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Quantitative assessment of left ventricular diastolic function via Longitudinal and Transverse flow impedances

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Abstract— **Flow impedance has been used to characterize the physical properties of the vascular system by assessing its phasic flow response to pulsatile pressure input in terms of resistance as a function of frequency. Impedance has also been used to characterize global diastolic left ventricular (LV) chamber properties. In early diastole the LV is a mechanical suction pump and accommodates filling by simultaneously expanding in two principal spatial directions: longitudinal (base-to-apex, long-axis) and transverse (radial, short-axis). Total (characteristic) impedance Z_C is the product of longitudinal (Z_L) and transverse (Z_T) impedance as $Z_C^2=Z_LZ_T$ where the two impedances reflect the relative spatial propensity for volume accommodation. In this work we compute Z_L and Z_T for the LV in early diastole. We analyze simultaneously recorded dual pressure-transducer and transthoracic echocardiographic flow data obtained during cardiac catheterization in 11 subjects. We found that Z_L was 2 orders of magnitude smaller than Z_T in all subjects, providing the first hemodynamic evidence, in concordance with cine-MRI imaging data that longitudinal volume accommodation is indeed, nature's preferred spatial filling mechanism. We also investigated the effect of impaired diastolic function on directional impedances and found that Z_L increased (becomes worse) while Z_T decreased (becomes better) indicating that as diastolic function becomes impaired radial filling compensates for decreased longitudinal volume accommodation to preserve stroke volume. These results provide mechanistic insight and show that normal diastolic function defines a properly impedance matched state and that diastolic dysfunction is equivalent to a state of impedance mismatch.**

I. Introduction

Left ventricular (LV) filling occurs in response to the development of pressure gradients. As the LV relaxes, LV pressure drops below atrial pressure, the chamber wall recoils faster than it can fill, thereby creating a gradient that aspirates (dP/dV<0) atrial blood into the chamber. Due to chamber geometry, the LV expands anisotropically as it accommodates the aspirated volume. The LV has two dominant volume accommodating spatial degrees of freedom- longitudinal (base to apex i.e. long-axis) and transverse (radial or short-axis).

The left heart, comprised of the left atrium and the LV, can be kinematically approximated as a (near) constant-volume pump [1]. Accordingly, the atrial and ventricular volumes simultaneously reciprocate so that when LV volume is ejected the atrium fills and vice-versa. The outer (epicardial) surface remains relatively stationary. The LV fills in diastole by thinning of the LV wall and simultaneous ascent of the plane of the mitral annulus. Chamber filling dynamics can be decomposed into longitudinal and radial expansion components or volume accommodation properties of the chamber.

The energetics associated with filling can be quantified by evaluating the characteristic impedance of the chamber. Because LV pressure and flow are oscillatory (pulsatile), flow impedance quantifies the resistance to filling by taking into account the phase difference between pressure and flow. Flow impedances have been previously employed to characterize properties of the aorta and the arterial system. Studies [2,3,4] have shown that the aortic impedance increased with vascular dysfunction (stiffening) and age. Arterial impedance has also been used to evaluate the power required by the LV to generate the needed pressure gradient [5]. Based on the ability of flow impedances to quantify vascular system properties, Wu et al [6] have applied the concept of impedance analysis to LV filling. They found that LV characteristic impedance increases with higher harmonics, concluding that efficient filling occurred at lower harmonics.

Total (characteristic) impedance can be decomposed into longitudinal and transverse impedance components. These directional impedances permit characterization of diastolic function. Hence, in this work, we extend Wu's global LV impedance analysis to include directional impedances during early, rapid filling. We compared longitudinal impedance to characteristic impedance and to transverse impedance. The lowest value of impedance reveals the preferred spatial mode of filling. Our analysis can also reveal how longitudinal or transverse impedances may be altered relative to control in response to diastolic dysfunction.

In this work we used established expressions for directional and characteristic impedance to compute impedances during early rapid filling using simultaneous cardiac catheterization and Doppler echocardiography data. We hypothesize that transverse and longitudinal impedance will reveal the preferred spatial mode of filling, i.e. filling volume accommodation.

