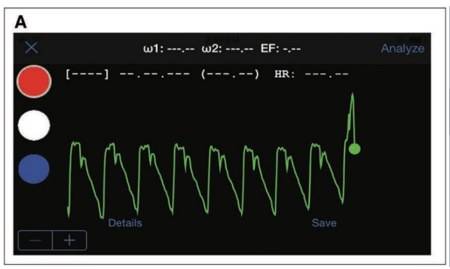
Marie Csete MD, PhD
Avicena LLC, Pasadena CA

Background

-Rapid, accurate non-invasive assessment of cardiac function, especially LV function, is a long-sought goal.
-Avicena LLC developed and is clinically testing algorithms based on new mathematical tools, applied to data collected with a novel non-invasive optical sensor/tonometer, to capture LV function
-Here we summarize evolution of the hardware and software during translation from the Caltech fluid dynamics labs to the first clinical studies

Methods & Results

Figure 1. Evolution of hardware supporting non-invasive cardiac diagnostics



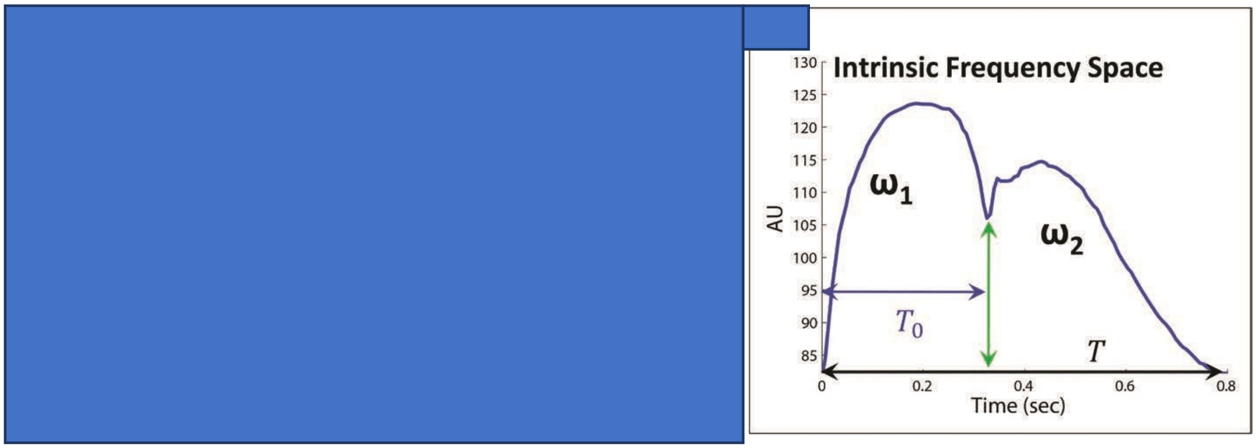
PICTURE of VIVIO HERE**

PICTURE OF VIVIO w/ECG patch and screen showing three waveform streams (sound, arterial waveform, ECG)

A. Originally waveform capture was accomplished by using an unmodified iPhone camera to record skin displacement over the carotid pulse [1], and then the waveform reconstructed mathematically. B. Waveform capture V.2 is now done with a novel optical sensor/tonometer ("Vivio"), which also captures heart sounds (orange) when the device is held over the carotid pulse. This version is currently in clinical studies for diagnosis of AS. C. Vivio + ECG is the next generation device, with synchronized ECG also transmitted to the iPad via BLE.

Predicate device: for the Vivio (waveform): SphygmoCor
Predicate device for the detection of murmurs: Eko stethoscope
Predicate device for the heart sounds: Littmann 3200 in bell mode

