Title:

Facilitating A Practical Evaluation of Heart Failure Patients: A Novel Method for Assessment of Aortic Characteristic Impedance and Arterial Compliance from Non-invasive Carotid Pressure Waveform in The Framingham Heart Study

Running title: Compliance and Impedance via Carotid Waveform

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ABSTRACT

The primary goal of this study was to test the hypothesis that a hybrid Intrinsic Frequency-machine-learning approach (IF-ML) can accurately evaluate total arterial compliance (TAC) and aortic characteristic impedance (Zao) from a single noninvasive carotid pressure waveform in both female and male with heart failure (HF). TAC and Zao are cardiovascular biomarkers with established clinical significance. TAC is lower and Zao is higher in females than males, so females are more susceptible to consequent deleterious effects of these. While the principles of TAC and Zao are pertinent to a multitude of cardiovascular diseases including HF, their routine clinical use is limited due to the requirement of simultaneous measurements of flow and pressure waveforms. For this study, the data were obtained from the Framingham Heart Study (n=6201, 53% females). The reference values of Zao and TAC were computed from carotid pressure and aortic flow waveforms. Intrinsic frequency (IF) parameters of carotid pressure waveform were used in machine-learning models. IF models were developed on n=5168 of randomly selected data and blindly tested the remaining data (n=1033). The final models were evaluated on HF patients. Correlations between IF-ML and reference values in all HF and HFpEF for TAC were 0.88 and 0.90 and for Zao were 0.82 and 0.80 respectively. The classification accuracy in all HF and HFpEF for TAC were 0.9 and 0.93 and for Zao were 0.81 and 0.89 respectively. In conclusion, IF-ML method provides an accurate estimation of TAC and Zao in all subjects with HF and in the general population.

Keywords: Heart Failure, Total arterial compliance, Aortic characteristic impedance, Cardiovascular intrinsic frequency

INTRODUCTION

Heart failure (HF) currently affects about 6 million American adults with more prevalence in females than males among the elderly population (≥80 years) [1]. By 2030, it is estimated that 3% of the total population will be living with HF [1]. Despite advances in treatment and therapy optimization, 30-day rehospitalization rates among HF patients remain high (>25%) [2]. Around 50% of patients have heart failure with preserved ejection fraction (HFpEF). The occurrence of HFpEF is increasing, and studies consistently indicate that HFpEF is more prevalent in females [3]. Previous studies have shown the significance of ventricular-arterial coupling (VAC) in cardiac and aortic mechanics, as well as its role in the pathophysiology of cardiac disease[4]. Total arterial compliance (TAC) and aortic characteristic impedance (Zao) are two important cardiovascular biomarkers that combine the effects of arterial load on LV function[4]. Furthermore, it is now well-accepted that comprehensive evaluations of VAC necessitate measurements of pulsatile workload determinants such Zao and TAC [4]. However, their routine clinical use is limited due to the requirement of simultaneous measurements of both central flow and pressure waveforms. Therefore, the evaluation of TAC and Zao from a single carotid pressure waveform may pave the way for routine clinical use of these biomarkers for risk assessment, management, and monitoring of not only HFpEF but also heart failure with reduced ejection fraction (HFrEF). Intrinsic frequency (IF) method is a physics-based systems approach for the analysis of coupled left ventricle-arterial system. The IF method uses a pressure waveform to extract the IF parameter ω_1 which is dominated by the contractile state of the heart and ω_2 which is strongly dependent on the vascular dynamics [5,6]. Using Framingham Heart Study (FHS) data, Cooper et al. [7] recently showed that both ω_1 and ω_2 predict heart failure events after adjustment for traditional CVD risk factors, heart rate, and the systolic ejection period. Given the reduced order nature of the IF methods and its clinical significance in detecting and predicting cardiovascular events such as HF, the IF method is an excellent candidate to be combined with machine learning approaches. The primary goal of this study was to test the hypothesis that hybrid IF-based machine learning (IF-ML) approaches can accurately evaluate TAC and Zao from a single carotid pressure waveform in healthy volunteers and HF patients.

METHODS

Our data is from Framingham Heart Study. Details about the participants and noninvasive hemodynamic measurements have been provided in previous publications[7,8]. This population consisted of individuals aged 19-90 and included both healthy participants and cardiovascular diseases including a minority with heart failure. HF patients with left ventricle ejection fraction (LVEF) lower than 40% are recognized as HFrEF and HF patients with LVEF>50% are always considered as HFpEF [9]. We considered LVEF=45% as a cutoff in this study to limit HF categorization to only two categories, HFpEF (above) and HFrEF (below)[7].