II. Methods

A. Data acquisition

We used the previously detailed [7, 8, 9] method of simultaneous cardiac catheterization and echocardiography. Briefly, immediately before catheterization, the patients were imaged using a Philips iE33 system (Philips, Best Netherlands). Two dimensional images in apical 2- and 4-chamber views were obtained. In accordance with convention, the apical 4-chamber view was used for Doppler E-wave recording with the sample volume located at the

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leaflet tips. Simultaneous LV pressure and volume was obtained using a Millar triple pressure transducer, conductance catheter (Model 560-1, 560-5, SSD-1034 Millar Instruments, TX). With the catheter in the LV, Doppler E-waves were recorded. High fidelity pressure and trans thoracic Doppler transmitral flow data were synchronized and analyzed off-line using custom software. Pressure-flow synchronization was achieved through the alignment of a fiducial pressure square-wave sent to both echocardiographic and pressure signals during data acquisition.

B. Data processing

Transmitral flow data: Echocardiographic transmitral flow velocity (Doppler E-wave) images were extracted from the imager and converted to image file format (.bmp). Images were cropped and conventional echo parameters of DF (E_{peak}, E-acceleration time, E-deceleration time) were determined using a custom MATLAB (MathWorks, Natick, MA) program. Additionally, the digitized maximum velocity envelope for each E-wave provided velocity as a function of time.

Pressure data: The method has been described before [9]. Briefly pressure was converted via a custom Matlab script (Matlab 6.0; MathWorks, Natick, MA). Data sets were smoothed digitally by using a five-point average to suppress noise in the derivative, attenuating 50% of signal at 40 Hz and 90% above 60 Hz, followed by calculation of continuous dP/dt vs. time t from the smoothed data.

C. Calculating flow impedance

The characteristic impedance is defined as the ratio of pressure and flow rate [10]. Impedance is defined in the frequency domain, and is calculated by taking the Fourier transform of pressure and flow. Mathematically the expression of the total (characteristic) impedance (Z_c) of the system is:

$$Z_C = \frac{P(\omega)}{Q(\omega)} \qquad \{1\}$$

P(ω) is the Fourier transform of LV pressure and Q(ω) is the Fourier transform of the flow rate. Z_c is calculated by taking the ratio of the amplitudes at the same harmonic. The longitudinal impedence (Z_L) is defined as the ratio of the spatial pressure gradient and flow rate. Z_L is also calculated by using the Fourier coefficients of pressure gradient and flow rate. Mathematically the expression is:

$$Z_L = -\frac{1}{Q(\omega)} \times \frac{dP}{dz}(\omega) \qquad \{2\}$$

dP(ω)/dz is the Fourier transform of the LV pressure gradient. Transverse impedance (Z_T) is defined as the ratio of the pressure to the flow gradient. Z_T is also calculated using the Fourier coefficients of pressure and flow gradient. The equation for Z_T is:

$$Z_T = -\frac{P(\omega)}{\frac{dQ}{dz}(\omega)} \qquad \{3\}$$

dQ(ω)/dz represents the Fourier transform of the LV flow gradient. From the multi pressure transducer catheter LV pressures recorded at two locations in the LV were obtained. These two pressure channels were averaged to get the value of LV pressure. Spatial pressure gradient was calculated by taking the difference between the two pressures and dividing by the distance between the transducer locations on the catheter (3 cm). This method assumes that the pressure gradient between the 2 transducers is linear. Flow rate was calculated as the product of transmitral flow (Doppler E-wave) velocity (cm/sec) and effective mitral orifice cross-sectional area (cm^2). From this data, Z_c was calculated from {1} and Z_L was calculated from {2}. We used the

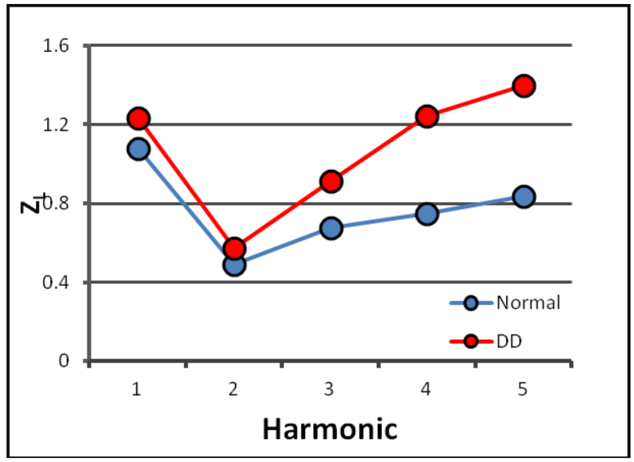

Figure. 1: Longitudinal impedance (Z_L) values for the DC component (labeled 1st) and the first 4 harmonics in 2 subjects. Blue indicates a subject with normal diastolic function. Red indicates a subject with dysfunction. See text for details.