Figure 2. Evolution of algorithms supporting non-invasive cardiac diagnostics



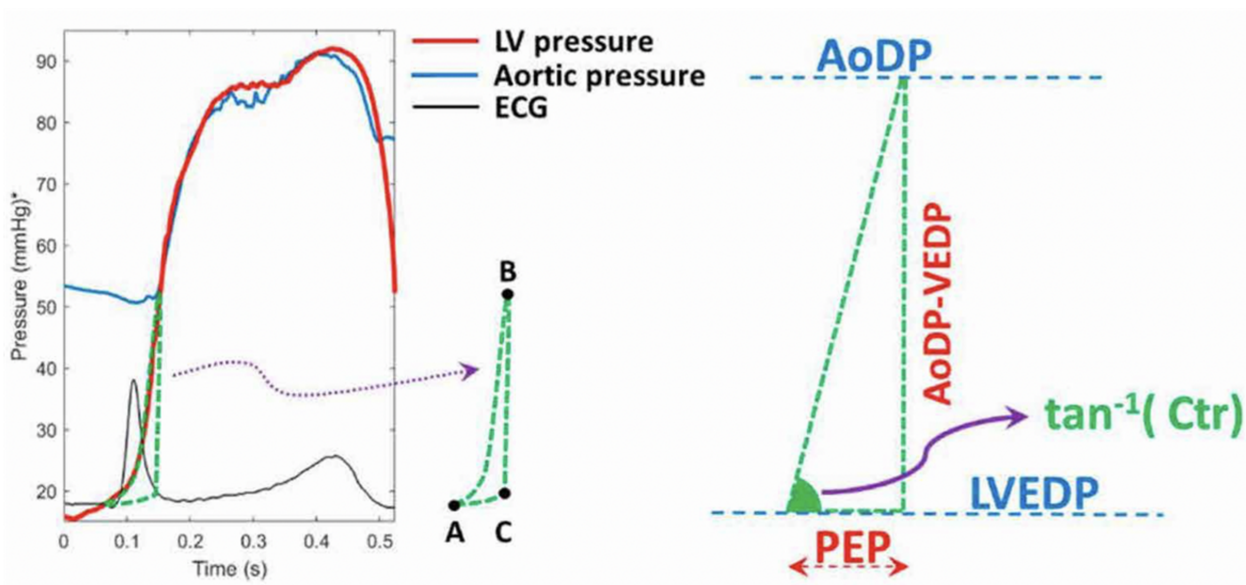
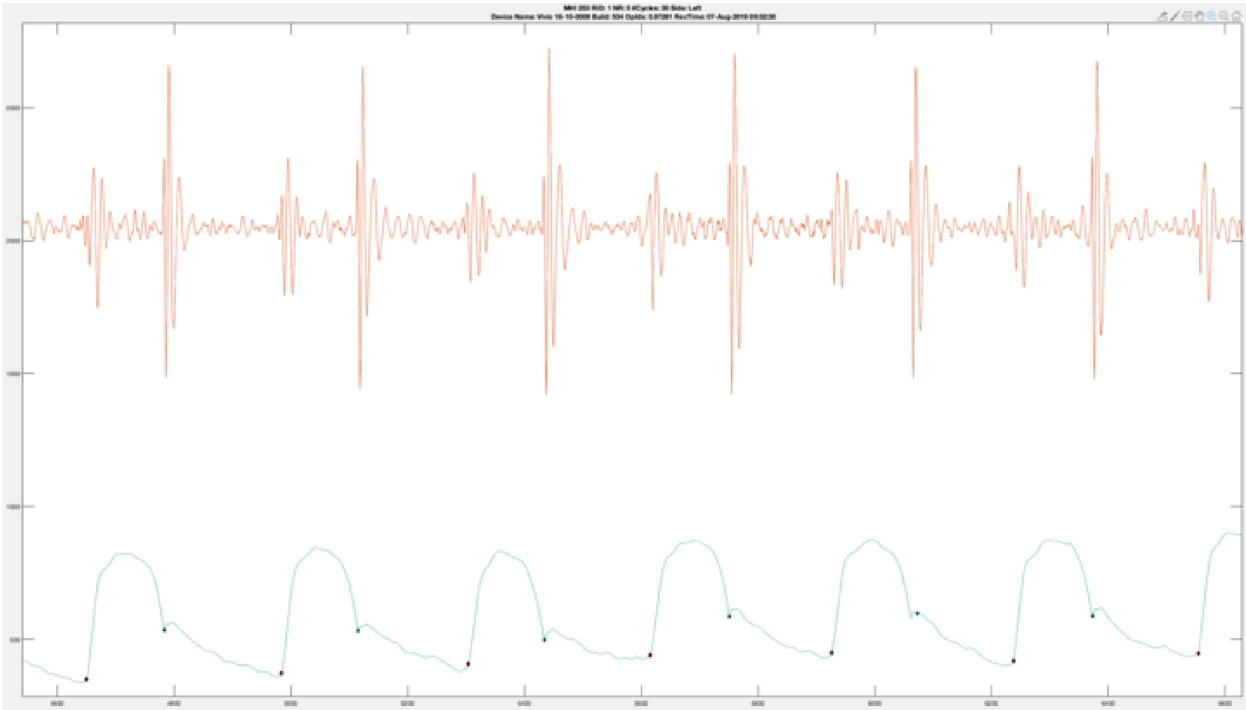


