15] Though more involved modelling techniques have been proposed, such as the 4-element Windkessel model, the simplicity of a generalized transfer function still makes it the best candidate for application in a potential diagnostic device.[16]

Table 1. The above table displays results for derivation accuracy of waveform transformation as measured by augmentation index accuracy. It was found that the waveform transformation method used resulted in an average augmentation index accuracy of 49.96%.

Derivation Accuracy

Patient	5	6	7
Average AIx (%) - Native	26.3	34.2	51.9
Average AIx (%) - Derived	16.9	11.7	26.8
Accuracy (%)	64.3	34.2	51.6

In recent decades, diagnostic methods have been revolutionized by the application of artificial intelligence (AI). For example, implementation in reading X-rays, interpreting MRIs, identifying cancer cells, and stratifying the severity of diabetic retinopathy all display the benefits that artificial intelligence can provide.[17] In cardiovascular medicine, AI has been used to assist in nuanced interpretation of echocardiography results and to enhance images in single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). In fact, there is currently an FDA-approved program that collects these MPI results and compares them to larger datasets in order to assist the physicians interpreting them.[18] The application of AI in PWA could prove a robust diagnostic tool for the detection of CVD and HF.

There exists a gap in early detection and diagnosis of CVD and HF due to the invasiveness and economic inaccessibility of traditional diagnostic techniques to large segments of the population. Due to the high death and economic burden the aforementioned conditions place on the U.S. and the entire world, there is an urgent need for a diagnostic device capable of efficient and inexpensive diagnosis of CVD and HF. Currently, there is no FDA-approved solution on the market, as competitors such as CareTaker Medical have not received approval for the predictive capabilities of their device.[19]

Thus, this project seeks to develop a non-invasive, easy-to-use diagnostic device that utilizes pulse wave analysis and machine learning to allow patients the ability to screen for and monitor cardiovascular conditions from the comfort of their own homes. More specifically, this project explored three major aims: 1) to develop an accurate central waveform derivation system, 2) to develop an accurate central waveform classification machine learning algorithm, and 3) to confirm congruent results for classification of both native and derived aortic waveforms for ultimate implementation into a novel diagnostic device.

Results

Waveform Transformation

This project aimed to develop an accurate central waveform derivation system using generalized transfer functions. After peripheral waveform collection, accuracy was measured in comparison to the native aortic waveforms recorded during cardiac catheterization. Augmentation index (AIx) congruence was used as the basis of the accuracy calculation as AIx is a compound measure that incorporates various different pulse waveform characteristics and is a relative rather than discrete measure. Analysis of the derived and native aortic pulse waveforms from three different patients was conducted and, as shown in Table 1, there was on average a 49.96% accuracy in AIx as measured from the derived versus native waveform. Statistical analyses were performed for each patient and across all patients, and revealed statistically significant differences in mean AIx values between derived and native waveforms in all comparisons except that for Patient 5. This leads to the rejection of the null hypothesis that there is not a difference in the mean AIx of the derived versus the native aortic waveform for all patients (individually and collectively) except Patient 5. These analyses were conducted using Student's T-tests with unpaired tests run for each individual patient and a paired test comparing means across all patients. Results for these tests are elaborated in Table S1 and graphically represented in Figure 3.

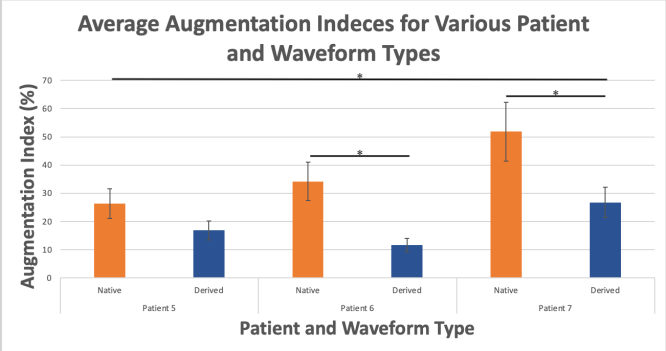

Fig. 3. The above figure displays a graphical representation of average augmentation indices of native and derived waveforms for patients 5, 6, and 7. Statistically significant differences between means are indicated with an asterisk. Overall trends showed lower derived versus native average augmentation indices.