relationship between Z_c, Z_L and Z_T to calculate Z_T and flow rate gradient.

$$Z_C = \sqrt{Z_L \times Z_T} \qquad \{4\}$$

A custom MATLAB program was used to match LV pressure with the simultaneous Doppler E-wave. The interval of early filling was determined, Fourier transform was performed on the pressure, pressure gradient and flow rate. The three impedances were calculated as described

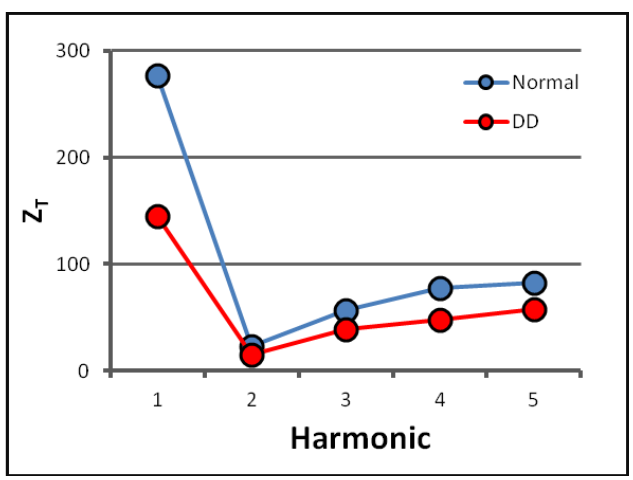

Figure 2: Transverse impedance (Z_T) values for the DC component (labeled 1st) and the first 4 harmonics in 2 subjects (Same subjects as Fig 1). Blue represents the subject with normal diastolic function. Red represents the subject with diastolic dysfunction. See text for details.

above.

D. Numerical and statistical analysis

For each subject, the desired parameters were calculated for an average of 37 beats per subject and averaged to obtain the parameter value for each subject.

III. Results

We selected 11 datasets (5 male) from our simultaneous echocardiography-catheterization database. The average age

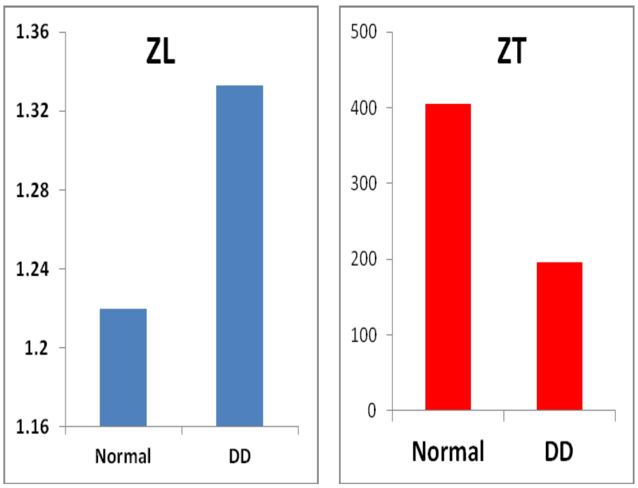

Figure 3: Comparing the value of Z_L and Z_T in normal and diastolic dysfunction groups. (Left) Z_L values increase between normal and DD groups. (Right) Z_T values decrease between normal and DD groups. See text for details.

of all subjects was 56 years. All subjects had normal ejection fraction. 7 of the subjects had normal diastolic function (DF) and 4 subjects had diastolic dysfunction (DD) (as defined by the ratio of total peak filling velocity and peak mitral annulus longitudinal velocity; E_{peak}/ $E'_{peak} > 8$ and $E'_{peak} < 8$ cm/s). We analyzed a total of 407 beats (average of 37 beats per subject).