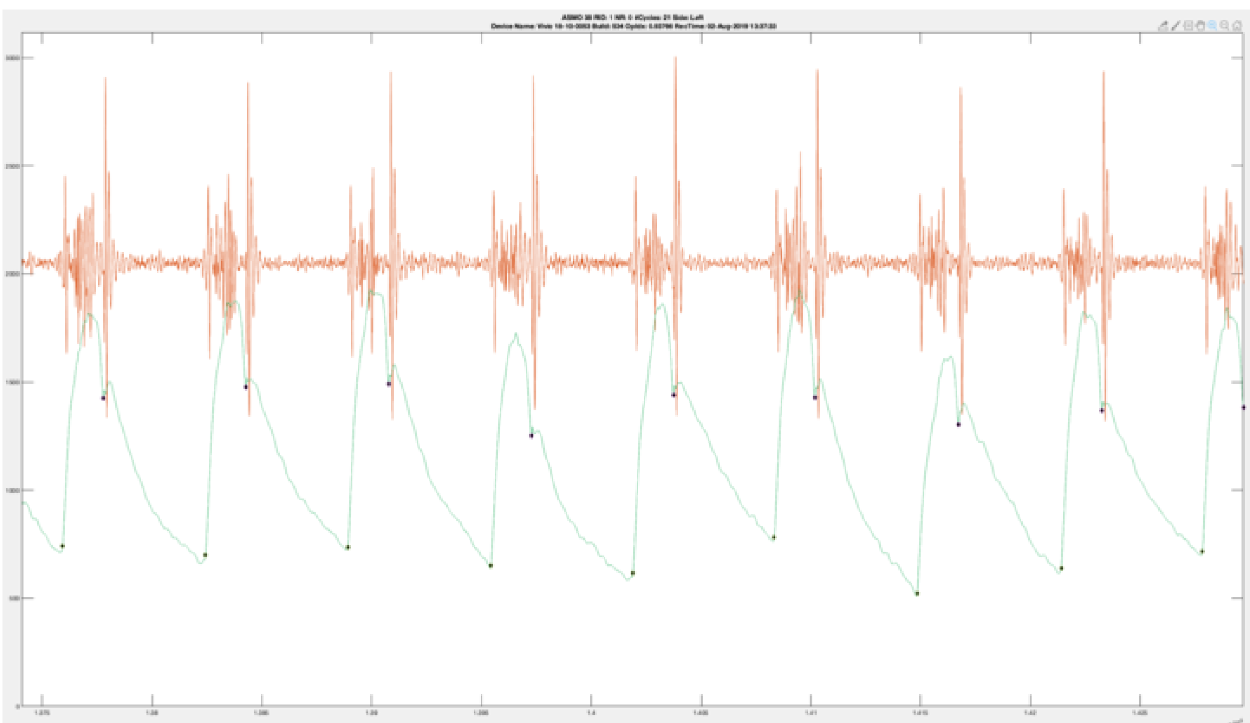
Figure 2. Evolution of the algorithms underlying Vivio diagnostic software. Left: Intrinsic Frequency Space shows the timing of oscillating frequencies in the cardiac cycle detected in the carotid waveform using sparse time frequency analysis. Right: IFs are used in the preliminary algorithm for measuring LVEDP from the carotid waveform and synchronized ECG. [From 1, 2]

-To describe ventricular function mathematically, the heart and aorta were treated as a coupled dynamical system—coupled when the aortic valve is open and decoupled with the AV closed.
-Sparse time frequency analysis was applied to the arterial waveform, revealing two sets of angular velocities (can be thought of as operating frequencies) in the waveform, called "Intrinsic Frequencies" or IF: ω_1 reflects the coupled system and ω_2 the aortic dynamics [3,4]
-IF methods assume that CV dynamics are nonlinear and non-stationary (unlike previous waveform analysis methods)
-IF methods were sufficient to derive LVEF from basic features of a non-calibrated waveform and ω_1 and ω_2 more accurately than 2D echo [1]
-However, the waveform features alone are insufficient for calculating LVEDP, which will require analysis of metrics of electrical-to-mechanical events, such as the pre-ejection period (PEP).
-Using IF metrics and PEP, a preliminary algorithm was constructed in yet a new mathematical framework, the cardiac triangle method (Niema Pahlevan PhD)
-The preliminary algorithm for using CTM to calculate LVEDP was compared to directly measured LVEDP in the cath lab at USC (Dr. Ray Matthews, Niema Pahlevan), showing reasonable performance (n=18, r=0.78) [5]
-Planned clinical study to develop LVEDP diagnostic will be cath-lab based, using Millar MikroCath (piezoelectric) catheters (inserted into the fluid-filled catheters) in patients scheduled for left heart cath.