Table 2. The above table displays results from machine learning algorithm classification accuracy testing. The greatest accuracy was achieved by Support Vector Machine and Gaussian Naïve Bayes algorithms (77.8%). This accuracy was also achieved using logistic regression, the non-machine learning control algorithm.

Classification Accuracy

Algorithm	Accuracy (%)
K-Nearest Neighbors	55.6
Decision Tree	66.7
Gaussian Naïve Bayes	77.8
Support Vector Machine	77.8
Logistic Regression	77.8

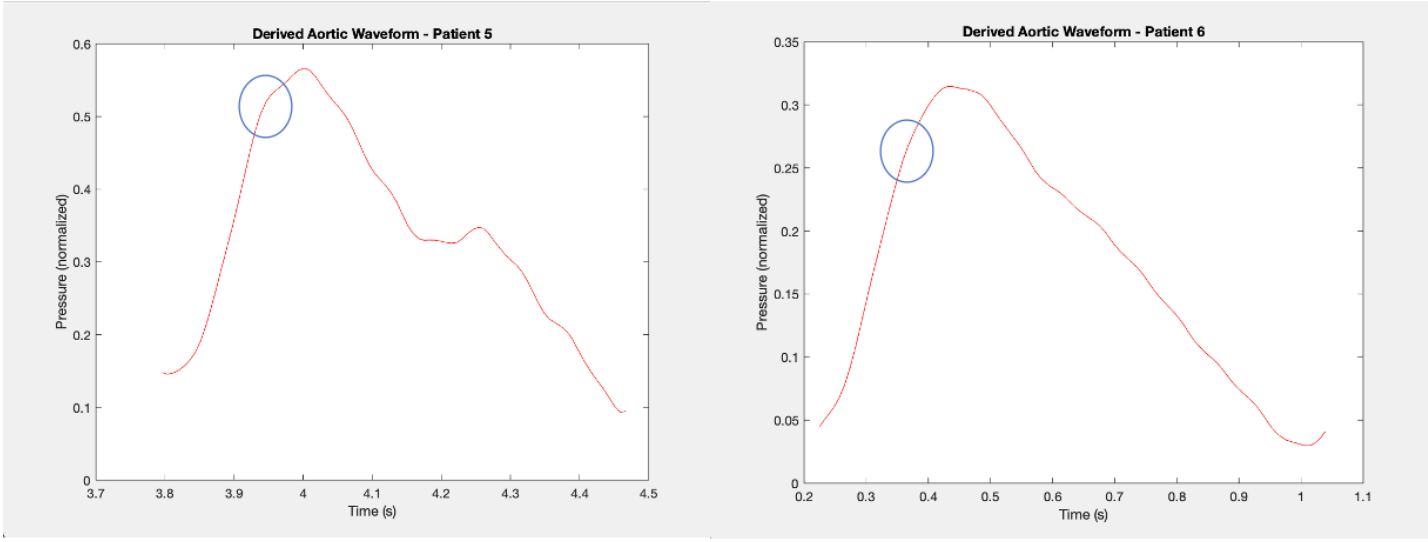

Fig. 4. The above figure displays representative derived aortic waveforms from patient 5 (left) and patient 6 (right), with normalized pressure along both y-axes and time along both x-axes. Circled in both images is the anacrotic notch of the waveform, which is visibly more defined and identifiable in patient 5's waveform compared to that in patient 6's waveform.

Machine Learning Algorithm Performance

This project aimed to develop a central waveform classification system using machine learning with at least a 90% accuracy, as this is an acceptable value for clinical relevance in other AI applications in healthcare.[20] Native aortic pressure waveforms collected from patients during cardiac catheterization procedures were procured post-hoc and utilized as training and testing sets for various machine learning algorithms. Ten waveforms were used to train the algorithms and nine waveforms were used to test classifying them as heart failure or non-heart failure waveforms. Of the four algorithms tested – namely K-Nearest Neighbors, Decision Tree, Gaussian Naïve Bayes, and Support Vector Machine (SMV) – the Gaussian Naïve Bayes and SVM algorithms yielded the best performance with an accuracy of 77.8% as shown in Table 2. Additionally, a simple logistic regression was built and tested as a non-machine learning control and also yielded a 77.8% accuracy in classification.

