Non-Invasive Venous Waveform Analysis (NIVA) for Estimation of Pulmonary Capillary Wedge Pressure

By

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LIST OF ABBREVIATIONS

AUC = Area under the curve

BMI = Body mass index

CKD = Chronic kidney disease

CO = Cardiac output

EF = Ejection Fraction

GFR = Glomerular filtration rate

HF = Heart failure

HTN = Hypertension

LVEDV = Left ventricular end diastolic volume

MAP = Mean arterial pressure

NIVA = Non-Invasive Venous waveform Analysis

PAC = Pulmonary artery catheter

PAD = Pulmonary artery diastolic pressure

PCWP = Pulmonary capillary wedge pressure

PIVA = Peripheral Intravenous waveform Analysis

PVR = Pulmonary vascular resistance

RAP = Right atrial pressure

RHC = Right heart catheterization

RHF = right heart failure

ROC = Receiver Operating Characteristic

SNR = Signal to noise ratio

SVR = Systemic vascular resistance

Introduction:

Clinical Assessment of Intravascular Volume

Accurate assessment of intravascular volume status remains a challenge for clinicians. Pathological volume overload is particularly problematic in patients with heart failure (HF), renal failure, and in the critically ill population that is prone to over-resuscitation with crystalloid solutions. Such volume overload ultimately results in decreased cardiac output due to overstretching of the myocardium, hypertension, tissue and pulmonary edema, and increased morbidity and mortality.[1,2] Current measures of volume status rely largely on clinical signs which have proven unreliable including vital signs, jugular venous distention, subjective shortness of breath, weight changes, extent of peripheral edema, and laboratory values.[3]

Hemodynamic measures of volume status, though more accurate, are largely limited to the inpatient setting and require an invasive approach which limits their utility. Pulmonary capillary wedge pressure (PCWP) is the gold standard measure for volume status utilized by clinicians and represents left-sided cardiac filling pressures, a surrogate for preload. This is obtained through insertion of a Swan-Ganz catheter (PAC) into a central vein -- risking infection, arterial, or pulmonary injury. The catheter is then advanced past the right heart and into a terminal pulmonary artery which is occluded by a balloon for distal pressure measurements, associated with the low but finite risk of pulmonary artery rupture. Its use is supported by the observation that elevated cardiac filling pressures have been associated with increased hospitalizations and mortality,[4,5] and often precede the development of symptoms related to HF decompensation.[6] Other hemodynamic parameters that have more limited accuracy for estimation of volume status include absolute central venous pressure measurements,[7] absolute

peripheral venous pressure measurements,[8] and arterial waveform analysis [which is limited in accuracy to mechanically ventilated patients with high tidal volumes (>8cc/kg)].[9]

There has been increasing interest in developing non-invasive methods to estimate volume status for use in the inpatient and outpatient settings to guide volume management and prevent costly hospital readmissions. Thoracic impedance is one such method developed for this purpose. This technique quantifies the resistance encountered by an electrical current through the chest, with decreased resistance (lower values) corresponding to increased fluid content. Such devices demonstrate moderate correlation with PCWP,[10,11] but the specificity of static impedence measurements is limited by patient positioning,[12] body tissue (fat) composition,[13] presence of cutaneous hair or sweat, and lead placement. Other described techniques utilize changes with Valsalva in the pulse amplitude or slope of non-invasively obtained plethysmograph[14,15] or arterial signals[16-18], respectively. Although these techniques also have moderate to strong correlations with PCWP, performance of a sustained Valsalva maneuver may present difficulties in patients with shortness of breath due to congestion. Thus, there remains an unmet clinical need for accurate, reliable, easy to use, non-invasive technologies that assess volume status.

Venous Waveform Analysis

Venous waveform analysis has recently been developed as a novel, alternative approach for monitoring intravascular volume status. The venous system consists of the central venous compartment which contains ~18% of the total blood volume and the peripheral venous compartment which contains ~45%.[19] The peripheral venous system has a high capacitance and serves as the body's main blood volume reservoir. This is because the peripheral venous system

is more compliant (110 mL/mmHg) than the arterial (2 mL/mmHg) or even the central venous compartment (4 mL/mmHg).[20] In response to physiological demand, neurohumoral input of venous tone allows shifting of blood between the peripheral and central venous compartments in order to maintain cardiac stroke volume. The central venous waveform consists of various peaks and troughs representing forward and backward waves as blood flows through the heart. Peripheral venous waveform morphology differs from the central venous waveform, potentially due to the direction of the waveform (forward vs. backward compression wave), dampening related to the presence of valves, increased compliance, and/or distance from the heart (***Figure 1***).

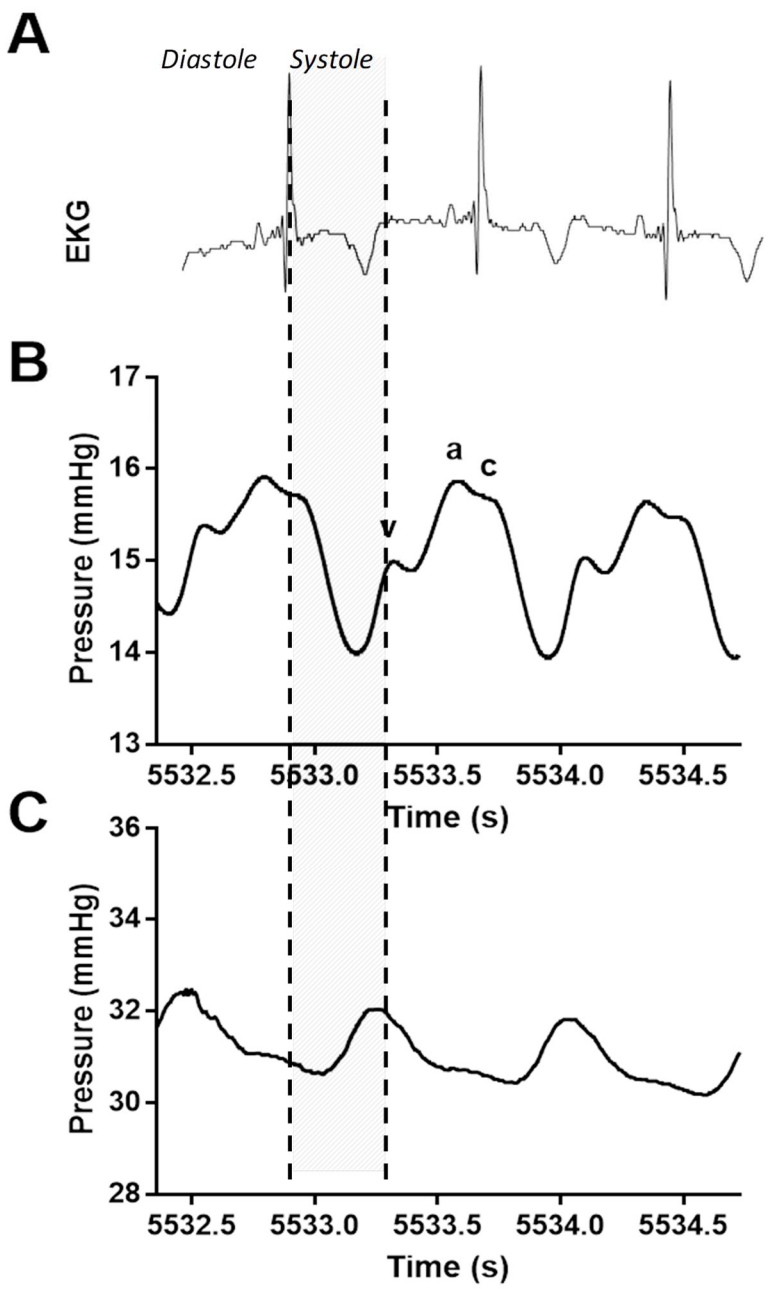

Figure 1 Comparison of central and peripheral venous waveforms. (A) Electrocardiogram (EKG) time-synced with directly transduced **(B)** central venous waveform obtained from the superior vena cava and **(C)** peripheral venous waveform obtained from the extremity in a pig. In the central venous waveform **(B)**, the a-wave corresponds to atrial contraction, which is followed by the c-wave which occurs due to bulging of the tricuspid valve during early systole. The v-wave occurs in late systole with filling of the right atrium.

Because the peripheral venous system serves as a volume reservoir, storing a majority of the total blood volume, it is a logical focus of technology aiming to estimate intravascular volume status. Acquisition of venous waveforms is most directly performed via direct transduction through a peripheral intravenous catheter. Venous signals may also be captured non-invasively with a piezoelectric sensor placed on the volar aspect of the wrist, directly over the superficial veins, known as Non-Invasive Venous waveform Analysis (NIVA, ***Figure 2***). The piezoelectric sensor is connected to a control box that amplifies the venous waveform detected from vibrations related to the low amplitude pulsatile flow of venous blood.

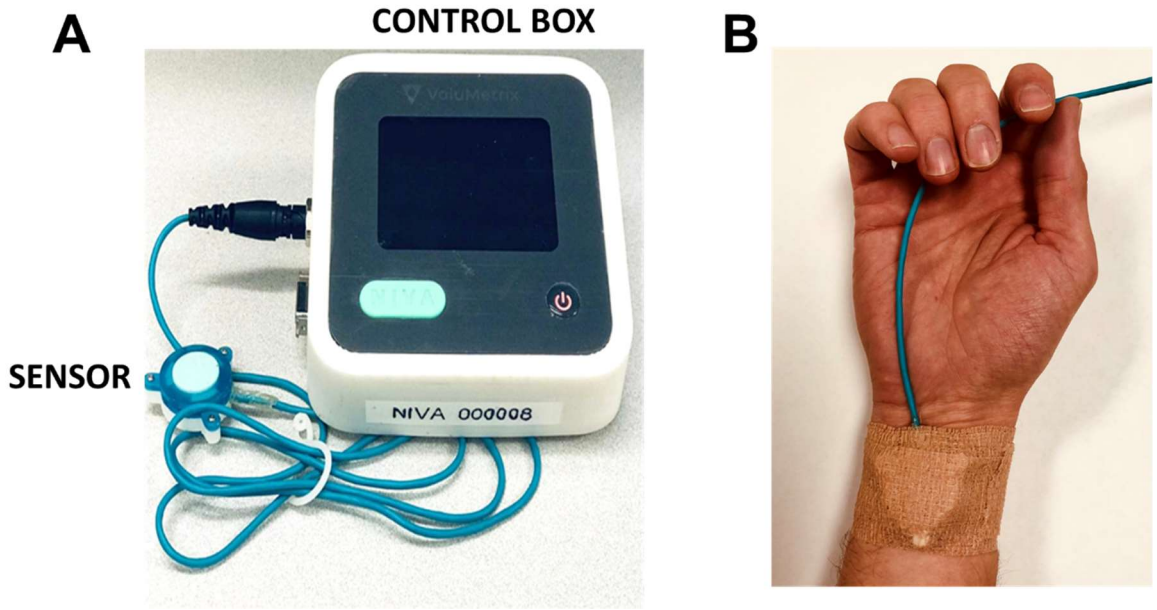

Figure 2 NIVA device. (A) Photograph of the NIVA device (sensor and control box) used for venous waveform capture. (B) Photograph of the NIVA device sensor placed on subject's wrist for waveform capture.