Figure 3. Using sound function of Vivio for diagnosis of aortic stenosis



3A. Vivio data reconstructed from sensed vibrations (perturbation of the Vivio membrane) in a subject without aortic stenosis.



3B. Vivio data reconstructed from sensed signals captured at the carotid pulse in a subject with aortic stenosis.

-Unlike predicate phonocardiogram diagnosis of AS, based only on AI, the Vivio algorithm again starts with a physiologic model.

Conclusions and future work

-Challenges in moving new hardware + software from academic to commercial labs are many including automation of cycle quality metrics and cycle selection
-Although the first target market for Vivio diagnostics are PCPs (AS diagnosis to prompt referral for echocardiography) and cardiologists (LVEDP to determine next steps in pulmonary vs. cardiac work-up), the Vivio diagnostics should ultimately be useful for anesthesiologists for perioperative screening and monitoring
-Transition from Vivio diagnostics in the hands of HCW to home monitoring is anticipated for patients with heart failure, requiring construction of both physician and patient portals

References cited

1. Crit Care Med 2017; 45(7):1115
2. Fluids 2019, 4, 16.
3. Adv Adapt Data Anal 2011; 3:1-28
4. R Soc Open Sci. 2015 Dec 16;2(12):150475
5. Circulation 2018; 138 (Suppl1), abstract 16274

describe the heart-aorta as a coupled dynamical system, based on basic fluid dynamics studies of a unique human heart-aorta simulator at Caltech. These studies led to new measures to describe heart function using sparse time frequency representation [1] called intrinsic frequencies (IFs); IFs were then characterized in preclinical models and in clinical studies. IFs are not measures of flow or pressure, but reflect the operating frequency of the coupled heart-aorta with the aortic valve open (IF omega-1, reflecting contractility) and the operating frequency of the aortic tree (IF omega-2, reflecting afterload). All IFs are derived from an uncalibrated (non-invasively captured) arterial waveform using a new optical sensor ("Vivio") developed by Avicena, held over the carotid pulse, which also captures heart sounds for mathematical analysis.

Methods: Summary of studies showing that IF methods can accurately calculate important hemodynamic parameters. Using only information embedded in the non-invasively acquired carotid waveform, IF methods were used to calculate left ventricular ejection fraction (LVEF), using LVEF from cardiac MRI as the gold standard. IF methods performed more accurately than echocardiography in two studies [2,3] of adult patients with n=192 subjects total, using the cMRI gold standard (Bland-Altman analysis). With addition of ECG to the waveform, so that pre-ejection period (reflecting preload) can be used as a variable in the algorithm, these methods were extended to compare calculation of LV end-diastolic pressure (LVEDP) using Avicena algorithms to a published LVEDP database [4]. Again the algorithm (using a new Cardiac Triangle Mapping method) outperformed echo for estimating LVEDP in this pilot study [4]. IF methods can also be used to calculate pulse wave velocity [5]. Analysis of waveforms and sound with a different signal processing algorithm was used to develop an accurate rapid screening test for aortic stenosis [5], now being investigated in a multicenter, 510(k) enabling study.

Conclusions: Avicena's novel sensor device + software algorithms using new mathematical tools has potential for wide clinical application anywhere cell phones are available. The device requires no calibration and non-medical personnel are easily trained in its use. Vivio-captured waveforms and sound are displayed on an iPad (or phone), analyzed automatically for quality, and results are available in seconds after a few good-quality waveforms are captured. Results can then be sent wirelessly to a health care provider. The company's current focus is on outpatient heart failure monitoring, and aortic stenosis screening, but the diagnostics are well-suited to pre-operative screening and perioperative monitoring. This disruptive technology has potential to improve heart failure monitoring and lower cost of care of heart failure patients, and improve pre-operative screening.

1. Adv Adapt Data Anal 2011; 3:1-28
2. CCM 2017; 45(7):1115
3. Clin Cancer Res 2018; 24(13):3119
4. Fluids 2019, 4, 16.
5. ACC 2019 abstract #1238-460, New Orleans.