

Aortic flow conditions predict ejection efficiency in the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE)

Mark Doyle¹, Gerald M. Pohost², C. Noel Bairey Merz³, Victor Farah¹, Leslee J. Shaw³, George Sopko⁴, William J. Rogers⁵, Barry L. Sharaf⁶, Carl J. Pepine⁷, Diane V. Thompson¹, Geetha Rayarao¹, Lindsey Tauxe⁵, Sheryl F. Kelsey⁸, Robert W. W. Biederman¹

¹Allegheny General Hospital, Pittsburgh, PA, USA; ²Keck Medical Center, University of Southern California, Los Angeles, CA, USA; ³Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, Los Angeles, CA, USA; ⁴National Heart Lung and Blood Institute, NIH, Bethesda, MD, USA; ⁵the University of Alabama at Birmingham, AL, USA; ⁶Brown University, Providence, RI, USA; ⁷University of Florida, Gainesville, FL, USA; ⁸Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

Contributions: (I) Conception and design: M Doyle, V Farah, RW Biederman; (II) Administrative support: G Rayarao, G Sopko; (III) Provision of study material or patients: L Tauxe, BL Sharaf, GM Pohost, WJ Rogers; (IV) Collection and assembly of data: DV Thompson; (V) Data Analysis and interpretations: M Doyle; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Mark Doyle, PhD. Division of Cardiology, CV MRI Center, Allegheny General Hospital, 320 East North Avenue, Pittsburgh, PA 15212-4772, USA. Email: mark.doyle@ahn.org.

Background: The Windkessel model of the cardiovascular system, both in its original wind-chamber and flow-pipe form, and in its electrical circuit analog has been used for over a century to modeled left ventricular ejection conditions. Using parameters obtained from aortic flow we formed a Flow Index that is proportional to the impedance of such a “circuit”. We show that the impedance varies with ejection fraction (EF) in a manner characteristic of a resonant circuit with multiple resonance points, with each resonance point centrally located in a small range of EF values, i.e., corresponding to multiple contiguous EF bands.

Methods: Two target populations were used: (I) a development group comprising male and female subjects (n=112) undergoing cardiovascular magnetic resonance (CMR) imaging for a variety of cardiac conditions. The Flow Index was developed using aortic flow data and its relationship to left ventricular EF was shown. (II) An illustration group comprised of female subjects from the Women's Ischemia Syndrome Evaluation (WISE) (n=201) followed for 5 years for occurrence of major adverse cardiovascular events (MACE). Flow data was not available in this group but since the Flow Index was related to the EF we noted the MACE rate with respect to EF.

Results: The EFs of the development population covered a wide range (9%–76%) traversing six Flow Index resonance bands. Within each Flow Index resonance band the impedance varied from highly capacitive at the lower range of EF through minimal impedance at resonance, to highly inductive at the higher range of EF, which is characteristic of a resonant circuit. When transitioning from one EF band to a higher band, the Flow Index made a sudden transition from highly inductive to capacitive impedance modes. MACE occurred in 26 (13%) of the WISE (illustration) population. Distance in EF units (Δ_{center}) from the central location between peaks of MACE activity was derived from EF data and was predictive of MACE rate with an area under the receiver operator curve of 0.73. Of special interest, Δ_{center} was highly predictive of MACE in the sub-set of women with EF >60% (AUC 0.79) while EF was no more predictive than random chance (AUC 0.48).

Conclusions: A Flow Index that describes impedance conditions of left ventricular ejection can be calculated using data obtained completely from the ascending aorta. The Flow Index exhibits a periodic variation with EF, and in a separate illustration population the occurrence of MACE was observed to exhibit a similar periodic variation with EF, even in cases of normal EF.