Mean peripheral venous pressures, which change minimally with volume due to the high compliance of peripheral veins, do not correlate strongly with PCWP.[8] Venous waveform parameters demonstrated in small studies to change with hypovolemia include time-domain parameters such as venous pulse pressure, mean venous pressure, pulse width, and maximum and minimum slope over the whole peak.[21] Analysis of the venous waveform in the frequency domain also yields predictable changes with changes in venous volume. Similar to other vascular waveforms, the raw venous signal is characterized most prominently by a wave generated by the cardiac cycle. Although this fundamental frequency (f_0), equal to the pulse rate is easily observed by eye in the time-domain, deconvolution of the waveform into the frequency domain with a Fourier transformation exposes additional frequencies which are not otherwise visible -- this includes a wave (low-frequency) generated by the respiratory cycle, as well as higher harmonics, or multiples, of the pulse rate (f_1-f_7, ***Figure 3***). The harmonics of the pulse rate are generated and transmitted as a result of local resonance, and therefore are more prominent in non-invasively obtained signals as the result of the soft tissue layer between the sensor and the vein. Ratiometric algorithms incorporating the relative amplitude or power contributions of these cardiac frequencies to their overall sum have been developed and validated in states of hypo- and hypervolemia in both directly transduced and non-invasively obtained waveforms.[22-26] These algorithms are referred to as Peripheral IntraVenous waveform Analysis (PIVA) in directly transduced waveforms and Non-Invasive Venous waveform Analysis (NIVA) in waveforms obtained non-invasively with a piezoelectric sensor placed on the wrist.

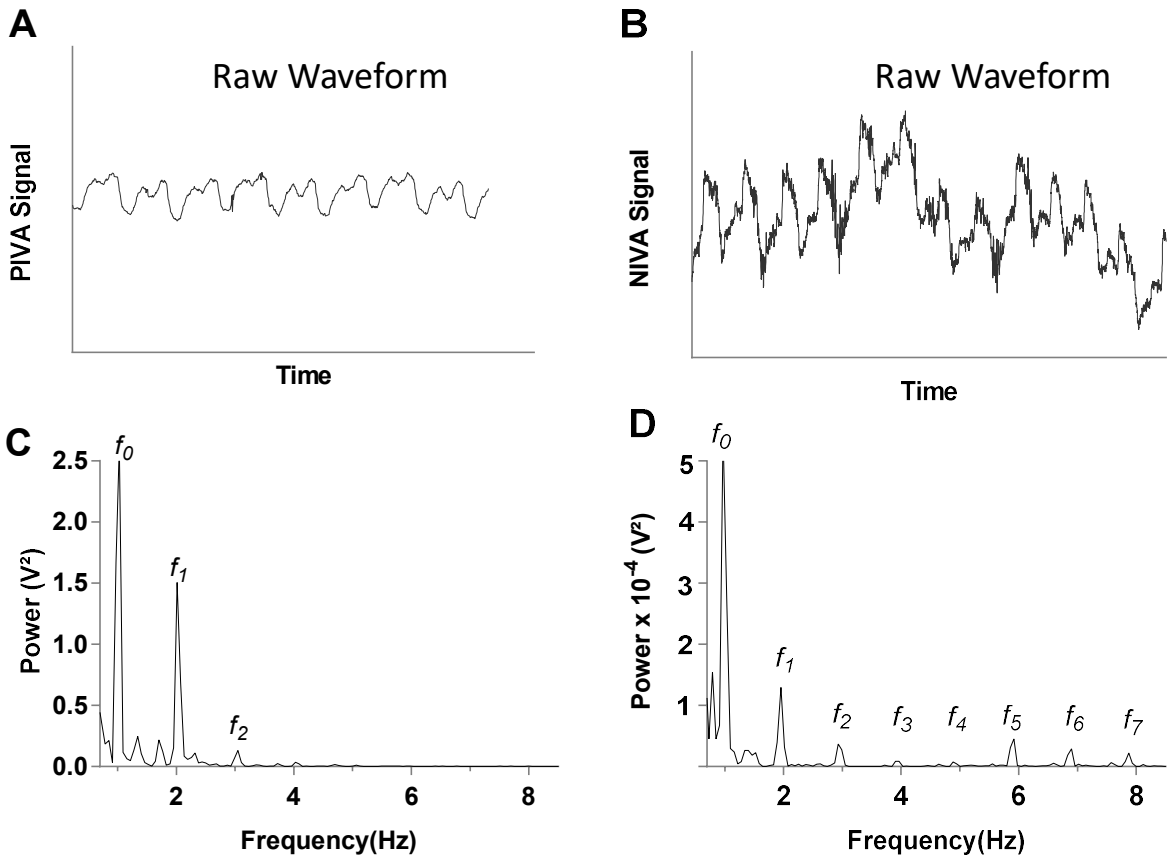

Figure 3 Representative venous waveform signals of a patient with volume overload (PCWP=28). **(A)** and **(C)** display the raw waveform and fast Fourier transform (FFT), respectively, of the peripheral intravenous pressure waveform (PIVA) obtained from an intravenous pressure transducer. **(B)** and **(D)** display the raw waveform and fast Fourier transform, respectively, of the peripheral venous waveform obtained noninvasively utilizing a piezo electric sensor (NIVA).

Current State of Non-Invasive Venous Waveform Analysis

NIVA holds particular promise as an easy to use, non-invasive method of venous waveform capture and analysis for assessment of volume status. In addition to the ability to detect small amounts of blood loss in normal human subjects donating blood (AUC 0.94, $p<0.05$),[22] an early prototype and algorithm have demonstrated strong correlation with a wide range of PCWP in patients undergoing elective right heart catheterization ($r=0.69$, $p<0.05$, $n=83$,

PCWP 4-40 mmHg) and ability to accurately predict PCWP >18 mmHg, a clinically accepted value indicating venous congestion, with a sensitivity of 80% and a specificity of 53%.[23] Subsequent technological improvements to improve signal acquisition have included the incorporation of a charge amplifier. With an improved prototype, the aim of this thesis was to use machine learning to refine an algorithm for estimation of PCWP from NIVA signals with the updated sensor. As input for algorithm development, non-invasively obtained venous signals were obtained from patients undergoing elective right heart catheterization. For comparison, the correlation between PCWP and thoracic impedance scores were also investigated (ZOE®).

Methods:

Cardiac Catheterization

Seventy-eight subjects undergoing elective right heart catheterization (RHC) were enrolled under approval from the University of Alabama Birmingham and Vanderbilt University Medical Center Institutional Review Boards. Indications for RHC included management of congestive heart failure, post-heart transplant biopsy, and workup for dyspnea. Subjects with severe valvular disease, active atrial fibrillation, congenital heart disease, or cardiac assist devices were excluded from this study.

The sensor of the NIVA device was secured to the middle volar aspect of the wrist overlying the superficial veins with Coban elastic wrap (3M; Minneapolis, MN). Placement laterality was preferential to an upper extremity without any existing peripheral IV lines. Signals were acquired for at least two minutes within one hour of catheterization keeping the extremity

still. All subjects were positioned in the semi-recumbent position (head of bed elevated to 30-60 degrees). Additional information obtained included demographic information, comorbidities, hemodynamic parameters obtained from the final catheterization report, and vital signs at the time of signal acquisition.

In twenty patients without visible chest hair, a ZOE® measurement was obtained per manufacturer's instructions. Prior to placement of the leads, it was ensured that the placement area was dry. Three consecutive ZOE® measurements were obtained and averaged for each subject.

RHC was performed by an experienced interventional cardiologist per standard protocol. An 8 French sheath was placed into either the internal jugular or femoral vein depending on anatomy. A 7 French Swan-Ganz catheter (Edwards Lifesciences; Irvine, CA) was introduced into the sheath and transducer was zeroed at the mid-axillary line. The Swan-Ganz catheter was positioned in the right heart system to record pressures and cardiac outputs. All subjects were spontaneously breathing with PCWP measurements obtained at end-expiration. RHC tracings were reviewed and PCWP values were assigned by an independent cardiologist. The PCWP values were assigned at an end expiratory measurement of the mean of the "a" wave, determined based on simultaneous electrocardiogram.

Signal Analysis

Data was collected using a three dimensional printed housing containing a mu rata piezoelectric sensor fashioned to the volar aspect of the wrist. This prototype device was attached via a cable to the monitoring data-logger device which used a low (~0.9 Hz) cutoff

frequency created by changing the input impedance on the charge amplifier. The data was then ported to a PC computer where an automated application (AlgorithmRunner.exe, ***Appendix A***) was used to determine the pulse rate as well as the power of various harmonics of the signal (f_0-f_7). This program used 50% overlapping 8K windows. The sampling rate for the device was 500 Hz. Adequate signal was defined as three or more signal segments with a signal to noise ratio estimation of greater than 20. This threshold was chosen based on previous data that examined the minimal threshold at which reproducibility of amplitude measurements with low variance could be obtained.

Algorithm Training

An algorithm was trained using data from 3-5 windows for each subject in Stata 16/IC (StataCorp; College Station, TX) to generate a "NIVA value" that estimates PCWP. In addition to heart rate, the raw powers of f_0-f_7 computed by the automated algorithm were used as input for model development, as well as calculated variables that included the relative power of each frequency, the ratio of each power to the power of f_0, and the high frequency component (sum of powers f_3-f_7) relative to total power or the power of f_0. Lasso technique was used to select and fit covariates to create a linear regression model. Lasso is a commonly used method invented by Tibshirani for building prediction models, and avoids overfitting by limiting the number of included predictor variables and minimizing an estimate of the out-of-sample prediction error.[27] Lasso orders models on a scalar parameter (λ) which is a parameter of the penalty function, defined over 0 to $+\infty$. A large λ corresponds to a large penalty and a model with few or no variables, while a model with smaller λ has more variables. Model selection was performed using cross-validation with ten folds to select a λ that minimizes an estimate of the out-of-sample

prediction error. Once a model was chosen, final predicted PCWP was calculated by averaging the NIVA values across the 3-5 windows for each subject.

Statistical Analysis

Statistical analysis was performed using Stata 16/IC (StataCorp; College Station,TX) and GraphPad Prism (GraphPad Software Inc.; La Jolla, CA). Results for continuous variables are reported as mean $\pm$ standard deviation. Pearson correlation coefficients were calculated for NIVA value compared to PCWP, pulmonary artery diastolic pressure (PAD), and right atrial pressure (RAP), as well as ZOE® value compared to PCWP. Residual analyses were performed to evaluate the effects of clinical right heart failure (RHF), systemic vascular resistance (SVR, Wood units), pulmonary vascular resistance (PVR, Wood units), cardiac output (CO, L/min), pulmonary hypertension (defined as mean pulmonary artery pressure $\geq$25 mmHg)[28], presence of diabetes, estimated glomerular filtration rate (GFR, mL/min/1.73m^2), heart rate, mean arterial blood pressure (MAP, mmHg), body mass index (BMI, kg/m^2), and wrist circumference (cm) on the predictive accuracy of NIVA to PCWP. Residuals were plotted as the standardized residual calculated from the linear regression of NIVA vs PCWP. Of note, SVR and PVR were recorded in the catheterization reports as Wood Units, with 1 Wood Unit = 80dynes*sec*cm^{-5}. A Receiver Operating Characteristic (ROC) curve was used to determine whether NIVA could predict clinical congestion, defined as a PCWP >18 mmHg, a threshold chosen based on prior literature defining a resting PCWP >18 mmHg as indicative of congestion and decompensation in heart failure. [3,29] P-values <0.05 were considered significant for all analyses.

Results:

Study Population

Of the 78 subjects enrolled, 23 (29.4%) were excluded due to a NIVA signal-to-noise ratio (SNR) <20 throughout the entire signal. An additional 5 (6.4%) were excluded because there were less than three windows with a SNR>20.