Congruence Testing

Finally, this project aimed to verify congruent classification results for both derived and native aortic waveforms using the machine learning algorithm developed in Aim 2. Due to the sequential nature of Aims 2 and 3, this testing was not conducted because the machine learning algorithm was not yet displaying a classification accuracy of greater than 90%.

Discussion

Of the three major aims declared at the beginning of this project, Aim 1's results saw an average derived AIx accuracy of 50% compared to native aortic waveforms, Aim 2's results displayed a maximum classification accuracy of 77.8% with Gaussian Naïve Bayes and Support Vector Machine algorithms, and Aim 3 was unable to be realized.

The aortic waveform derivation portion of the project yielded an average derived AIx accuracy of 50% compared to native aortic waveforms and showed statistically significant differences between mean AIx measures for derived and native waveforms for all comparisons except for Patient 5 independently. It is possible that the AIx measurement was more accurate for Patient 5's derived waveforms, as they displayed more pronounced anacrotic notches than those of Patients 6 and 7 as seen in Figure 4. Additionally, the generalized transfer function utilized was referenced from literature as COVID-19 restrictions prevented the collection of enough derived and native waveforms to develop novel generalized transfer functions; thus, the transfer function used was not derived from the unique patient population being observed. Studies have also shown the inefficacy of generalized transfer functions on large sample sets, and this taken in conjunction with the previously mentioned limitations could have resulted in the low accuracy of the central waveform derivation system.[21] Future studies should develop novel generalized transfer functions specific to the patient population of interest, as this would increase accuracy of the waveform transformation process for future implementation into a diagnostic device.

The machine learning algorithm portion of the project showed a maximum classification accuracy of 77.8%, which was achieved by Gaussian Naïve Bayes and

Support Vector Machine algorithms as well as the non-machine learning logistic regression control. This result is probably due to the small sample set used to train the algorithms, as machine learning algorithm performance is directly related to training set size.[22] A major limitation to training dataset size was stringent conditions for acceptable patients; data collection required left heart catheterization or coronary angiography procedures to have been performed and for those patients to have been previously phenotyped by resident physicians. Future studies should implement methods to counteract small datasets; for example, crude estimation of parameters could increase accuracy without losing precision due to an increase in degrees of freedom.[23] Additionally, fewer parameters could be used to decrease the degrees of freedom for preliminary algorithm development until more training data can be obtained.

The congruence testing portion of this project could not be completed because the desired accuracy of the classification system was not reached. Future studies should prioritize the successful development of the machine learning algorithm using aforementioned techniques of overcoming small training dataset size. This portion of the project is essential to apply the machine learning algorithm to a diagnostic device, as the device would input peripheral waveforms whereas the algorithm is trained on native aortic waveforms.

General limitations faced by this project included difficulties with patient recruitment, device failures, and COVID-19 restrictions suspending patient research. First off, patient recruitment was difficult due to the general condition of the patient population of interest; patients with heart failure often suffer from comorbid conditions and are not in good health, which in our experience makes them wary to agreeing to participate in the study. Additionally, the prospect of their catheterization procedure was very anxiety-inducing, further deterring the patients from participating in the study.

Finally, COVID-19 restrictions imposed by the UVA Health system limited access to patients as undergraduate researchers were not permitted in research and clinical areas for most of the year. The IRB protocol was adjusted to accommodate for minimal patient access, but the reduced patient sample tested amplified the aforementioned errors of declining participation and device failure.

As mentioned above, future studies should aim to test a larger cohort of patients and utilize a subset of these to develop novel generalized transfer functions to achieve an accuracy of at least 90% as measured by augmentation index between the derived and native aortic waveforms. Future work should also utilize this larger patient sample to optimize machine learning algorithms until a candidate algorithm achieving at least 90% classification accuracy is identified for device implementation. Then, congruence testing should be conducted as detailed below in Materials and Methods. Finally, the current device should be consolidated into a more ergonomic, easy-to-use device that has an interactive user interface.

Once device development is complete, the novel diagnostic device can follow the 510(k) de novo pathway for FDA approval and eventual commercialization. Through the aforementioned future directions, this device will serve to offer patients early detection and monitoring of CVD and HF from their own homes, offering potentially better outcomes and cost savings for both patients and hospitals.