Hybrid Intrinsic Frequency-Machine Learning (IF-ML) Model Development

To test this our hypothesis, we developed and validated hybrid IF-ML models for computation of TAC and Zao using patients and healthy volunteers from the Framingham Heart Study (FHS) (n=6201; 53% females). The "pulse pressure method" (PPM) was used to compute the reference total arterial compliance (TAC) from aortic flow and pressure waveforms [10]. The reference aortic characteristic impedance (Zao) was computed using the pressure-flow loop method as described by Bollache et al. [11]. In this method, Zao is computed from the slope of the early systolic part of the pressure-flow loop. IF method, which is a reduced-order approach for capturing the dynamics of the cardiovascular system, was applied to carotid pressure waveforms. IF parameters were calculated using an L2-minimization formulation with a non-calibrated pressure waveform as an input[6,12]. The outputs are first and second main IFs, to ω_1 and ω_2, intrinsic phases, φ_1 and φ_2, and intrinsic envelops, R_s and R_d. Further details about the mathematics, convergence, and robustness of the intrinsic frequencies (IFs) calculation have been described in previous studies [6,12-14]. Visualization of the IF method and its related physical representations are provided in the supplementary material (Supplement A).

To avoid bias, and overcome the limitation associated with the total number of HF patients (n=65) in the Framingham database, we developed, validated, and blind-tested the IF-Model using 83% of the entire population (n=5168) that also included healthy participants and non-HF CVD patients. Before starting the development of the IF-ML models, we set aside randomly selected portion of the data (n=1033, 17%) for a blind stratified test (a so-called "external validation"). This holdout set was kept blind to all the stages of the parameter selection, training, and development of the models. In the final step, the accuracy of the IF-ML models were assessed among HFpEF and HFrEF patients in both males and females. By adopting this procedure, we sought to avoid any bias that may be introduced by hemodynamic similarities between HFpEF or HFrEF patients.

IF-ML method for Estimation of TAC and Zao

After setting aside the blind holdout set described above, a feature selection procedure was performed using permutation feature importance and random forest feature importance methods applied on a comprehensive set of physically and physiologically relevant parameters (Set_{all}). The Set_{all} contained 3 groups of parameters. Group 1 consisted of the main IF parameters mentioned above (ω_1, ω_2, φ_1, φ_2, and E_r). Group 2 included normalized and corrected versions of ω_1 and ω_2 such as $\omega_{1N}, \omega_{2N}, \bar{\omega}_1, \bar{\omega}_2, \omega_{1C}$, and ω_{2C} (see Supplement A for definitions). Group 3 consisted of physiological and demographic data such SBP, DBP, pulse pressure (PP), heart rate (HR), age, height, and weight (see details in Supplement B).

STATISTICAL ANALYSES

Values are presented as means ± standard deviation (SD). Pearson's correlation coefficient (R score), root mean square error (RMSE) were used to assess the accuracy between actual and predicted values. Limit of agreement (LoA) and bias form Bland-Altman (BA) analysis were used to quantify the agreement between predicted and reference values. In addition to estimating TAC and Zao, we tested the classification performance of the estimated TAC and Zao among HF patients. We used thresholds of 0.6 (mL/mmHg) and 0.15(mmHg.s/mL) for TAC and Zao classifications respectively (see details in Supplement C). Sensitivity, specificity, and accuracy were used as evaluation metrics for classification:

$$Sensitivity = (True\ Positive)/(True\ Positive + False\ Negative)\ ,$$

$$Specificity = (True\ Negative)/(True\ Negative + False\ Positive)\ ,$$

$$Accuracy = (True\ Positive + True\ Negative)/(All\ Positive + All\ Negative)$$

True positive are the cases that are predicted as low compliance/high impedance and are labeled as diseased. True negative are cases that are predicted as high compliance/low impedance and are labeled as healthy.

RESULTS

Table 1 represents the characteristics of the entire study population as well as patients with HF. Figure 1 demonstrates the agreement between estimated TAC and Zao by IF-ML models and the reference values in the blind holdout set (external validation). The R score, RMSE, and bias of the IF-ML model for TAC in the blind holdout set were 0.89 (P-value<0.0001), 0.16 (mL/mmHg), and 0 respectively. The R score, RMSE, and bias of the IF-ML model for Zao in the blind holdout set were 0.80 (P-value<0.0001), 0.03 (mmHg.s/mL), and 0 respectively (Table 2).