Keywords: Ejection fraction; aortic flow; impedance; prognosis

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Introduction

Multiple aspects of the cardiovascular system have been successfully modeled using resistive, inductive and capacitive circuit elements (1). In these models, resistance is typically associated with the microvasculature, capacitance represents compliance of the cardiovascular system (typically focusing on large conduit vessels such as the aorta) and inductance represents blood inertia. Others have shown that the pulsatile and periodic ejection of blood can be considered to be a wave phenomenon transmitting into a “tuned” system. Here we show that the left ventricular (LV) ejection of blood into the aorta can be characterized by an impedance which can be dominantly capacitive or a dominantly inductive in this tuned system (2). A typical behavior of tuned circuits is that at frequencies lower than resonance the impedance is predominantly capacitive, while at frequencies higher than resonance the impedance is predominantly inductive. A resonance condition is observed when the two sources of impedance are balanced to produce a low net impedance/resistance, *Figure 1*. Of special interest here, when the frequency exceeds one end of a tuned band, there is a sudden transition from maximal inductive impedance to maximal capacitive impedance. We show that the cardiovascular system behaves as a tuned circuit with periodic resonances observed at approximately 10% intervals of ejection fraction (EF), e.g., for an individual, resonances might occur at 55%, 65% and 75% etc. Further, major adverse cardiovascular events may be more likely to occur when ejection conditions are remote from the local resonance condition (likely reflecting the high mechanical work load associated with high impedance). We introduce these concepts in terms of an aortic Flow Index which reflects impedance conditions within each EF range, illustrating its prognostic potential and use as a surrogate for likely adjustments made by the cardiac and vascular system to accommodate a variety of cardiac loading conditions.

While cardiovascular magnetic resonance (CMR) chamber volumetric imaging is widely regarded as the gold standard for calculating left ventricular ejection fraction (LVEF), reproducibility is at best 4% (3). As an alternative, we sought to measure ejection impedance conditions more directly by examining blood flow in the ascending aorta and relating them to LVEF. The pulsatile and periodic ejection of blood can be considered to be a wave phenomenon transmitting into a tuned circuit, analogous to the transmission of sound waves by a loud-speaker. In the case of the loud-speaker, impedance is optimal when the ratio of

the diameter of the sound wave and the speaker are close to one, Eq. [1]:

$$\text{Impedance} = \frac{\text{Wavelength}}{\text{Diameter}} \quad [1]$$

Here, two patient populations were examined, the first population was used to develop a method to measure and characterize left ventricular-aortic impedance, and the second population was used to illustrate its potential prognostic value.

Methods

Model development population

To assess impedance and examine its relationship to EF we performed a retrospective review of patients undergoing a CMR volumetric evaluation of the LV between January 1 2012 to June 1 2015, and in whom a phase velocity scan of aortic flow was available. The Institutional Review Board approved this retrospective use of data. Patients with aortic stenosis were excluded to avoid distortion of the aortic flow pattern. We identified 112 male and female subjects who were evaluated for a wide variety of conditions including LV function evaluation, valvular assessment, myocardial infections and pulmonary artery hypertension. The ejection fractions ranged from 9% to 76% and demographics are given in *Table 1*.

The flow wavelength is difficult to measure directly, and here we use parameters that are proportional to wavelength and that are widely assessable from the clinical CMR data, which are used to form a Flow Index. Classically, wavelength (λ) is related to wave velocity and frequency by Eq. [2]:

$$\lambda = \frac{\text{Velocity}}{\text{Frequency}} \quad [2]$$

Frequency is inversely proportional to the pulse time, and here we used the inverse of the end-systolic ejection time as proportional to the frequency term. Pulsatile blood contains multiple oscillatory velocity terms (which can be quantified by Fourier analysis) but it has been noted that the zeroth Fourier Coefficient of flow is undistorted by non-linear aspects of the intact cardiovascular system (4). Here the zeroth Fourier coefficient, corresponding to average velocity of blood in the aortic outflow tract, was used. Since the aortic outflow tract is typically circular in cross section we took the aortic area as representative of the diameter of

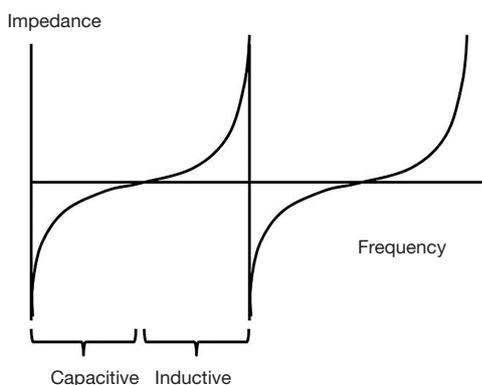


Figure 1 For a tuned circuit with inductive and capacitive components the impedance typically varies in a characteristic way with increasing frequency: at low frequencies it is highly capacitive, at the midpoint impedance is minimized as it goes through a resonance and then transitions to highly inductive impedance at higher frequencies. When transitioning from one tuned band to the next higher band, there is sudden transition from maximal inductance to maximal capacitance.

the transmission orifice, yielding the Flow Index formula:

$$\text{Flow Index} = \frac{(\text{End systolic time} \times \text{Average blood flow velocity})}{(\text{Aortic cross sectional area})} \quad [3]$$

Medis analysis software (Leiden, the Netherlands) was used to contour the aorta in the phase velocity scans to extract the flow parameters of average flow velocity and the area of the aorta. Ejection fraction was calculated from the end diastolic and end systolic left ventricular volumes extracted from a contiguous series of short axis slices covering the LV from base to apex using the Medis software to contour the endocardial LV boundaries. For each tuned band the Flow Index was fitted to model the volumetric EF using a power relationship. For the full range of EF, the power relationship terms were manually adjusted to minimize the least square error between the measured EF and the modeled EF.