Demographic information for the analyzed cohort (n=50) and characteristics of excluded patients are displayed in ***Table 1.*** Mean age was 53 (±15) years, 64% of subjects were male, and 10 (20%) were black. Indications for RHC included heart failure evaluation in 15 (30%), post-cardiac transplant rejection surveillance in 28 (56%), or as diagnostic workup in 7 (14%). Of those patients undergoing RHC for heart failure evaluation that had an echocardiogram within the preceding year, ejection fraction was reduced (EF<40%) in 8 (53%) and preserved in 7 (47%).

Right Heart Catheterization (n= 78)			
	Included (n=50)	**Excluded (n=28)**	**p-value**
Age (years)	53 (±15)	60 (±13)	**0.04**
Gender			
Male	32 (64%)	17 (61%)	0.77
Female	18 (36%)	11 (39%)	
Race			0.25
Black	10 (20%)	2 (7%)	
White/Asian	39 (78%)	25 (93%)	
Other	1 (2%)	0	
BMI (kg/m^2)	31.1 (±9.2)	29.4 (±1.0)	0.06
Indication for RHC			
Diagnostic	7 (14%)	6 (21%)	0.36
Heart Failure Evaluation	15 (30%)	11 (39%)	
Transplant Follow-up	28 (56%)	11 (39%)	
Comorbidities			
Diabetes	20 (40%)	10 (36%)	0.71
HTN	34 (68%)	17 (61%)	0.52
CKD (GFR<60 mL/min)	29 (58%)	14 (50%)	0.43
Ejection Fraction			0.28
Reduced (EF<40%)	8 (17%)	7 (28%)	
Preserved (EF≥40%)	39 (83%)	18 (72%)	
Edema grade			0.86
0	31 (62%)	16 (57%)	
1	12 (24%)	8 (29%)	
2	4 (8%)	1 (4%)	
3	2 (4%)	2 (7%)	
4	1 (2%)	1 (4%)	
Heart rate (bpm)	83 (±16)	78 (±14)	0.18
Mean arterial pressure (mmHg)	93 (±13)	95 (±16)	0.45
Hemodynamic Data			
Pulmonary capillary wedge pressure (mmHg)	16 (±6)	14 (±6)	0.11
Cardiac output (L/min)	5.3 (±1.4)	4.7 (±1.2)	0.052
Right atrial pressure (mmHg)	8 (±4)	8 (±5)	0.77
Mean pulmonary artery pressure (mmHg)	24 (±7)	24 (±10)	0.85
Systemic vascular resistance (Woods Units)	18.4 (±5.4)	19.7 (±5.4)	0.34
Pulmonary vascular resistance (Woods Units)	2.01 (±1.31)	2.38 (±1.86)	0.40

Table 1. Characteristics of included and excluded right heart catheterization subjects. Data presented as mean (±SD) for continuous variables or count (%) for categorical variables.

PCWP measurements used in the analysis were those obtained from a post hoc independent review of the hemodynamic tracings. These correlated with PCWP measurements in

the computerized report (r=0.83, p<0.05, ***Figure 4***). PCWP in the analyzed cohort ranged from 7 to 30 mmHg, with a mean of 16 (±6) mmHg. Other hemodynamic indices obtained during catheterization are displayed in ***Table 1***. Other than age, no notable differences were noted between included and excluded subjects.

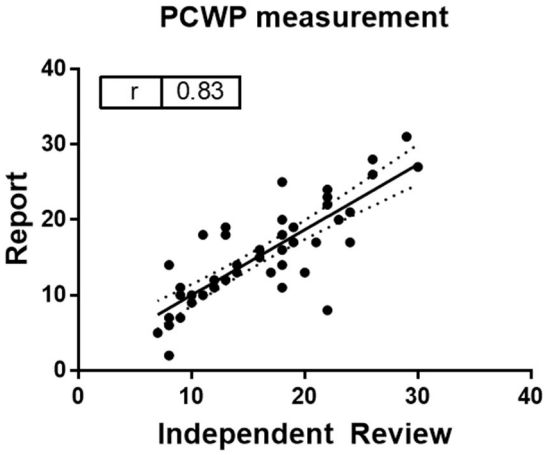

Figure 4 Correlation between pulmonary capillary wedge pressures (PCWP) obtained from report versus blinded review of hemodynamic waveform.

NIVA Algorithm

Of the 26 potential predictor variables included in the Lasso, 22 were included in the final model with a λ=0.015 selected (***Appendix B***). Goodness of fit of predictions using penalized coefficients from the selected model demonstrated an R-squared of 0.49. Final NIVA values demonstrated a significant positive correlation with PCWP (r=0.76, p<0.05, ***Figure 5A***). NIVA values also demonstrated a positive correlation with RAP (r=0.54, p<0.05, ***Figure 5B***) and PAD (r=0.60, p<0.05, ***Figure 5C***).

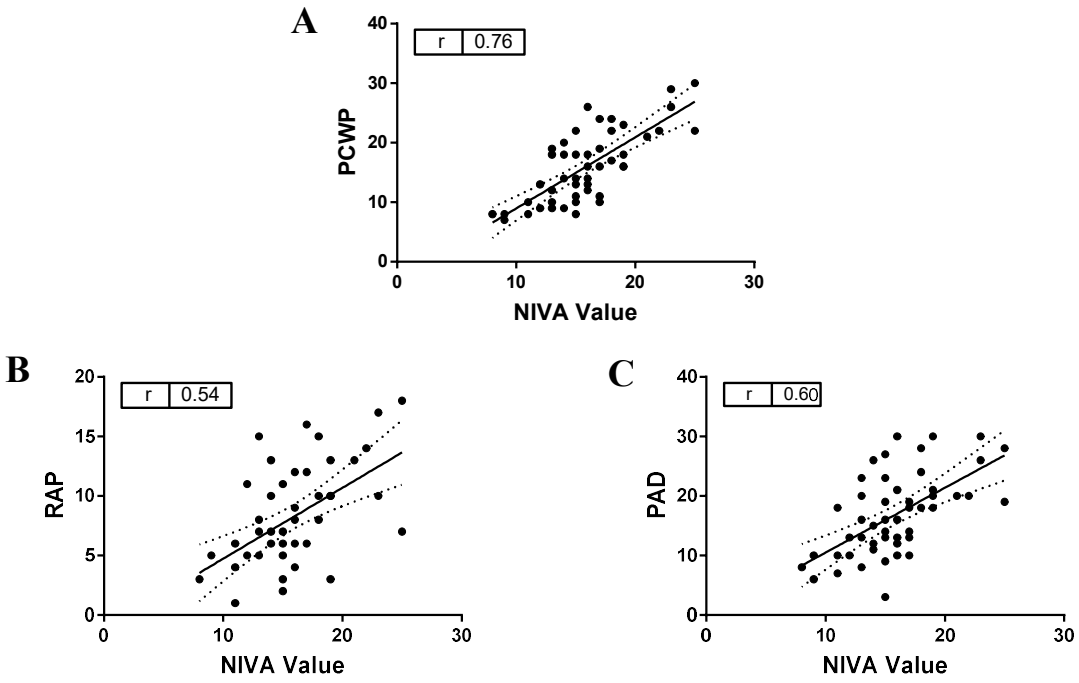

Figure 5 Correlation of NIVA value to measured PCWP, right atrial pressure (RAP) and pulmonary artery diastolic pressures (PAD) in subjects undergoing right heart catheterization. (A) NIVA values correlate with PCWP (mmHg) in elective right heart catheterization (n=115, r=0.89, p<0.05). **(B)** NIVA values correlate with right atrial pressure (n=114, r=0.60, p<0.05) and **(C)** pulmonary artery diastolic pressure (n=115, r=0.55, p<0.05) measurements (mmHg) in elective right heart catheterization. Abbreviations: NIVA= non-invasive venous waveform analysis, PCWP=pulmonary capillary wedge pressure, RAP= right atrial pressure, PAD= pulmonary artery diastolic pressure.

ROC analysis demonstrated that NIVA is able to identify a PCWP >18 mmHg with a sensitivity of 73% and a specificity of 80% (AUC=0.83, p<0.05, ***Figure 6***).

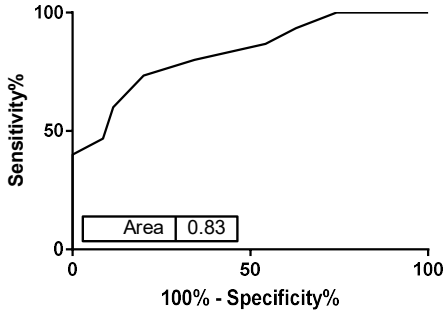

Figure 6 ROC curve for ability of NIVA to detect PCWP>18mmHg.

Residual analyses demonstrated that the accuracy of NIVA to predict PCWP was not significantly affected by SVR, PVR, CO, GFR, RHF, diabetes, BMI, wrist circumference, heart rate, or mean arterial pressure (***Figure 7***). Residuals were higher (mean 0.41 vs -0.38, $p<0.05$) in subjects with pulmonary hypertension.

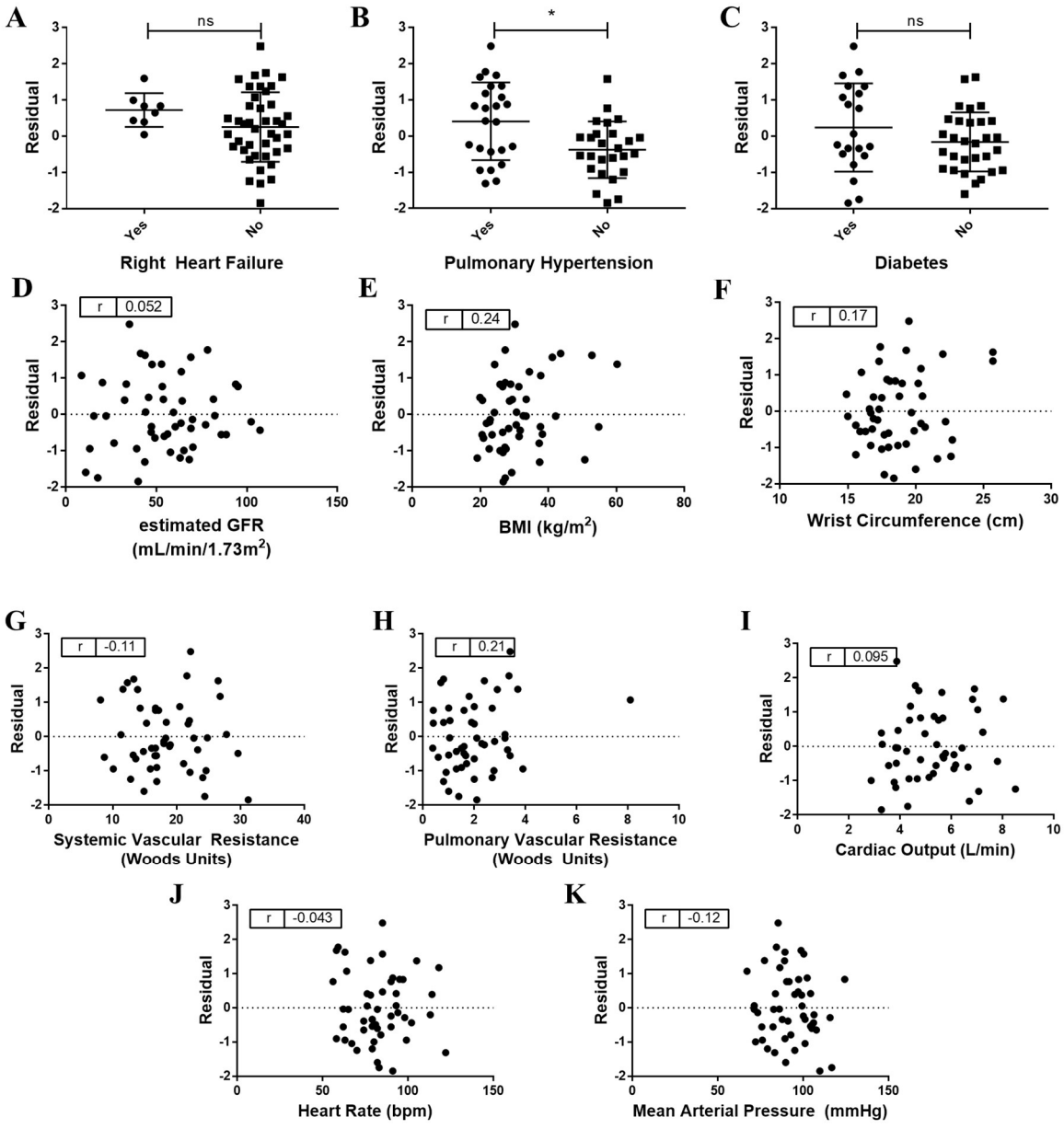

Figure 7 Predictive accuracy of NIVA to estimate PCWP based on clinical variables and catheterization data. * signifies p-value <0.05. All other correlations were nonsignificant (p>0.05). Pulmonary hypertension is defined as a mean pulmonary arterial pressure ≥ 25 mmHg.