Materials and Methods

This project involved various processes being conducted in parallel to achieve the overall goal of developing a novel diagnostic device for heart failure and also to complete the three specific aims introduced previously. In addition to descriptions of each step in following subsections, Figure 5 displays a block diagram of the project and interactions between each step.

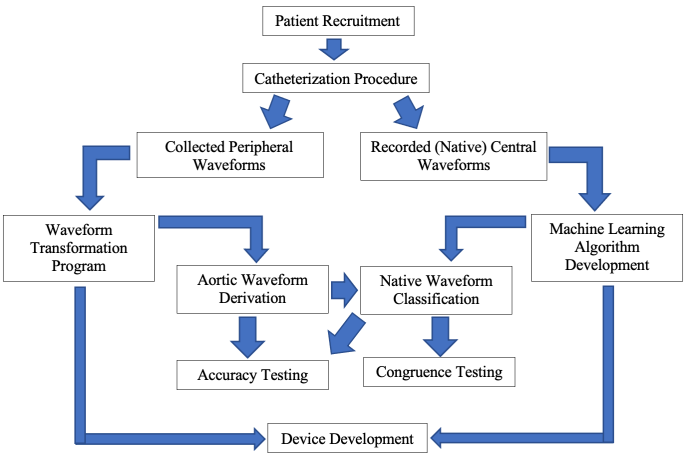

Fig. 5. The above figure displays a block diagram flowchart of the methods undertaken during this project. Notably, the waveform transformation methods (left half) and the machine learning algorithm development methods (right half) occurred concurrently.

Patient Recruitment

IRB approval for the previous year's project was extended to this project with slight protocol alterations due to COVID-19. Specifically, the original 6-minute walk test and EKG measurements at various seated positions were

foregone in favor of a single pulse oximeter measurement in triplicate during the catheterization procedure. This was chosen because many of the physiologic characteristics of the patients were already recorded in the EPIC system and phenotyping by resident physicians, and because this method would limit patient contact and promote COVID-19 safety for both patients and researchers.

Catheterization Procedure

The peripheral waveform collection was performed during a catheterization procedure performed by one of the UVA Cardiology attending physicians. Specifically, left heart catheterizations and coronary angiography procedures were attended by researchers because these procedures gather pressures at the aorta, whereas right heart catheterizations do not reach the left side of the heart. These procedures were generally conducted as exploratory catheterizations to determine pressures across the heart and to identify any blockages in the vasculature feeding the cardiac muscle. During the procedure, a Swan Ganz catheter is thread up either the patient's radial or femoral artery up to the aorta, after which various hemodynamic measurements and pressure recordings are taken throughout the left side of the heart.

Peripheral Waveform Collection

During the catheterization procedure detailed above, peripheral waveform recordings were conducted by researchers. More specifically, a pulse oximeter was connected to the patient's left index finger (as the physician was working on the patient's right side) and attached to an Arduino board with plethysmography shield (ProtoCentral AFE4490 Pulse Oximeter Shield). The plethysmography shield, shown in Figure S1, was constructed by the previous year's group and repurposed for this project; namely, the EKG electrodes were no longer utilized and the code was reworked.

The program developed for this code integrated Arduino files in C++ and MATLAB code to first gather data from the pulse oximeter for eight seconds. Then, the input was fed to an Arduino program that parsed the data and exported relevant measures of Red and IR light to the MATLAB program that displayed the waveform. The data collection and exporting were done through a consolidated function created by the previous year's group, but the parsing of relevant values and displaying of waveforms was developed this year.

Waveform Transformation

Once the relevant patient data were exported to MATLAB and the peripheral waveforms were displayed, a Fourier transform was applied to the data to convert it into the frequency domain. After this, a transfer function was applied to the data to transform the peripheral waveform to a derived aortic waveform. As stated in limitations above, due to small sample sizes this project was unable to determine novel generalized transfer functions and thus referenced generalized transfer functions from literature that utilized a similar method of aortic waveform derivation.[14] This transfer function's parameters can be found in Figure S2.