Prognostic illustration population

To illustrate the potential for prognostic value we studied a separate population of women with ischemic heart disease in whom follow-up data existed. Among the 935 Women's Ischemia Syndrome Evaluation (WISE) participants undergoing a clinically indicated coronary artery angiography, a sub-population consisting of 213

Table 1 Patient demographics

Variable	Development population (n=112)	Prognostic population (n=201)
Age (years)	54±16	59±11
Body mass index (kg/m ²)	29±7	29±6
Systolic blood pressure (mmHg)	136±19	141±24
Heart rate (bpm)	69±15	69±13
Ejection fraction (%)	49±15	62±11
Gender female	57%	100%

women with suspected myocardial ischemia also underwent a clinically indicated CMR functional evaluation. This prospective sub-study was performed at a single WISE site, the University of Alabama at Birmingham, and included those with no contraindications for CMR examination. All subjects provided written informed consent using forms and procedures approved by the Institutional Review Board. The WISE study design and methodology have been previously described (5,6). In brief, upon enrollment, demographic, CAD risk factors, medical and reproductive history, and functional capacity data were collected as well as blood sampling for Lipid Core Laboratory evaluation. Only patients with CMR EF data were included for this analysis (n=201).

Follow-up consisted of a scripted telephone interview performed by an experienced WISE Research Coordinator at 6-week after enrollment and annually thereafter. The major adverse cardiovascular events (MACE) collected were reduced from the standard WISE MACE to only include cardiovascular-related mortality, first incidence of nonfatal myocardial infarction or hospitalization for heart failure. Follow-up was conducted for 38±14 months. In the event of death, a death certificate and/or hospital record was obtained and a panel of experts adjudicated whether death was cardiovascular related using predetermined criteria.

Statistical analysis

Continuous values were presented as mean ± SD and categorical variables as percent frequency. Continuous clinical and demographic characteristics were compared between groups using the independent samples *t*-test;

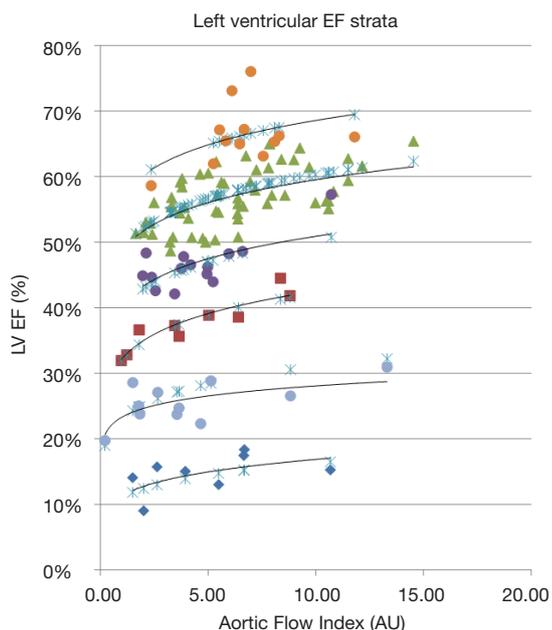


Figure 3 Plot of the measured LV EF for 112 patients against the Flow Index. For each of six distinct vertical Flow Index strata a line fit of the form: $EF_b \cdot Flow-Index^{Power}$ (black solid lines) is shown for each EF band (1-6, orange, green, purple, red, gray, and blue, respectively). The blue crosses represent the Flow Index model fit over the whole range of EF using the parameters of *Table 2*.

positions of MACE. The Δ_{center} parameter was entered into a ROC analysis, along with the raw EF values, and generated area under the curve (AUC) values of 0.73 and 0.62, respectively. Focusing on the patients with EF greater than 60%, the corresponding ROC analysis AUC values are 0.79 and 0.48 for the Δ_{center} and raw EF values, respectively.