Thoracic Impedance (ZOE®)

With impedance technology, lower resistance is associated with increased thoracic fluid content (thus, ZOE® values inversely correlate with volume status). ZOE® demonstrated a nonsignificant negative correlation with PCWP (r= -0.03, p=0.89, ***Figure 8***).

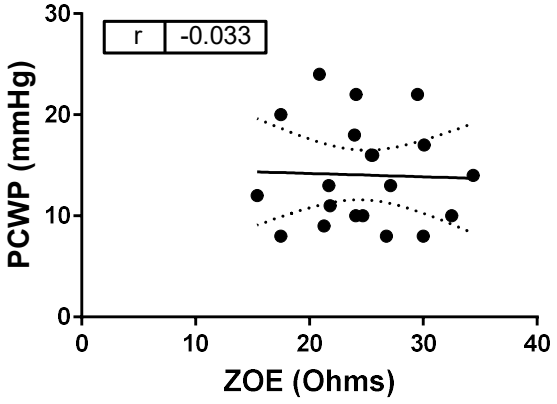

Figure 8 Correlation between ZOE® and PCWP. ZOE® did not correlate significantly with PCWP (r=-0.03, p=0.89, n=20)

Discussion:

The NIVA value is a numerical value generated from algorithmic analysis of the harmonics of peripheral venous waveforms derived from a non-invasive sensor. This report demonstrates the ability to use machine learning to generate an algorithm to calculate a NIVA value that estimates PCWP with a high degree of accuracy ($r=0.76$, $p<0.05$) over a range of clinical variables including systemic vascular resistance, pulmonary vascular resistance, and

cardiac output. Unlike PCWP, which requires invasive catheterization, NIVA is non-invasive and therefore may be used to monitor congestion in the inpatient, outpatient, and home settings with minimal risk. NIVA was able to detect a PCWP>18, clinically indicative of congestion, with a sensitivity of 73% and a specificity of 80% (AUC=0.83, $p<0.05$). These findings represent an improvement from the earlier prototype[23] and demonstrate the ability of venous waveform analysis to accurately and non-invasively estimate PCWP, which has the potential to help guide therapy in patients with heart failure in and out of the hospital.

The current clinical gold standard utilized by clinicians to assess volume status is pulmonary capillary wedge pressure, which represents left-sided cardiac filling pressures, a surrogate of preload, and carries inherent risks due to the invasive nature of the procedure. In 2005, data from the multicenter Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial was published evaluating 433 patients admitted with acute decompensated heart failure, assigned to receive therapy guided by clinical assessment alone or in conjunction with PAC targets.[30] Although use of the PAC demonstrated improvements in exercise and quality of life endpoints, patients in this cohort also had increased risk of adverse events with no differences in observed mortality. Therefore, although the routine use of PAC-obtained measurements in management of HF has not been established, the 2013 ACCF/AHA Guidelines for the Management of Heart Failure continue to support the use of invasive hemodynamic monitoring in select patient populations. These include "patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment" as well as patients with worsening renal function and/or persistently low systolic blood pressure in the setting of unclear fluid status.[31]

Additionally, there has been data to support the use of an implantable wireless pulmonary artery pressure monitor to guide outpatient management of HF to reduce hospitalizations. The CHAMPION trial (2010) evaluated patients with persistent NYHA Class III heart failure randomized to usual disease management strategies versus therapy guided by daily pressure measurements from an implanted pulmonary artery pressure monitor, and demonstrated a significant reduction in heart failure related hospitalizations in the latter group.[32] Therefore, these hemodynamic measurements, although risky to obtain, have clinical value in patient management and quality of life. Therefore, a device that could provide a similar measure while abolishing the risks involved with an invasive procedure has clear promise toward improving inpatient and outpatient care of patients with HF with expansion toward other disorders that lead to pathological alterations in intravascular volume. These results demonstrate that NIVA, a noninvasive device, correlates strongly with a wide range of PCWP (r=0.76) and PAD (r=0.60). Given these promising results, further studies are warranted to determine if the NIVA device can provide the same improved clinical outcomes as the invasive measures with which it correlates.

In comparison, the correlation between PCWP and existing thoracic impedance technology (ZOE®) was not significant. A limitation is that only a small number of enrolled patients lacked chest hair and were thus able to participate in obtaining an impedance measurement, and future comparisons should attempt to obtain a higher number of subjects. Impedance technology relies on downstream effects of congestion, such as pulmonary edema and intrathoracic fluid content, rather than estimation of intracardiac filling pressures, and it is unclear whether resolution of pulmonary edema correlates with complete intravascular decongestion.[33,34] Another difficulty in interpreting measures of thoracic impedance is that the output value (Ohms) is difficult to understand clinically as it does not equate to any existing

understood measures of intravascular volume, and the scale is inverse to volume status (lower number = higher intravascular volume). NIVA is simple to use and can provide a numeric output that predicts a widely understood clinical measure of intravascular volume, PCWP.

Though the algorithm used in this report was tailored to correlate with PCWP, which may raise the concern of overfitting, use of a Lasso regression model avoids overfitting by limiting the number of included predictor variables and minimizing an estimate of the out-of-sample prediction error. As displayed in ***Supplementary Table 1,*** selection of the described model using cross-validation has an estimated out-of-sample R-squared of 0.37 – future enrollment of patients undergoing RHC to generate a "test" dataset not involved in model training will be useful for validation of this algorithm and to determine a more accurate R-squared. Alternatively, future enrollment of a larger dataset with lasso model selection using the plugin estimator, rather than the cross-validation method, may further control for overfitting by calculating a value for λ that dominates the noise in the estimating equations, which results in fewer variables in the final model and ensures that the variables selected belong to the true model with high probability.

Data was obtained at a single institution (VUMC). The RHC population incorporated a wide range of demographics, BMI, and PCWP. Residual analysis demonstrated that prediction error was not altered over a range of systemic vascular resistance, pulmonary vascular resistance, cardiac output, heart rate, mean arterial blood pressure, and presence of diabetes (which may affect vessel compliance). Additionally, although a linear relationship between predictor variables and PCWP is assumed in the model development chosen for this study, future iterations of algorithm development may use more sophisticated machine learning techniques, such as neural networks, to better identify and quantify complex nonlinear relationships between waveform parameters and PCWP.

Limitations

The major limitation of this study is the large number of waveforms excluded due to signal noise, accounting for approximately one-third of enrolled subjects. This is almost certainly related to the low-amplitude nature of the peripheral venous signal (10-15 mmHg), which is easily obscured by motion artifact. A comparison of the included and excluded cohorts did not identify any other obvious explanations for poor signal quality in excluded subjects (***Table 1***). This suggests that ongoing improvements in sensor apposition, signal acquisition and amplification are required for future prototypes if they are to be used in awake patients. A SNR threshold of 20 was chosen for this study based on previous data that examined the minimal threshold at which reproducibility of amplitude measurements with low variance could be obtained. A minimum of three windows was also employed to enhance reproducibility during algorithm development. As newer prototypes are developed, these threshold values can be reassessed to ensure optimization of maximal signal capture with minimal signal variance. Potential future sensor and analysis improvements include incorporation of a photoplethysmograph to assist with validation of the pulse rate by the automated program, incorporation of an accelerometer to automatically discard signal segments with significant motion artifact, use of band or notch filters to attenuate signals due to respiration or motion, adjustment of amplifier gain, or attempts to subtract noise from the signal through incorporation of additional piezos to detect motion.

Strict exclusion criteria were utilized including subjects with active atrial fibrillation, congenital heart disease, or cardiac assist devices as it remains unclear whether accurate measurements can be obtained in these populations, and further studies are warranted to further investigate these. Although not relevant in this particular study population, the effect of

vasoactive drugs and altered venous tone on the venous signal also remains incompletely understood. Henry et al. demonstrated that isoflurane, a vasodilating volatile anesthetic, affects the peripheral venous waveform morphology in a dose-dependent manner, which may directly impact waveform analysis.[35] Further studies are needed to quantify these effects and how they may affect assessment of volume. Another limitation of this study is that inherent to the question of whether PCWP accurately reflects left ventricular end-diastolic volume (LVEDV),[35] however this correlate was chosen given the improved clinical outcome data described earlier as well as its relative availability for ease of data collection and objectivity over radiographic measures of LVEDV, which may be more user-dependent. Another inherent limitation in comparison of NIVA to PCWP lies in the reproducibility and accuracy of PCWP measurements.[35] To overcome this, PCWP measurements were analyzed in patients undergoing RHC, a controlled setting, and tracings reviewed by an independent, blinded cardiologist.

Conclusion

NIVA is a promising non-invasive technology for estimation of volume status. This study demonstrates a process of iterative algorithm development as the sensor is modified and improved, resulting in an improved correlation with PCWP and specificity in detection of congestion. Machine learning is used to incorporate the amplitude changes of the cardiac component of the venous waveform, a fundamental concept of venous waveform analysis for volume assessment, toward estimation of a clinical gold-standard, PCWP. Further validation of this algorithm in a separate test set is needed. Importantly, this study also highlights that ongoing improvements in signal acquisition and reduction of noise are still required. As the device is

updated, and this process repeated, additional machine learning techniques such as neural networks may be used to improve accuracy through identification of complex nonlinear relationships between waveform parameters and volume status.

Potential Impact and Future Directions

Future applications for a user-friendly, non-invasive device that can accurately estimate volume status are broad, including in resource scare environments and the inpatient and outpatient settings. The ability to quickly identify and guide resuscitation in life-threatening states of hypovolemia, such as that due hemorrhage, would have great impact not only in the hospital and operating room, but for emergency triage, in combat, and globally. Dehydration, another etiology of hypovolemia, is rampant in the elderly, athletes, and worldwide secondary to malnutrition, malignancy, and gastrointestinal illness. To be most useful, application of NIVA to these settings may also benefit from expansion of the current device output. For example, development of an algorithm that quantifies *rate* of volume loss may be more practical in the setting of hemorrhage; this could be elucidated first in a porcine model of controlled hemorrhage and subsequently validated in human studies. In a small number of patients undergoing hemodialysis, rate of volume loss as detected by an early NIVA prototype has demonstrated the ability to predict intradialytic hypotension – highlighting a potential use for NIVA to guide both ultrafiltration amounts and rate.[36]

Prevention and treatment of volume overload, or congestion, is an every day worry in the inpatient and outpatient setting for patients with heart failure or end stage renal disease.