To confirm the validity of the methods used, peripheral and derived aortic waveforms were visually compared by this project's clinical advisor (himself a cardiology attending physician) to determine whether expected trends were discernable. Specifically, it was observed that the systolic peak in the derived waveforms was lower and that the slope to the systolic peak in the derived waveforms was also lower. Differences in features used to validate transformation methods can be seen in Figure 6.

Native Waveform Collection

Native aortic waveforms were collected after catheterization procedures from recruited patients. To accomplish this, researchers accessed electronic records from the UVA Cath Lab's MacLab program. Timestamps surrounding aortic pressure recordings were selected and data were exported to a USB drive. These waveforms were then transferred to a secure server on the UVA Health network and copies of anonymized waveforms were used by researchers for machine learning algorithm

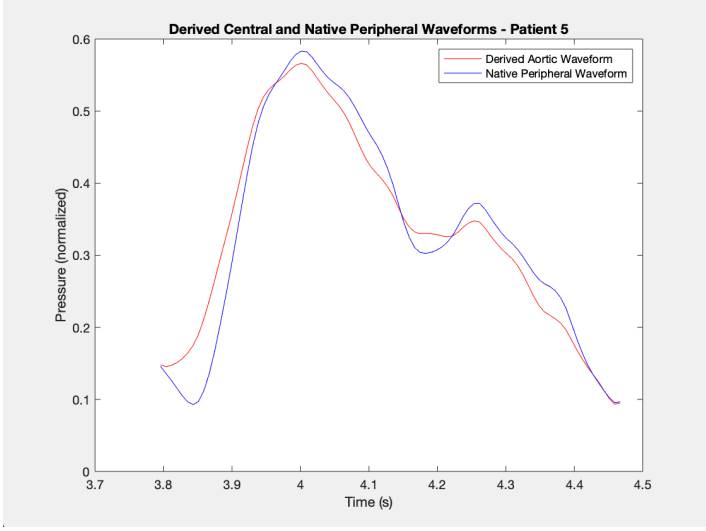

Fig. 6. The above figure displays a graphical representation of representative native peripheral (blue) and derived aortic (red) waveforms from patient 5. Pressure in mmHg is along the y-axis and time is along the x-axis. Notable differences include a higher systolic peak and slope leading up to the systolic peak in the peripheral versus the aortic waveform.

development. All patient data was handled in a HIPAA-compliant fashion throughout the collection and analysis processes.

Machine Learning Algorithm Development

Native aortic waveforms gathered during catheterization procedures were first parsed through a MATLAB program that isolated the relevant data channels and displayed the raw native waveform for each patient. Then, a representative waveform was manually selected from each recording. Next, features were manually measured on each representative waveform; these included systolic, diastolic, anacrotic notch, dicrotic notch, and mean arterial pressures, as well as time to rise, time to fall, and area under the curve measurements.

After characteristics were extracted from representative waveforms, these data were sent to collaborators from the UVA Department of Computer Science. The collaborators then created feature arrays for each waveform and gathered phenotype data for each patient that had been procured by resident physicians previously. Through the phenotype data, they were able to determine which patients had HF and which ones did not; this assisted them in training various machine learning algorithms. The collaborators then used 10 of the 19 collected waveforms to train four machine learning algorithms – K-Nearest Neighbors, Decision Tree, Gaussian Naïve Bayes, and Support Vector Machine – to be tested for classification accuracy.

Accuracy and Congruence Testing

To determine the accuracy of both the waveform transformation and the machine learning classification methods described above, accuracy and congruence of results were tested.

For the waveform transformation, the Augmentation Index (AIx) for both the derived and native aortic waveforms was calculated manually for five representative waveforms from three distinct patients. Then, percent accuracy was calculated and Student's T-tests were run to determine whether there was a difference in mean AIx values; these statistical tests were conducted both inter- and intra-patient.

For the machine learning classification, the four machine learning algorithms introduced above were used to classify nine native waveforms. Additionally, a non-machine learning logistical regression was used as a control. The classification accuracy was calculated for each of the five algorithms to determine the most effective candidate to move forward with.

To determine whether the machine learning algorithm selected produced consistent classification results when evaluating both native and derived aortic waveforms from the same patient, congruence testing was planned to be conducted. However, this step was not completed due to incomplete algorithm performance optimization.