Performance of IF-ML models among HF population

We further investigated the model's performance for all HF patients, including the HFpEF and HFrEF subgroups. The correlation (R score) between IF-ML values of TAC and the reference values for all HF, HFpEF and HFrEF were 0.88, 0.90, and 0.84 respectively. The R score between IF-ML values and reference values of Zao for all HF, HFpEF and HFrEF were 0.82, 0.80, and 0.77 respectively (Table 2). The regression statistics between reference values and model predictions in males and females is presented in Table 2. The sensitivity, specificity, and accuracy of IF-ML models for classifying reduced TAC and elevated Zao in HF groups are provided in Table 3 (The details of selecting the TAC and Zao cutoff values are provided in Supplement C).

DISCUSSION

In this study, we introduced a hybrid intrinsic frequency machine learning (IF-ML) method for calculating TAC and Zao using a single noninvasive carotid pressure waveform and baseline patient characteristics without requiring flow or velocity measurements. This method can significantly improve the practicality of usage of TAC and Zao in heart failure patients. The principal finding of this study is that the proposed pressure-only IF-ML method provides an accurate estimation of TAC and Zao in heart failure patients (both HFpEF and HFrEF) and in the general population of community-based Framingham Heart Study. The performance of our IF-ML approach for calculation of TAC and Zao was excellent particularly among the females HF patients.

Our IF-ML algorithm has several notable advantages: (1) it requires fewer input features and has better performance than brute-force methods that use the entire pressure waveform (See supplementary material); (2) IF is robust against signal noise on pressure waveforms[12]; and (3) this IF-ML algorithm can be deployed on inexpensive handheld devices (e.g. optical tonometry, iPhone) to facilitate the routine noninvasive evaluation of TAC and Zao[13,15]. Additionally, scalability and reconciliation of IF parameters have been established across various measurement platforms and different species such as rat, rabbit and human[14]; therefore, the results of the preclinical studies that are focused on specific therapeutic approaches can be translated and reconciled for clinical use with minimal effort.

The relatively low-cost nature of our proposed method and its technology platform has relevance in socioeconomically disadvantaged groups. One application of our hybrid IF-ML model is in assessing the role of TAC and Zao as therapeutic response biomarker. This is particularly important in monitoring and treatment of patients with HF, especially HFpEF. Our IF-ML may be an appropriate therapeutic response tool to serially monitor HF patients with a remote monitoring platform. Moreover, such a platform could rely on inexpensive wireless hand-held devices[15] or a smartphone [5] and reach more patients due to smaller upfront costs. Similarly, our proposed approach could serve as a non-invasive alternative in early-stage (Phase 1 and 2) clinical trials. This could have significant implications, potentially reducing costs and enhancing efficiency in the development of new drug and device therapies.

LIMITATIONS

Although our study has several strengths as noted above, it also has limitations. All carotid pressure waveforms were measured using one type of platform, piezoelectric arterial applanation tonometry (Cardiovascular Engineering Inc). However, this may not affect the performance of our approach since IF method is agnostic to the measurement platform as shown by Alavi et al[14]. Finally, our data from were comprised predominantly of white participants of Western European descent from Framingham Heart Study, so our models may not be generalizable to other racial or ethnic groups.

CONCLUSIONS

We present a novel hybrid intrinsic frequency machine learning approach (IF-ML) for calculating total arterial compliance (TAC) and aortic characteristic impedance (Zao) from a single noninvasive carotid pressure waveform in HF patients. This method only relies on uncalibrated noninvasive carotid waveform and concurrent systemic blood pressure and patient characteristics. As such, this method can be programmed into a hand-held device for an at-home, patient administered test to assess TAC and Zao. Future studies in HF patients are needed to evaluate the role for IF-ML based TAC and Zao as potential therapeutic response biomarkers for a non-invasive remote hemodynamic monitoring platform. Our method facilitates the evaluation of TAC and Zao in clinical practice that may be used for risk assessment, management, and monitoring of HF, especially in females who have lower TAC and higher Zao than men.

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DISCLOSURES

Niema M. Pahlevan holds equity and has a consulting agreement with Avicena LLC. The remaining authors report no relevant conflicts.

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Fig. 1 The agreement between intrinsic-frequency-machine-learning (IF-ML) models and the reference values in the blind holdout set (external validation). **A** (left): scatter plot of the total arterial compliance (TAC) form IF-ML (y-axis) versus the reference value (x-axis). **B** (right): scatter plot of the aortic characteristic impedance (Zao) form IF-ML (y-axis) versus the reference value (x-axis).