Hemodynamic congestion and pulmonary edema may also occur in the acute setting as a complication of sepsis and critical illness; early identification has the potential to improve outcomes and prevent progression to respiratory failure and prolonged intubation. Additionally, in the setting of highly contagious infectious disease (i.e. COVID-19), a non-invasive device that can be monitored from a distance may assist in guiding care for critically ill patients while minimizing provider contact and potential exposure. Future studies in these populations are warranted to define the areas in which NIVA can improve clinical care.

For the use of NIVA to be practical and safe in such a wide assortment of clinical pathology, further work toward understanding additional physiologic parameters that may be altered by disease and affect non-invasively obtained venous waveforms are required. Local resonance of the venous waveform through soft tissue results in amplification of the higher harmonics of the pulse rate in non-invasively obtained signals compared to directly transduced waveforms (***Figure 3***). In clinical states of volume overload, varying degrees of edema alter the stiffness of the extravascular tissue in between the vein and NIVA sensor, potentially altering the amplitudes of the higher harmonics. Vessel compliance, altered by venous tone, may also affect the transmission of these higher harmonics.

Future work will examine these potential effects with an *in vivo* porcine model and an *ex vivo* hemodynamic flow loop. Phenylephrine, a vasoconstrictor, or sodium nitroprusside, a vasodilator, can be administered during controlled blood loss or crystalloid volume overload in a porcine model to determine the effect of venous tone on captured venous waveforms at various volume states. Venous compliance will be measured through diameter and pressure changes recorded with an intravenous ultrasound (ComboWireXT, Philips). Ongoing work is also

underway to design a hemodynamic flow loop (***Figure 9***) for controlled benchtop tuning of physiologic parameters that may confound or differentially affect the NIVA signal. This will consist initially of a single synthetic vein construct with tunable dimensions and mechanical properties to reflect altered compliance and tone, and will eventually be expanded to include an arterial and microvascular system. Sacrificial molding with ice allows for the creation of freestanding hierarchal synthetic vessels from a variety of natural or synthetic polymers, with wall thickness determined by dipping time.[37] Alternatively, vessel scaffolds can be created using a 3-D printer. These synthetic vessels will be embedded in a poly-vinyl alcohol (PVA) hydrogel that represents soft tissue. A 6% PVA hydrogel mimics normal fatty tissue and will be covered by a 2mm layer of 10% PVA hydrogel to mimic skin.[38,39] The effect of soft tissue mechanical properties on the NIVA signal will be investigated through variation in PVA concentration to represent altered levels of edema. A physiological flow pump (Compuflow 1000, Simutec) will be used that contains a database of pre-programmed waveforms and also allows user input of venous waveforms obtained directly from patients. 40% glycerol solution will be used as a blood-mimicking fluid.

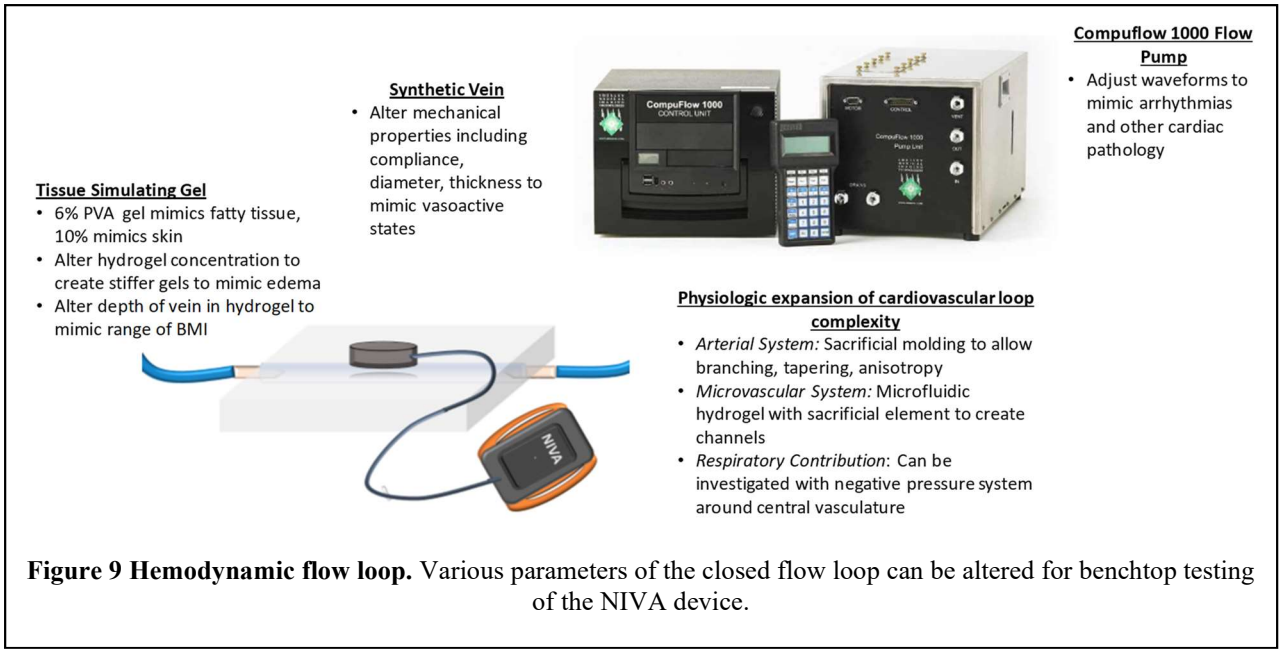

Figure 9 Hemodynamic flow loop. Various parameters of the closed flow loop can be altered for benchtop testing of the NIVA device.

The closed flow loop will also assist with device testing in the setting of various arrhythmias, which can be programmed using the pump. Atrial fibrillation, the most common arrhythmia in patients with heart failure, is characterized by an irregularly irregular heart rate. This results in multiple peaks corresponding to f_0 and its harmonics (***Figure 10***). It is unknown at this time whether NIVA can accurately estimate volume status in these patients. The flow loop will assist with determining whether NIVA can consistently differentiate between atrial fibrillation (or other arrhythmias) and normal sinus rhythm, and whether the NIVA algorithm can be accurately tailored to this setting. After defining the noise floor to identify "true peaks", examples of power estimation at each frequency for analysis include direct summation of peak amplitudes or calculation of the integral of a gaussian curve fit to the peaks.

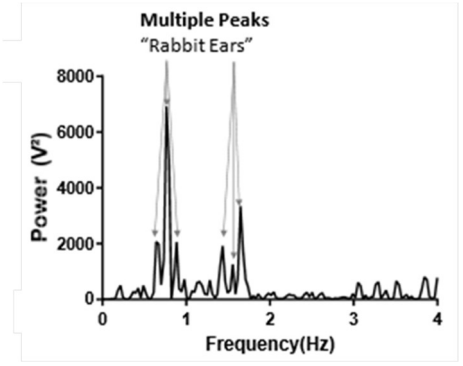

Figure 10 NIVA signal obtained from patient with atrial fibrillation. Frequency distribution demonstrates multiple peaks corresponding to the pulse rate and its harmonics.

In conjunction with additional clinical validation studies, these *in vivo* and *in vitro* experiments will help ensure the safe and accurate broadening of future clinical applications for the NIVA device.