Novel Diagnostic Device Development

After testing the accuracy and congruence of the waveform transformation and machine learning classification methods detailed above, the machine learning algorithm was to be incorporated into the peripheral waveform collection device. Then, the scaffold of this device was to be reconstructed to include a user interface and more ergonomic design. However, this step was not completed due to incomplete waveform transformation and algorithm performance optimization.

End Matter

Author Contributions and Notes

J.S.M., S.M., and J.A.H. designed research, J.S.M. performed research, J.S.M wrote software, J.S.M analyzed data; and J.S.M wrote the paper.

The authors declare no conflict of interest.

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Supplemental Information

Table S1. The above table displays results of statistical analysis conducted on the average augmentation indices of native and derived waveforms from Patients 5, 6, and 7. Statistically significant differences in mean augmentation index were found within patients 6 and 7 as well as across all patients (alpha = 0.05).

Statistical Analysis

Comparison	Test	P-value
Patient 5 Native vs. Patient 5 Derived	Student's Unpaired T-test	0.133
Patient 6 Native vs. Patient 6 Derived	Student's Unpaired T-test	0.0278
Patient 7 Native vs. Patient 7 Derived	Student's Unpaired T-test	0.0051
All Native vs. All Derived	Student's Paired T-test	0.0004

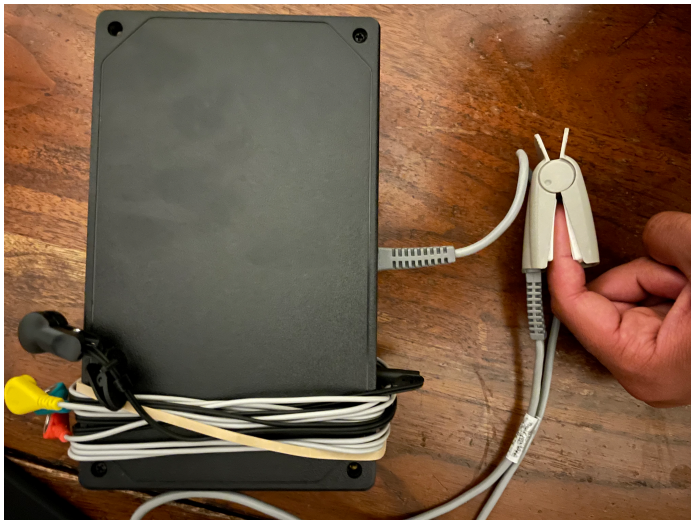

Fig. S1. The above figure displays the device utilized to collect native peripheral waveforms from recruited patients during catheterization procedures. Shown is the pulse oximeter extension connected to a researcher's finger to demonstrate the patient data collection process.

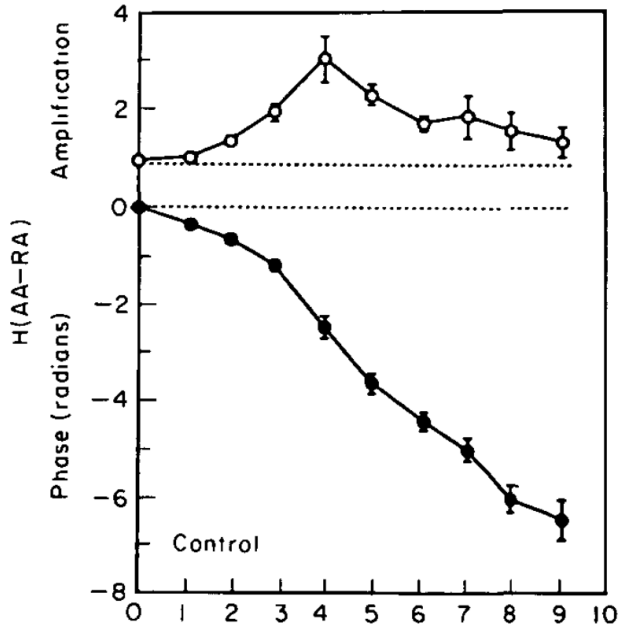

Fig. S2. The above figure displays the amplification and phase parameters for the generalized transfer function used for aortic waveform derivation in the waveform transformation program. The parameters (y-axis) vary with frequency (x-axis). These values were referenced from literature.[14]