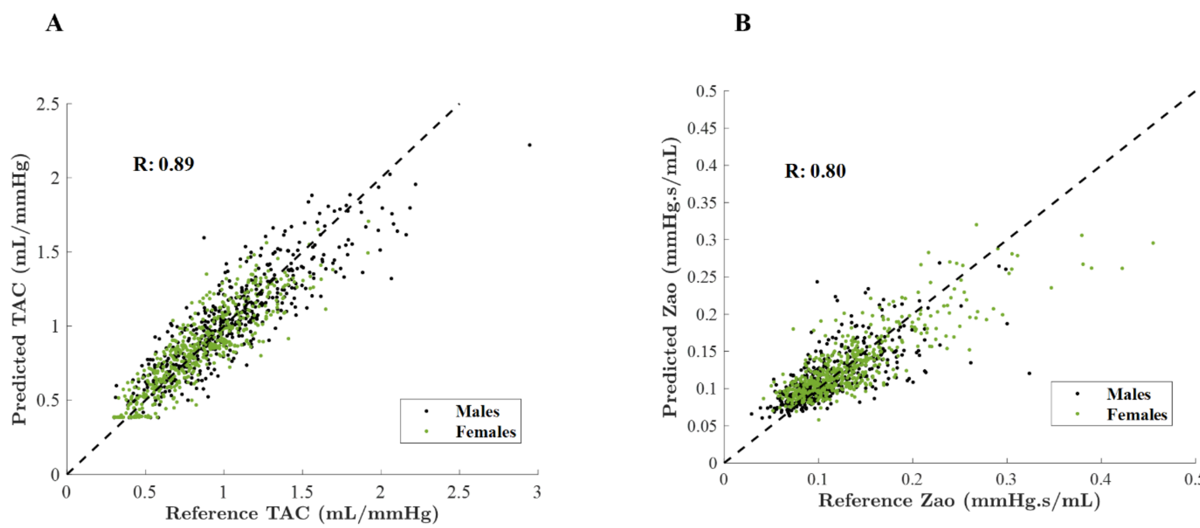

Table 1. Characteristics of the study population

All participants

Parameter	All population (n=6201)	Males (n=2931)	Females (n=2931)	HF (n=65)*	HFpEF (n=30)	HFrEF (n=30)
Age, y	49.74 ± 15.27	49.95± 15.23	49.55± 15.31	68.83 ± 13.57	72.73 ± 11.76	65.26 ± 14.27
ω_1, bpm	87.56 ± 8.59	88.49 ± 8.72	86.73 ± 8.38	93.60 ± 11.04	88.68 ± 7.38	98.83 ± 12.37
ω_2, bpm	52.84 ± 20.79	51.90 ± 20.80	53.68 ± 20.75	50.96 ± 25.61	46.37 ± 17.93	58.58 ± 31.31
TAC, [mL/mmHg]	0.93 ± 1.494	1.03 ± 0.35	0.84 ± 0.31	0.75 ± 1.46	0.65 ± 1.61	0.84 ± 1.22
Zao, [mmHg.s/mL]	0.12 ± 0.035	0.11 ± 0.04	0.13 ± 0.05	0.15 ± 0.341	0.18 ± 0.360	0.13 ± 0.313

HF patients

Parameter	Female HF (n=22)	Male HF (n=43)	Female HFpEF (n=16)	Male HFpEF (n=14)	Female HFrEF (n=5)	Male HFrEF (n=15)
Age,y	69.36 ± 16.06	69.58 ± 12.25	72.18 ± 14.92	73.35 ± 7.13	57.20 ± 11.09	66.88 ± 14.46
ω_1, bpm	90.31 ± 7.39	95.28 ± 12.25	88.53 ± 7.29	88.85 ± 7.74	96.21 ± 5.53	99.36 ± 13.35
ω_2, bpm	51.23 ± 19.73	50.82 ± 28.36	49.83 ± 19.99	42.41 ± 14.99	58.87 ± 20.06	58.52 ± 33.43
TAC, [mL/mmHg]	0.60 ± 0.28	0.83 ± 0.34	0.52 ± 0.23	0.80 ± 0.42	0.78 ± 0.36	0.84 ± 0.31
Zao, [mmHg.s/mL]	0.19 ± 0.08	0.13 ± 0.05	0.20 ± 0.08	0.15 ± 0.06	0.14 ± 0.05	0.12 ± 0.04

*HF group are a combination of HFrEF and HFpEF and five HF patients whose LVEF values were not available.