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APPENDIX

Appendix A: C++ Script for AlgorithmRunner.exe

```
Usage: algorithmRunner <path> [-e <file extension>] [-o <path>] [-s <value>]
Must include input path

options:
    -e  Supply file extension, program will find analyze all files found in -- if
omitted '.txt' is used -- '.rene' for niva/ppg analysis
    -o  Supply output path for analysis file to be stored -- if omitted input path
is used
    -s  Supply start sample, number of lines to skip at the beginning of the file -
- if omitted 25 is used
    -x  1 for extended algorithm output, 0 for normal output
    -d  1 to enable taking the derivative of the input signal before analysis, 0
for normal input
```

```
/**
 *  @file: main.cpp
 *
 *  @date: Sep 5, 2018
 *  @author: Volumetrix, Jonathan Whitfield
 *
 *  @copyright Copyright (c) 2018 VoluMetrix LLC
 *
 *  All Rights Reserved.
 *
 *  All information contained herein is, and remains the
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 *
 */

#include <string>
#include <vector>
#include <iostream>
#include <istream>
#include <fstream>
#include <iterator>
#include <algorithm>
#include "dirent.h"
#include <map>
#include <string.h>
#include <sys/types.h>
#include <sys/stat.h>

#include "algorithm.hpp"
#include "fir.hpp"
#include "ppg_detection.hpp"

typedef struct {
    std::string absolutePath;
```

```
    std::string fileName;
}inputFile_t;

typedef struct {
    inputFile_t niva;
    inputFile_t ppg;
}nivaPpgFilePair_t;

/**
 * @ingroup algorithm-host
 * @{
 */

typedef enum {
    TXT = 0,
    AFE,
    RAW,
    RENE,
    OTHER,
}FileType_t;


float getStd(float * data, size_t len, float mean) {
    float sum = 0.0f;

    /* sanity check */
    if (len < 1) {
        return NAN;
    }

    /* sum sample minus mean squared */
    for (int i = 0; i < (int)len; i++) {
        float temp = data[i] - mean;
        sum += temp * temp;
    }

    /* scale ny number of samples */
    sum /= (float)len;

    /* square root for standard deviation */
    return (float)std::sqrt(sum);
}


static constexpr float PPG_SCALE              = 5.72204589843750e-07;
static constexpr float NIVA_SCALE             = 2.88486480712891e-07;  //!< (2.42 / 2^23)

/**
 * @brief Print help for the program to the console
 */
void printHelp() {
    std::cout << std::endl;

    std::cout << "Usage: algorithmRunner <path> [-e <file extension>] [-o <path>] [-s <value>]"
<< std::endl;

    std::cout << "Must include input path" << std::endl << std::endl;

    std::cout << "options: " << std::endl;
    std::cout << "\t-e\tSupply file extension, program will find analyze all files found in -- if
omitted '.txt' is used -- '.rene' for niva/ppg analysis" << std::endl;
    std::cout << "\t-o\tSupply output path for analysis file to be stored -- if omitted input
path is used" << std::endl;
    std::cout << "\t-s\tSupply start sample, number of lines to skip at the beginning of the file
-- if omitted 25 is used" << std::endl;
    std::cout << "\t-x\t1 for extended algorithm output, 0 for normal output" << std::endl;
    std::cout << "\t-d\t1 to enable taking the derivative of the input signal before analysis, 0
for normal input" << std::endl;
}

/**
```

```
 * @brief Parse input arguments for a
 * @param argc: argument count
 * @param argv: argument array
 * @param option: option to search for
 * @return empty string on failure
 */
const std::string getOption(int argc, char * argv[],
        const std::string option) {

    /* populate options */
    std::vector<std::string> inputs;
    for(int i = 1; i < argc; i++) {
        inputs.push_back(std::string(argv[i]));
    }

    std::vector<std::string>::const_iterator itr;
    itr =  std::find(inputs.begin(), inputs.end(), option);

    /* check that we found the option and an option parameter exists */
    if( itr != inputs.end() && (itr + 1) != inputs.end() ) {
        /* return option */
        return *(++itr);
    }

    static const std::string empty("");
    return empty;
}

/**
 * @brief Check if path is an actual directory
 * @param path: path to check
 * @return: non-zero if path is not a directorys
 */
int directoryExists(const std::string& path) {
    DIR * dir = opendir(path.c_str());

    if(dir != nullptr) {
        return 0;
    }

    return -1;
}

/**
 * @brief Get list of files in directory of a given file type
 * @param path: path to directory
 * @param extension: file extension to filter by
 * @param files: output list of files
 * @return number of files found in directory
 */
int getFilesForDirectory(const std::string& path, const std::string& extension,
        std::vector<std::string>& files) {
    DIR * dir = opendir(path.c_str());
    struct dirent * d;
    while( (d = readdir(dir)) != nullptr) {
        std::string fName = d->d_name;
        std::size_t found = fName.find(extension);

        if(found != std::string::npos) {
            files.push_back(fName);
        }
    }
    closedir(dir);

    return files.size();
}

int getFileSize(const std::string &fileName) {
    std::ifstream file(fileName.c_str(), std::ifstream::in | std::ifstream::binary);

    if(!file.is_open()) {
```

```
        return -1;
    }

    file.seekg(0, std::ios::end);
    int fileSize = file.tellg();
    file.close();

    return fileSize;
}

/**
 * @brief Get list of files in directory of a given file type
 * @param path: path to directory
 * @param extension: file extension to filter by
 * @param files: output list of files
 * @return number of files found in directory
 */
int getFilesForDirectory(const std::string& path, const std::string& extension,
        std::vector<inputFile_t>& files) {
    DIR * dir = opendir(path.c_str());
    if(dir == nullptr) {
        return -1;
    }
    struct dirent * d;
    while( (d = readdir(dir)) != nullptr) {
        std::string fName = d->d_name;
        std::size_t found = fName.find(extension);

        if(found != std::string::npos) {
            inputFile_t file;
            file.absolutePath = std::string(path);
            if(file.absolutePath.back() != '/') {
                file.absolutePath.append("/");
            }
            file.absolutePath.append(fName);
            file.fileName = fName;

            files.push_back(file);
        } else if (directoryExists(fName)) {
            std::string downPath = std::string(path);
            if(downPath.back() != '/') {
                downPath.append("/");
            }
            downPath.append(fName);
            getFilesForDirectory(downPath, extension, files);
        }
    }
    closedir(dir);

    return files.size();
}

int getRawFilesForDirectory(const std::string& path, std::vector<inputFile_t>& files) {
    DIR * dir = opendir(path.c_str());
    if(dir == nullptr) {
        return -1;
    }
    struct dirent * d;
    while( (d = readdir(dir)) != nullptr) {
        std::string fName = d->d_name;
        std::string fPath = ((std::string)path).append(fName);

        /* No file extension */
        std::size_t found = fName.find(".");

        if(found == std::string::npos && (getFileSize(fPath) != 0) ) {
            inputFile_t file;
            file.absolutePath = std::string(path);
            if(file.absolutePath.back() != '/') {
                file.absolutePath.append("/");
            }
```

```
            file.absolutePath.append(fName);
            file.fileName = fName;

            files.push_back(file);
        } else if (directoryExists(fName)) {
            std::string downPath = std::string(path);
            if(downPath.back() != '/') {
                downPath.append("/");
            }
            downPath.append(fName);
            getRawFilesForDirectory(downPath, files);
        }
    }

    closedir(dir);

    return files.size();
}

int getReneFilesForDirectory(const std::string& path, std::vector<nivaPpgFilePair_t>& files) {
    DIR * dir = opendir(path.c_str());
    if(dir == nullptr) {
        return -1;
    }
    struct dirent * d;
    while( (d = readdir(dir)) != nullptr) {
        std::string fName = d->d_name;
        std::string fPath = ((std::string)path).append(fName);

        /* No file extension */
        std::size_t found = fName.find(".niva");

        if(found != std::string::npos && (getFileSize(fPath) != 0) ) {
            /* Extract NIVA file */
            inputFile_t nivaFile;
            nivaFile.absolutePath = std::string(path);
            if(nivaFile.absolutePath.back() != '/') {
                nivaFile.absolutePath.append("/");
            }
            nivaFile.absolutePath.append(fName);
            nivaFile.fileName = fName;

            inputFile_t ppgFile;
            ppgFile.absolutePath = std::string(path);
            if(ppgFile.absolutePath.back() != '/') {
                ppgFile.absolutePath.append("/");
            }

            std::string ppgName = fName.substr(0, fName.length() - 4);
            ppgName.append("ppg");
            ppgFile.absolutePath.append(ppgName);
            ppgFile.fileName = ppgName;

            nivaPpgFilePair_t filePair = {nivaFile, ppgFile};

            files.push_back(filePair);
        } else if (directoryExists(fName)) {
            std::string downPath = std::string(path);
            if(downPath.back() != '/') {
                downPath.append("/");
            }
            downPath.append(fName);
            getReneFilesForDirectory(downPath, files);
        }
    }

    closedir(dir);

    return files.size();
}
```

```
/**
 * @brief Write header to analysis file
 * @param fileStream: open file stream to write to
 * @return non-zero on failure
 */
int writeResultsHeader(std::ofstream& fileStream) {
    if(fileStream.is_open()) {
#ifdef TASK
        fileStream << "Time [s]\t\tSNR\t\tRMS\t\tPR\t\tPPG_PR\t\tNIVA\t\tERROR" << std::endl;
#else
        fileStream <<
"time\tniva_score\tsnr\tpulse_rate\tpulse_rate_ppg\tf0\tf1\tf2\tf3\tf4\tf5\tf6\tf7\ta0\ta1\ta2\ta
3\ta4\ta5\ta6\ta7\trms\thf\tclassifier\t+30\terror\n";
#endif
        return 0;
    }
    return -1;
}

/**
 * @brief Parse line with given delimiter
 * @param line: line to parse
 * @param delim: delimiter to parse file
 * @param lineContents: output vector of contents after parsing
 * @return non-zero on failure
 */
int readFromLine(std::string line, char delim, std::vector<std::string>& lineContents) {
    std::stringstream ss(line);
    std::string item;
    while( std::getline(ss, item, delim) ) {
        lineContents.push_back(item);
    }

    return 0;
}

/**
 * @brief Callback for algorithm
 * @param results: results strucure from algorithm
 * @param outputFile: pointer to output file stream to write results to
 * @return None
 */
static void processResults(Algorithm::Results_t results, void * outputFile) {
    std::pair<std::string, std::ofstream*> * resultsPair =
            (std::pair<std::string, std::ofstream*> *)outputFile;
    std::ofstream * nivaResults = resultsPair->second;

//    float nivaScore = (2 * results.amp[0] +
//            0.4 * results.amp[1] +
//            0.2 * results.amp[2] ) /
//                    (results.amp[0] + results.amp[1] + results.amp[2]);

    float hf = (results.amp[3] + results.amp[4] + results.amp[5] + results.amp[6] +
results.amp[7]) /
            (results.amp[0] + results.amp[1] + results.amp[2] + results.amp[3] + results.amp[4] +
                    results.amp[5] + results.amp[6] + results.amp[7]) * 100;

    if(nivaResults->is_open()) {
        /* time */
        *nivaResults << (results.startSample * .002) << "\t";
        /* niva score */
        *nivaResults << results.nivaScore << "\t";
        /* signal to noise */
        *nivaResults << results.snr << "\t";
        /* pulse rate */
        *nivaResults << results.freq[0] * 60 << "\t";
        /* ppg pulse rate */
        *nivaResults << results.ppgPulseRate << "\t";

        /* Frequencies */
        for(int i = 0; i < Algorithm::NUM_HARMONICS + 1; i ++) {
```

```
            *nivaResults << results.freq[i] << "\t";
        }

        /* amplitudes */
        for(int i = 0; i < Algorithm::NUM_HARMONICS + 1; i ++) {
            *nivaResults << results.amp[i] << "\t";
        }

        *nivaResults << results.rms << "\t";

        *nivaResults << hf << "\t";

        *nivaResults << results.classifier << "\t";

        *nivaResults << results.niva30plus << "\t";

        *nivaResults << results.errorFlags.errorFlags << "\t";

        *nivaResults << std::endl;
    }
}

static constexpr uint32_t NUM_CLEAN_WINDOWS   = 15;  //!< Number of clean windows
static constexpr uint32_t MAX_NUM_WINDOWS     = 30; //!< Maximum number of windows
static constexpr uint32_t SNR_THRESH_DEFAULT  = 20; //!< Signal to Noise Ratio default threshold
static constexpr uint32_t NUM_WIN_ABOVE_HIGH_THRESH = NUM_CLEAN_WINDOWS / 2;

static constexpr uint32_t NUM_THRESHOLDS      = 3;

static constexpr uint32_t SNR_THRESH_ONE      = SNR_THRESH_DEFAULT;
static constexpr uint32_t SNR_THRESH_TWO      = 40;
static constexpr uint32_t SNR_THRESH_THREE    = 60;

static constexpr uint32_t SNR_COUNT_ONE       = 15;
static constexpr uint32_t SNR_COUNT_TWO       = 10;
static constexpr uint32_t SNR_COUNT_THREE     = 5;

typedef struct SnrThreshold_t{
    int thresholdSnr;
    int thresholdCount;
    int count;
    bool exceededThreshold;
} SnrThreshold_t;

typedef struct IncomingResults_t {
    uint32_t count;
    SnrThreshold_t snrThreshold[NUM_THRESHOLDS];
    Algorithm::Results_t results[MAX_NUM_WINDOWS];

    void reset() {
        count = 0;
        memset(results, 0x00, sizeof(Algorithm::Results_t) * MAX_NUM_WINDOWS);

        snrThreshold[0] = {SNR_THRESH_ONE, SNR_COUNT_ONE, 0, false};
        snrThreshold[1] = {SNR_THRESH_TWO, SNR_COUNT_TWO, 0, false};
        snrThreshold[2] = {SNR_THRESH_THREE, SNR_COUNT_THREE, 0, false};
    }
} IncomingResults_t;

IncomingResults_t mHighResults;     //!< High results
IncomingResults_t mLowResults;      //!< Low results
IncomingResults_t mValidResults;    //!< All valid results

uint32_t mTotalResultsIndex = 0;    //!< Total (valid and invalid results) index

bool mLastWindowGood = false;           //!< Flag to allow measurement to complete if good
windows are still coming in

bool checkSnrThresholdCount(IncomingResults_t * results, float snr) {
    for (int i = 0; i < (int)NUM_THRESHOLDS; i++) {
        if (snr >= results->snrThreshold[i].thresholdSnr) {
```

```
            if (++results->snrThreshold[i].count >= results->snrThreshold[i].thresholdCount) {
                results->count = results->snrThreshold[i].count;
                results->snrThreshold[i].exceededThreshold = true;
                return true;
            }
        }
    }

    return false;
}

void averageResults(IncomingResults_t validResults, Algorithm::Results_t * averageResults) {
    memset(averageResults, 0x00, sizeof(Algorithm::Results_t));
    SnrThreshold_t snrThreshold;

    /* check which threshold we've crossed */
    for (int i = 0; i < (int)NUM_THRESHOLDS; i++) {
        if (validResults.snrThreshold[i].exceededThreshold) {
            snrThreshold = validResults.snrThreshold[i];
            break;
        }
    }
    int count = 0;
    int i = 0;
    float stdIntermediate[MAX_NUM_WINDOWS];
    while ((count < (int)validResults.count) && (i < (int)MAX_NUM_WINDOWS)) {
        /* Accumulate niva scores */
        float snr = validResults.results[i].snr;
        if (snr >= snrThreshold.thresholdSnr) {
            float score = validResults.results[i].nivaScore;

            stdIntermediate[count++] = score;
            if (!std::isnan(score) && (score > 0)) {
                averageResults->nivaScore += score;
            }

            /* Accumulate fundamental frequencies */
            float freq = validResults.results[i].freq[0];

            if (!std::isnan(freq)) {
                averageResults->freq[0] += freq;
            }

            /* Accumulate snr's */
            if (!std::isnan(snr)) {
                averageResults->snr += snr;
            }
        }
        i++;
    }

    /* Calculate averages */
    averageResults->nivaScore /= snrThreshold.count;
    averageResults->freq[0] /= snrThreshold.count;
    averageResults->snr /= snrThreshold.count;

    /* calculate the standard deviation of the scores */
    float std = getStd(stdIntermediate, snrThreshold.count, averageResults->nivaScore);

    averageResults->rms = std;
}

static void processResultsTask(Algorithm::Results_t results, void * outputFile) {
    std::pair<std::string, std::ofstream*> * resultsPair =
            (std::pair<std::string, std::ofstream*> *)outputFile;
    std::ofstream * nivaResults = resultsPair->second;
    nivaResults->precision(4);

    /* Check to see that we've run out of time (or windows) -- continue if we're on a streak */
    if (++(mTotalResultsIndex) >= MAX_NUM_WINDOWS && !mLastWindowGood) {
        /* we've taken too long, measurement incomplete */
```

```
        *nivaResults << "Measurement Incomplete" << std::endl;

        //reset();
        mTotalResultsIndex = 0;
        mLastWindowGood = false;

        mHighResults.reset();
        mLowResults.reset();
        mValidResults.reset();
    } else if (results.snr > SNR_THRESH_DEFAULT) {


        /* set last good window flag */
        mLastWindowGood = true;

        /* add results to array to later average */
        mValidResults.results[mValidResults.count++] = results;

        /* Check to see if how good the window is */
        bool enoughWindowsHigh = false;
        bool enoughWindowsLow = false;

        /* split results into high/low */
        if (results.above18) {
            mHighResults.results[mHighResults.count++] = results;
            enoughWindowsHigh = checkSnrThresholdCount(&mHighResults, results.snr);
        } else {
            mLowResults.results[mLowResults.count++] = results;
            enoughWindowsLow = checkSnrThresholdCount(&mLowResults, results.snr);
        }

        if (enoughWindowsHigh || enoughWindowsLow) {//(mLowResults.count >= NUM_CLEAN_WINDOWS ||
mHighResults.count >= NUM_CLEAN_WINDOWS) {
            /* Send the last window to the storage task */
            //Progress Update
            /* Update status */
            *nivaResults <<
                    results.startSample << "\t\t" <<
                    results.snr << "\t\t" <<
                    results.rms << "\t\t" <<
                    results.freq[0] * 60  << "\t\t" <<
                    results.ppgPulseRate  << "\t\t" <<
                    results.nivaScore  << "\t\t" <<
                    results.errorFlags.errorFlags  << "\t\t" <<