Discussion

Possible Flow Index association with MACE

The Flow Index presented here was derived from conditions measured in the aorta in the development population and was predictive of EF with a distinct periodic pattern repeating approximately every 10 EF points. In the illustration population we noted that MACE rates exhibited a clear pattern of increased MACE at EF positions separated by approximately 10 points. Further, for the illustration population, we characterized the distance from the central position within each EF band between the MACE peak response positions, and showed that it was more predictive of MACE than the raw

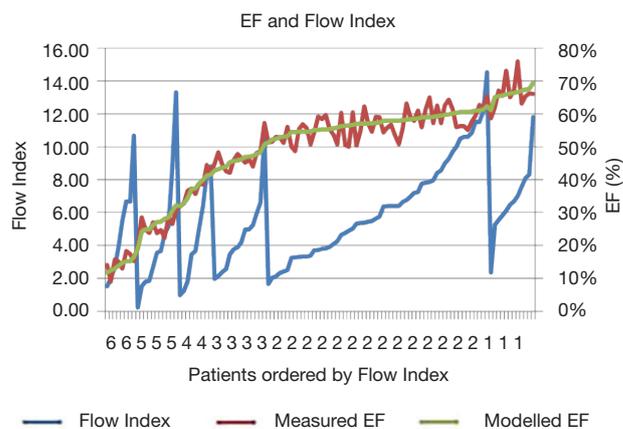


Figure 4 Plot of the measured LV EF for 112 patients (red) along with the Flow Index model fitted-EF (green) right axis, and the Flow Index (blue), left axis. Data are ordered by Flow Index band, and by the fitted EF within each band.

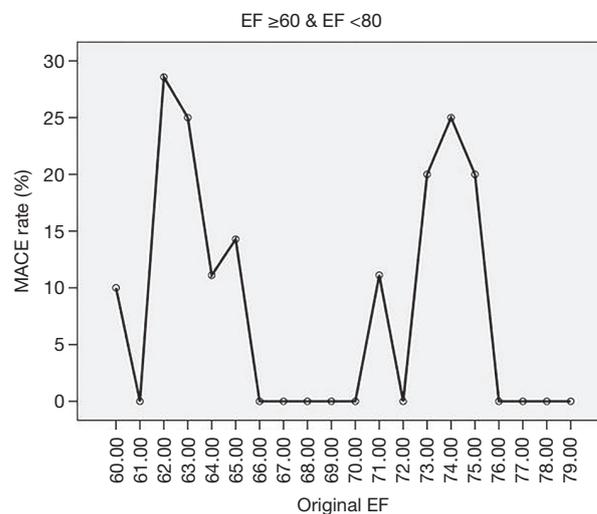


Figure 5 For the WISE population with EF in the 60s and 70s the major adverse cardiovascular event rate is plotted for each EF value in increments of unity.

EF value. These data are strongly suggestive that MACE rates are related to impedance conditions, but the exact relationship cannot be determined from this data. Solomon *et al.* noted that above 45%, EF has no predictive value in heart failure patients (7), which is consistent with the data presented here, where for the range 60–79% EF had a negligible predictive value. Nevertheless, high MACE rates may still be expected in patients with preserved EF as noted by Owan *et al.* (8). Here we observed that distance from a central position within

each EF band (Δ_{center}) for women with preserved EF was predictive of MACE. It is reasonable to suppose that this may correspond to a certain condition of the Flow Index, but we note that while the Flow Index can be used to derive the LVEF, knowledge of EF does not allow us to unambiguously calculate the Flow Index due to the inherent limits on accuracy in measuring EF. Consider that in transitioning from an EF of 69% to 71%, conditions may correspond to transitioning over a resonance band boundary or they might correspond to the subject remaining in the same EF band (*Figure 1*). However, when measuring the Flow Index directly, for the same change in EF, whether the subject remains within a resonance band or transitions to another band is clearly discernible in the smooth *vs.* sudden transition of the Flow Index. Thus, while Flow Index relates to EF (equation 4), knowledge of EF does not allow unambiguous calculation of the Flow Index. Consequently, because aortic flow is not typically measured with traditional imaging modalities and protocols, this phenomena has not been previously observed, and currently, the AHA/ACC guidelines for assessment of risk for cardiovascular disease do not recommend differentiating patients based on aortic flow conditions (9,10).