HF= Heart Failure
HFpEF= Heart Failure with Preserved Ejection Fraction
HFrEF= Heart Failure with Reduced Ejection Fraction
TAC= Total Arterial Compliance
Zao= Aortic Characteristic Impedance
ω_1= First (systolic) intrinsic frequency
ω_2= Second (diastolic) intrinsic frequency

Table 2. Regression statistics between reference value and model prediction in women and men populations

All Population

	HF Patients(n=65)				HFpEF Patients(n=30)				HFrEF Patients(n=30)			
	R	**RMSE**	**Bias**	**Lower/Upper LoA**	**R**	**RMSE**	**Bias**	**Lower/ Upper LoA**	**R**	**RMSE**	**Bias**	**Lower/ Upper LoA**
TAC [mL/mmHg]	0.88	0.17	0.01	-0.28/ 0.3	0.9	0.16	-0.01	-0.25/ 0.21	0.84	0.19	0.05	-0.28/ 0.41
Zao [mmHg.s/mL]	0.82	0.04	0	-0.07/ 0.07	0.8	0.05	0.01	-0.08/ 0.1	0.84	0.03	-0.01	-0.06/ 0.04

Females

	HF Patients(n=22)				HFpEF Patients(n=16)				HFrEF Patients(n=5)			
	R	**RMSE**	**Bias**	**Lower/Upper LoA**	**R**	**RMSE**	**Bias**	**Lower/ Upper LoA**	**R**	**RMSE**	**Bias**	**Lower/ Upper LoA**
TAC [mL/mmHg]	0.88	0.14	0.02	-0.25/ 0.3	0.91	0.01	-0.02	-0.22/ 0.16	0.96	0.23	0.18	-0.1/ 0.05
Zao [mmHg.s/mL]	0.81	0.04	0	-0.08/ 0.1	0.79	0.05	0.01	-0.08/ 0.12	0.84	0.03	-0.01	-0.07/ 0.03

Males

	HF Patients(n=43)				HFpEF Patients(n=14)				HFrEF Patients(n=15)			
	R	**RMSE**	**Bias**	**Lower/Upper LoA**	**R**	**RMSE**	**Bias**	**Lower/Upper LoA**	**R**	**RMSE**	**Bias**	**Lower/Upper LoA**
TAC [mL/mmHg]	0.87	0.18	0.03	-0.3/ 0.4	0.90	0.20	0.04	-0.35/ 0.45	0.80	0.18	0.03	-0.32/ 0.39
Zao [mmHg.s/mL]	0.82	0.03	0	-0.06/ 0.05	0.85	0.03	0	-0.06/ 0.07	0.77	0.03	0	-0.06/0.04

* In all the cases p-values are < 1e-4

HF= Heart Failure

HFpEF= Heart Failure with Preserved Ejection Fraction

HFrEF= Heart Failure with Reduced Ejection Fraction

TAC= Total Arterial Compliance

Zao= Aortic Characteristic Impedance

LoA= Limit of agreement

Table 3. Classification performances of IF-ML models in HF groups

All Population									
	HF Patients			**HFpEF Patients**			**HFrEF Patients**		
	Accuracy	**Specificity**	**Sensitivity**	**Accuracy**	**Specificity**	**Sensitivity**	**Accuracy**	**Specificity**	**Sensitivity**
TAC	0.90	0.92	0.88	0.93	0.92	0.93	0.86	0.90	0.75
Zao	0.81	0.78	0.86	0.89	0.90	0.88	0.72	0.70	0.78
Females									
	HF Patients			**HFpEF Patients**			**HFrEF Patients**		
	Accuracy	**Specificity**	**Sensitivity**	**Accuracy**	**Specificity**	**Sensitivity**	**Accuracy**	**Specificity**	**Sensitivity**
TAC	0.91	0.8	1	0.94	0.83	1	0.8	0.67	1
Zao	0.90	0.87	0.92	0.93	1	0.92	0.8	0.67	1
Males									
	HF Patients			**HFpEF Patients**			**HFrEF Patients**		
	Accuracy	**Specificity**	**Sensitivity**	**Accuracy**	**Specificity**	**Sensitivity**	**Accuracy**	**Specificity**	**Sensitivity**
TAC	0.88	0.93	0.78	0.93	1	0.83	0.84	0.90	0.67
Zao	0.77	0.75	0.78	0.86	0.87	0.83	0.72	0.72	0.71

HF= Heart Failure
HFpEF= Heart Failure with Preserved Ejection Fraction
HFrEF= Heart Failure with Reduced Ejection Fraction
TAC= Total Arterial Compliance
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