                    results.above18 << std::endl;
//
//            if (results.above18) {
//                *nivaResults << "High window: "<< results.nivaScore << " SNR: " << results.snr
<< std::endl;
//            } else {
//                *nivaResults << "Low window: " << results.nivaScore << " SNR: " << results.snr
<< std::endl;
//            }

            /* average results */
            Algorithm::Results_t avgResults;

            if (enoughWindowsHigh) { /* Measurement is high */
                /* check classifier outputs */
                int over30Count = 0;

                /* Get count of windows over 30 */
                for (int i = 0; i < (int)mHighResults.count; i++) {
                    /* Accumulate windows that are 30+ */
                    if (mHighResults.results[i].niva30plus) {
                        over30Count++;
                    }
                }

                /* If we've got enough over */
                if (over30Count >= ((int)mHighResults.count / 2)) {
```

```
                    /* just set the flag true -- we dont need to average results here */
                    avgResults.niva30plus = true;
                } else {
                    /* Average results here */
                    averageResults(mHighResults, &avgResults);
                }

            } else {
                /* Measurement is low */
                averageResults(mLowResults, &avgResults);
            }

            /* we got enough windows, send results */
            /* Construct message to let everyone know that we're done */
            /* niva score */
            *nivaResults <<
                    "000000" << "\t\t" <<
                    avgResults.snr << "\t\t" <<
                    avgResults.rms << "\t\t" <<
                    avgResults.freq[0] * 60  << "\t\t" <<
                    avgResults.ppgPulseRate  << "\t\t" <<
                    avgResults.nivaScore  << "\t\t" <<
                    avgResults.errorFlags.errorFlags  << "\t\t" <<
                    avgResults.above18 << std::endl;

//            *nivaResults << avgResults.nivaScore << "\t";
//            /* standard deviation*/
//            *nivaResults << avgResults.rms << '\t';
//            /* signal to noise */
//            *nivaResults << avgResults.snr << "\t";
//            /* pulse rate */
//            *nivaResults << avgResults.freq[0] * 60 << "\t";
//
//            *nivaResults << avgResults.niva30plus << "\t";
//
//            *nivaResults << avgResults.errorFlags.errorFlags << "\t";
//
//            *nivaResults << std::endl;

            //reset();
            mTotalResultsIndex = 0;
            mLastWindowGood = false;

            mHighResults.reset();
            mLowResults.reset();
            mValidResults.reset();
        } else {
            /* Update status */
            *nivaResults <<
                    results.startSample << "\t\t" <<
                    results.snr << "\t\t" <<
                    results.rms << "\t\t" <<
                    results.freq[0] * 60  << "\t\t" <<
                    results.ppgPulseRate  << "\t\t" <<
                    results.nivaScore  << "\t\t" <<
                    results.errorFlags.errorFlags  << "\t\t" <<
                    results.above18 << std::endl;

//            if (results.above18) {
//                *nivaResults << "High window: "<< results.nivaScore << " SNR: " << results.snr
<< std::endl;
//            } else {
//                *nivaResults << "Low window: " << results.nivaScore << " SNR: " << results.snr
<< std::endl;
//            }
        }
    } else {
        /* SNR below threshold */
        mLastWindowGood = false;
    }
}
```

```
static void processExtendedResults(Algorithm::ResultsExtended_t resultsEx, void * outputFile) {
    /* handle extended results here */
    std::pair<std::string, std::ofstream> * resultsPair =
            (std::pair<std::string, std::ofstream> *)outputFile;

    std::ofstream extendedOutput;
    std::string path = resultsPair->first.substr(0, resultsPair->first.length() - 8);
    path.append("_");
    path.append( std::to_string(resultsEx.results.startSample) );
    extendedOutput.open(path, std::ofstream::out | std::ios::binary | std::ofstream::trunc);

    if(extendedOutput.is_open()) {
        extendedOutput.write((const char *) resultsEx.detectedPeaks, sizeof(int32_t) * 100);
        extendedOutput.write((const char *) resultsEx.magnitudeOut, sizeof(float) * 2000);
    }

    extendedOutput.close();
}

/**
 * @brief Algorithm Host Runner main function
 * @param argc: argument count
 * @param argv: argument array
 * @return non-zero on failure
 */
int main(int argc, char *argv[]) {
    /* check for help */
    for(int i = 0; i < argc; i ++) {
        if(std::string(argv[i]) == "--help") {
            printHelp();
            return 0;
        }
    }

    /* Input path */
    std::string dataPath;
    if(argc < 2) {
        std::cout << "Too few arguments -- No path to data supplied" << std::endl;
        printHelp();
        return -1;
    } else {
        /* Assign first to path string*/
        dataPath = std::string(argv[1]);
        if(dataPath.back() != '/') {
            dataPath.insert(dataPath.end(), '/');
        }

        if(directoryExists(dataPath) != 0) {
            std::cout << "Supplied path not a directory" << std::endl;
            return -3;
        }
    }

    /* check file extension parameter*/
    FileType_t fileType;
    std::string fileExtension = getOption(argc, argv, "-e");
    if (fileExtension.empty()) {
        std::cout << "no file extension supplied, using '.txt'" << std::endl;
        fileExtension = std::string(".txt");
    }

    /* check if this is a valid option */
    if (fileExtension.compare(".txt") == 0) {
        fileType = FileType_t::TXT;
    } else if (fileExtension.compare(".afe") == 0) {
        fileType = FileType_t::AFE;
    } else if (fileExtension.compare(" ") == 0 || fileExtension.compare(".raw") == 0) {
        fileType = FileType_t::RAW;
    } else if (fileExtension.compare(".rene") == 0) {
```

```
        fileType = FileType_t::RENE;
    } else {
        fileType = FileType_t::OTHER;
    }

    /* Check if the output path is supplied */
    std::string outputPath = getOption(argc, argv, "-o");
    if(outputPath.empty()) {
        std::cout << "no output path supplied, using input data path" << std::endl;
        outputPath = std::string(dataPath);
    } else if(outputPath.back() != '/') {
        outputPath.insert(outputPath.end(), '/');
    }

    /* check if the output path exists */
    struct stat outputPathInfo;
    if (stat(outputPath.c_str(), &outputPathInfo) != 0 ) {
        std::cout << "Output directory does not exist -- attempting to create..." << std::endl;
#ifdef MINGW_X64
        if (mkdir(outputPath.c_str()) == 0) {
#else
        if (mkdir(outputPath.c_str(), ALLPERMS) == 0) {
#endif
            std::cout << "Directory created -- moving on" << std::endl;
        }
    }

    int startSample = 25;
    std::string startSampleStr = getOption(argc, argv, "-s");
    if(startSampleStr.empty()) {
        std::cout << "no start sample supplied, default (25) is being used" << std::endl;
    }

    bool extended = false;
    std::string extend = getOption(argc, argv, "-x");
    if(extend.back() == '1') {
        extended = true;
    }

    bool derivative = false;
    std::string deriv = getOption(argc, argv, "-d");
    if (deriv.back() == '1') {
        derivative = true;
    }

    /* get files in directory */
    std::vector<inputFile_t> files;
    std::vector<nivaPpgFilePair_t> nivaPpgFiles;

    if(fileType == FileType_t::TXT || fileType == FileType_t::AFE || fileType ==
FileType_t::OTHER) {
        if( getFilesForDirectory(dataPath, fileExtension, files) < 1) {
            std::cout << "No files found in directory!" << std::endl;
            return -1;
        }
    } else if (fileType == FileType_t::RENE) {
        if (getReneFilesForDirectory(dataPath, nivaPpgFiles) < 1) {
            std::cout << "No files found in directory!" << std::endl;
            return -1;
        }
    } else {
        /* raw files */
        if( getRawFilesForDirectory(dataPath, files) < 1) {
            std::cout << "No files found in directory!" << std::endl;
            return -1;
        }
    }

    for(unsigned int i = 0; i < nivaPpgFiles.size(); i++) {
        /* reset 'task' results */
        mHighResults.reset();     //!< High results
```

```
        mLowResults.reset();      //!< Low results
        mValidResults.reset();    //!< All valid results

        mTotalResultsIndex = 0;    //!< Total (valid and invalid results) index
        mLastWindowGood = false;          //!< Flag to allow measurement to complete if good
windows are still coming in


        /* Algorithm Object */
        Algorithm nivaAlgorithm;

        /* Algorithm buffers */
        Algorithm::NivaAlgorithmMemMap_t algorithmBuffers;

        /* Set memory map */
        nivaAlgorithm.setMemMap(&algorithmBuffers);

        /* PPG detection memory map */
        PpgDetection::PpgDetectionMemMap_t ppgBuffers;

        /* PPG detection algorithm */
        PpgDetection ppgDetection(&ppgBuffers);

        /* get filename (without extension) */
        std::string outputFile;
        std::pair<std::string, std::ofstream*> results;
        outputFile = nivaPpgFiles[i].niva.fileName.substr(0,
nivaPpgFiles[i].niva.fileName.length() - fileExtension.length());
        outputFile.append(".results");

        /* output path */
        std::string resultsOutputPath = outputPath;
        resultsOutputPath.append(outputFile);

        /* results output file stream */
        std::ofstream nivaResults;
        nivaResults.open(resultsOutputPath, std::ofstream::out | std::ofstream::trunc);

        results.first = resultsOutputPath;
        results.second = &nivaResults;

        /* Write header to file */
        writeResultsHeader(nivaResults);

        /* assign callback */
        if(extended) {
            nivaAlgorithm.init(&processResults, &processExtendedResults, &results);
        } else {
#ifdef TASK
            nivaAlgorithm.init(&processResultsTask, &results);
#else
            nivaAlgorithm.init(&processResults, &results);
#endif
        }

        /* open the files */
        std::ifstream mNivaFile (nivaPpgFiles[i].niva.absolutePath);
        std::ifstream mPpgFile (nivaPpgFiles[i].ppg.absolutePath);

        float currentBpm = -1;

        /* Setup the moving average filter */
        float mvgAvgBuffer[8192];
        memset(mvgAvgBuffer, 0x00, sizeof(float) * 8192);
        CircularBufferFloat mvgAvg;
        mvgAvg.assign(&mvgAvgBuffer[0], 8192);

        float coefficients[4] = {0.25f, 0.25f, 0.25f, 0.25f};
        Fir movingAverage;

        movingAverage.setCoefficients(&coefficients[0], 4);
```

```
        if (mNivaFile.is_open() && mPpgFile.is_open()) {
            std::cout << "******** START " << nivaPpgFiles[i].niva.fileName << " ********" <<
std::endl;
            int index = 0;
            std::string line;
            float previousSample = 0;
            float nivaStartTime = 0;
            float ppgStartTime = 0;


            for(index = 0; index < startSample; index++) {
                std::getline(mNivaFile, line);
                std::vector<std::string> lineContents;
                readFromLine(line, '\t', lineContents);

                if (index == 1) {
                    nivaStartTime = std::stod(lineContents[0]);
                }

                std::string ppgLine;
                std::getline(mPpgFile, ppgLine);
                lineContents.clear();

                readFromLine(ppgLine, '\t', lineContents);

                if (index == 1) {
                    ppgStartTime = std::stod(lineContents[0]);
                }
            }

            ppgStartTime = (ppgStartTime - nivaStartTime);

            while(std::getline(mNivaFile, line))
            {
                if ((index & 3) == 0 && (((float)index/125.0f) > ppgStartTime)) {
                    std::string ppgLine;
                    std::getline(mPpgFile, ppgLine);

                    std::vector<std::string> lineContents;
                    readFromLine(ppgLine, '\t', lineContents);

                    if(lineContents.size() < 1) {
                        continue;
                    }

                    float ppgSample = std::stod(lineContents[1]);

                    ppgDetection.process(ppgSample, PPG_SCALE);

                    if (ppgDetection.getBeats()->getTotalSampleCount() >
PpgDetection::VALID_BEAT_SIZE) {
                        currentBpm = ppgDetection.getBeats()->getMean();
                    }
                }

                std::vector<std::string> lineContents;
                readFromLine(line, '\t', lineContents);

                float sample = std::stod(lineContents[1]);
                float expectedBpm = (currentBpm > 0) ? currentBpm : -1;

                if (derivative) {
                    float diff = sample - previousSample;
                    previousSample = sample;
                    mvgAvg.add(diff);
                    float output = 0;
                    movingAverage.update(&mvgAvg, &output);

                    nivaAlgorithm.process(output * NIVA_SCALE, sample,  expectedBpm);
                } else {
```

```
                    nivaAlgorithm.process(sample * NIVA_SCALE, sample, expectedBpm);
                }


                index++;
            }
            std::cout << "******** END " << nivaPpgFiles[i].niva.fileName << " ********" <<
std::endl;
            mNivaFile.close();
            mPpgFile.close();
            nivaResults.close();
        }
    }

    for(unsigned int i = 0; i < files.size(); i++) {
        /* Algorithm Object */
        Algorithm nivaAlgorithm;

        /* Algorithm buffers */
        Algorithm::NivaAlgorithmMemMap_t algorithmBuffers;

        /* Set memory map */
        nivaAlgorithm.setMemMap(&algorithmBuffers);

        /* get filename (without extension) */
        std::string outputFile;
        std::pair<std::string, std::ofstream*> results;
        if(fileType == FileType_t::TXT || fileType == FileType_t::AFE || fileType ==
FileType_t::OTHER) {
            outputFile = files[i].fileName.substr(0, files[i].fileName.length() -
                    fileExtension.length());
        } else {
            outputFile = files[i].fileName;
        }
        outputFile.append(".results");

        /* output path */
        std::string resultsOutputPath = outputPath;
        resultsOutputPath.append(outputFile);

        /* results output file stream */
        std::ofstream nivaResults;
        nivaResults.open(resultsOutputPath, std::ofstream::out | std::ofstream::trunc);

        results.first = resultsOutputPath;
        results.second = &nivaResults;

        /* Write header to file */
        writeResultsHeader(nivaResults);

        /* assign callback */
        if(extended) {
            nivaAlgorithm.init(&processResults, &processExtendedResults, &results);
        } else {
            nivaAlgorithm.init(&processResultsTask, &results);
        }

        /* Setup the moving average filter */
        float mvgAvgBuffer[8192];
        memset(mvgAvgBuffer, 0x00, sizeof(float) * 8192);
        CircularBufferFloat mvgAvg;
        mvgAvg.assign(&mvgAvgBuffer[0], 8192);

        float coefficients[4] = {0.25f, 0.25f, 0.25f, 0.25f};
        Fir movingAverage;

        movingAverage.setCoefficients(&coefficients[0], 4);

        std::string inputFilePath = files[i].absolutePath;
        std::ifstream mFile;
```

```
        if(fileType == FileType_t::TXT || fileType == FileType_t::AFE || fileType ==
FileType_t::OTHER) {
            mFile.open(inputFilePath, std::ios::in);
            if(mFile.is_open())
            {
                std::cout << "******** START " << files[i].fileName << " ********" << std::endl;
                int index = 0;
                std::string line;
                float previousSample = 0;
                while(std::getline(mFile, line))
                {
                    if(index++ > 25)
                    {
                        std::vector<std::string> lineContents;
                        readFromLine(line, '\t', lineContents);

                        float sample = std::stod(lineContents[1]);

                        if (derivative) {
                            float diff = sample - previousSample;
                            previousSample = sample;
                            mvgAvg.add(diff);
                            float output = 0;
                            movingAverage.update(&mvgAvg, &output);

                            nivaAlgorithm.process(output, (int32_t)output, -1);
                        } else {
                            nivaAlgorithm.process(sample, (int32_t) sample, -1);
                        }
                    }
                }
                std::cout << "******** END " << files[i].fileName << " ********" << std::endl;
                mFile.close();
                nivaResults.close();
            } else {
                continue;
            }
        } else if (fileType == FileType_t::RAW) {
            mFile.open(inputFilePath, std::ios::binary | std::ios::in);
            if(mFile.is_open())
            {
                std::cout << "******** START " << files[i].fileName << " ********" << std::endl;
                int index = 0;
                int32_t rawSample;
                float previousSample = 0;
                while(mFile.read((char*)&rawSample, 4))
                {
                    if(index++ > 25)
                    {
                        float sample = (float)( (float)rawSample * 2.43425369262695e-07 );

                        if (derivative) {
                            float diff = sample - previousSample;
                            previousSample = sample;
                            mvgAvg.add(diff);
                            float output = 0;
                            movingAverage.update(&mvgAvg, &output);

                            nivaAlgorithm.process(output, rawSample, -1);
                        } else {
                            nivaAlgorithm.process(sample, rawSample, -1);
                        }
                    }
                }
                std::cout << "******** END " << files[i].fileName << " ********" << std::endl;
                mFile.close();
                nivaResults.close();
            } else {
                continue;
            }
        }
```

```
    }

    return 0;
}

/**
 * @}
 */
```