Flow Index matching to EF

The concept of modeling the efficiency of cardiac ejection has been extensively approached from the ventricular performance side (11). For instance, Yotti *et al.* (12) noted that often EF is an inadequate metric for ventricular assessment due to differences in loading conditions. They found that the interventricular pressure differences that occurred during peak ejection strongly correlate with the more fundamental measure of maximal myocardial elastance over a wide range of conditions. Interestingly, their model incorporated the velocity of ejected blood and the ejection time assessed at the level of the LV outflow tract, which are similar to the parameters contributing to the aortic-derived Flow Index described here. In the development population we showed that while EF varied in a smoothly continuous manner over consecutive Flow Index bands, the Flow Index demonstrated a sudden discontinuity at band boundaries. Further, the Flow Index likely indicates the net result of adjustments made by the cardiac and vascular systems which has potential to accommodate a variety of cardiac loading conditions.

Physiologic response of Flow Index variables

As shown in the development population, as the transition

is made from one EF band to another, the individual components of the Flow Index make sudden, discontinuous changes at both the upper and lower boundaries of each band. In particular the aortic area makes a large transition (e.g., form a high cross sectional area to a low cross sectional area). The data presented here represent a cross-sectional view of conditions for 112 individuals in the development population. However, we have no information on how physiologic conditions vary to affect the transition between resonant bands for an individual. Rosen *et al.* indicated that the transition from compensatory concentric remodeling to myocardial failure is not completely understood (13) and further distinction is made between systolic and diastolic heart failure (14). In the Multi-Ethnic Study of Atherosclerosis, Lilly *et al.* showed that alternations in the large conduit vessels, rather than changes in microvascular resistance, are primarily related to the incident cardiovascular disease (15), which is consistent with the large changes in aortic area noted during transition between bands. Boom *et al.* (16) have shown that there is interplay between ejection volume, blood velocity and pressure. Further, Lam *et al.* (17) have shown that high flow conditions affect vasorelaxation via the generation of nitric oxide, which again may influence both capacitive and inductive impedance components that influence the Flow Index. Under experimental conditions, Chang *et al.* (18) administered streptozotocin to rats to induce diabetes and observed that paradoxically as the maximal myocardial elastance reduced, the blood flow velocity increased, which in this model is consistent with transitioning to a lower Flow Index band. In a similar experiment, Yeih *et al.* (19) demonstrated that early responses to failure involve increases in blood velocity, and over time as velocity decreases a period of preserved function is observed, only to subsequently decline as velocity decreases, which is well explained in terms of the Flow Index model. Chang *et al.* (20) demonstrated that as rats age, at 24 months, maximal flow velocity increased, which is consistent with adjustments of Flow Index that occur within a single band. Davies *et al.* (21) have shown that an excess pressure integral index that can be derived from dynamic blood pressure data is associated with high event rates. Since pressure gradient is a driver of flow, this likely corresponds to conditions directly described by the Flow Index, which importantly, can be derived from flow conditions and which may be easier to obtain non-invasively.

Limitations

The Flow Index was derived in a population of men and women, while the prognostic data were obtained in an

exclusively female population characterized by EF, which only indirectly relates to the Flow Index. Modeling the EF in 6 bands, even with a poor model, would produce a very good correlation with the measured EF (since the goodness of fit is dominated by the high data range). However, confidence in the Flow Index model is reinforced when considering that in the development population each EF band had a width of approximately 10 EF points, and that in the illustration population regions of high MACE rates were separated by approximately 10 EF points, especially in the sub group with EF >60%. However, further work is needed to relate the occurrence of MACE with respect to the exact Flow Index conditions, and to determine if there are characteristic differences in this index between men and women. The present study focused on LV systolic function, with no specific consideration of diastolic properties. Zile *et al.* have speculated that alterations in arterial stiffness may also affect properties of active relaxation and passive stiffness (22). Further studies will be needed to determine these interrelationships and their clinical prognostic value.

Conclusions

In a development population we have shown that a Flow Index can be used as a measure of impedance of LV ejection and that it can be derived from measurements of aortic flow. The Flow Index can be used to derive EF and exhibits characteristics of a resonance phenomenon. In a separate exclusively female illustrative population with only a measurement of EF available, the occurrence of MACE exhibited a periodic nature. Further investigation is needed to characterize the Flow Index, determine its exact relationship to MACE, and to determine how it transitions for an individual.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board (IRB) [study number: RC-1717; study title: WISE Study (Women's Ischemic Syndrome Evaluation)], and written informed consent was obtained from all patients.

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