Appendix B: Supplementary Information for Selected Lasso Model

Lasso linear model — No. of obs = **241**; No. of covariates = **25**

Selection: **Cross-validation** — No. of CV folds = **10**

ID	Description	lambda	No. of nonzero coef.	Out-of-sample R-squared	CV mean prediction error
1	first lambda	**2.343468**	**0**	**0.0081**	**36.83854**
54	lambda before	**.0169217**	**23**	**0.3724**	**22.93415**
* 55	selected lambda	**.0154185**	**22**	**0.3724**	**22.93219**
56	lambda after	**.0140487**	**22**	**0.3724**	**22.93357**
62	last lambda	**.0080392**	**22**	**0.3714**	**22.97211**

* lambda selected by cross-validation.

Supplementary Table 1. Lasso linear model and out-of-sample goodness of fit with lambda selected by 10-fold cross-validation. * signifies the selected lambda.

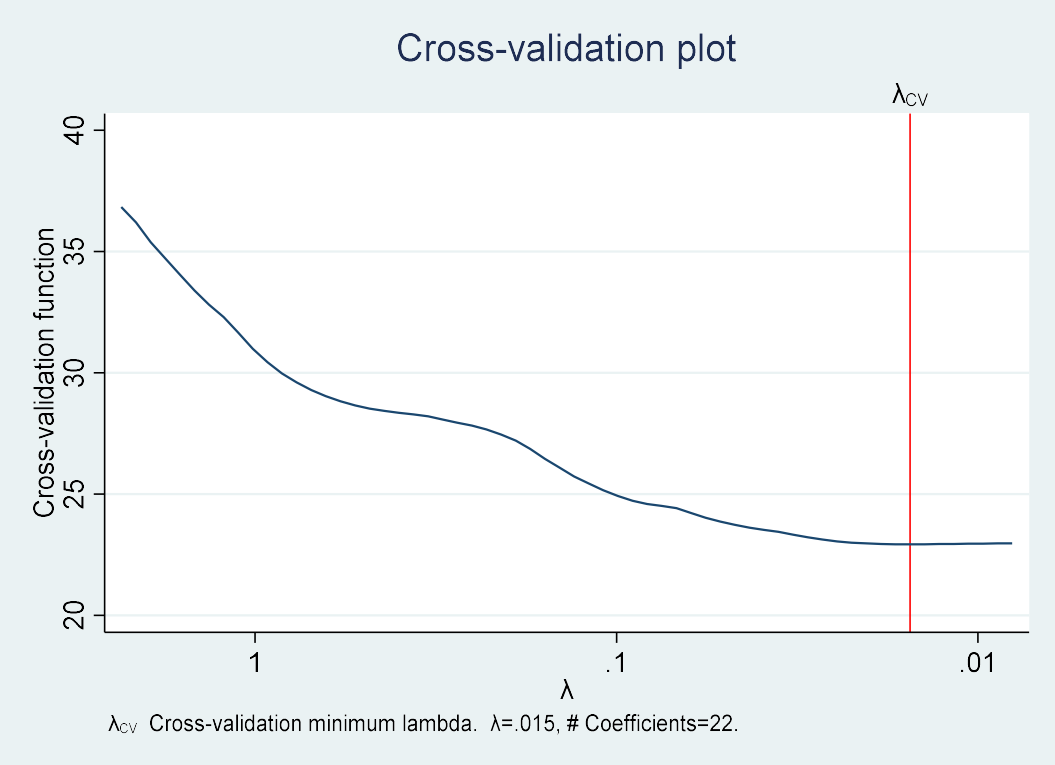
Penalized coefficients

MSE	R-squared	Obs
18.55185	**0.4923**	**241**

Postselection coefficients

MSE	R-squared	Obs
18.40169	**0.4964**	**241**

Supplementary Table 2. Goodness of fit of in-sample predictions using penalized (*top*) and postselection (*bottom*) coefficients from the selected model.



Supplementary Figure 1. Selected lasso penalty parameter λ is at the minimum of the cross-validation function, which is the mean squared error of the predictions in the cross-validation samples.