Fig. 1 shows the DC component and the first 4 harmonics of Z_L for 2 selected subjects. The subject in blue has normal DF and the subject in red has DD. In both, the amplitude of the DC component is higher than the first harmonic, which has the lowest amplitude. The higher harmonics increase in magnitude. The average value of the DC component of Z_L for the normal groups was 1.2±0.3 mm Hg. s/(cm)^4. For subjects with DD, the average value of the DC component of Z_L was 1.3±0.1 mm Hg. s/(cm)^4. The average value of the first harmonic for normals is 0.8±0.3 mm Hg. s/(cm)^4 and for the DD group is 0.5±0.2 mm Hg. s/(cm)^4. These differences were not statistically significant.

Fig. 2 shows the DC component and the first 4 harmonics of Z_T for 2 subjects shown in Fig. 1. Blue denotes the subject with normal DF and red denotes the subject with DD. Similar to the trends seen in Z_L, the DC component of Z_T is higher than the first harmonic and subsequent harmonics increase in value. However, the amplitude of higher harmonics of Z_T are lower than the amplitude of the DC component. The average value of the DC component of Z_T for the normal group was 403±277 mm Hg. s/(cm)^2 and for the DD group was 195±175 mm Hg. s/(cm)^2. The value of the first harmonic for the normal DF group was 29±12 mm Hg. s/(cm)^2 and the DD group was 16±16 mm Hg. s/(cm)^2. The average values of Z_L and Z_T for the 2 groups are shown in Fig. 3. These differences were not statistically significant.

We also calculated the value of Z_c using {1}. The average value of the DC component of Z_c for normal subjects was 19±6 mm Hg. s/(cm)^3 and for DD subjects was 15±6 mm Hg. s/(cm)^3.The value of the first harmonic of Z_c for normals was 5±2 mm Hg. s/(cm)^3 and for DD subjects was 3±2 mm Hg. s/(cm)^3. The average value of Z_L was the smallest of the three impedances and it was 2 orders of magnitude smaller than Z_T. These differences were not statistically significant.

IV. Discussion

In this study we calculated left ventricular longitudinal and transverse impedance during the early rapid (Doppler E-wave) phase of diastole using human in-vivo data obtained in a clinical setting. We computed the directional impedances in 11 subjects. We found that longitudinal impedance was much lower than transverse impedance. We therefore provided evidence that longitudinal (long-axis) is nature's preferred directional mode of filling (based on the relative values of Z_L and Z_T). Harmonic analysis of LV filling and quantification of impedances offers a new approach for quantitative DF assessment. Using impedances the alterations in the LV filling due to chamber dysfunction including the effects of compensatory mechanism can be appreciated. Because impedance calculation requires simultaneous LV pressure and flow data, it reveals how phase manifests in both and how changes in pressure are reflected in changes in filling patterns.

As the LV relaxes, pressure drops rapidly and it creates an atrio-ventricular pressure gradient which aspirates the blood into the ventricle as the mitral valve opens. In accordance with the laws of fluid mechanics, in a pulsatile setting, such as LV filling, flow lags pressure. Hence quantifying flow resistance in terms of frequency and amplitude takes into account the phase difference. Wu et al [6] have previously shown based on energetics associated with filling that in the lowest harmonic; the LV has to do the least amount of work to maximize filling volume. They also showed that the characteristic impedance of the LV (Z_c) was lowest for the first harmonic and increased with subsequent harmonics.

Pioneering work using cardiac MRI by the physiology group in LUND [11] has shown that the near constant volume physiology of the four-chamber heart [1] requires reciprocation of atrial and ventricular volumes so that when the ventricles empty the atria fill and vice-versa. The requirement that the epicardial surface be essentially immobile while that plane of the atrioventricular valves move longitudinally, resulting in the internal LV diameter to change atleast 4 times as much as the apex- base length as a consequence of conservation of myocardial mass between systole and diastole [12]. Hence, longitudinal volume accommodation in diastole is an established observational phenomenon. However the hemodynamic consequences in terms of impedance as a function of spatial direction have not been previously characterized.

In this study, we expand on this prior knowledge and resolve characteristic LV impedance into its longitudinal and transverse components corresponding to long-axis and short-axis chamber properties. The longitudinal volume accommodating attribute of the LV is measured directly using Doppler tissue imaging of the lateral mitral annulus (E'-wave). With progressive diastolic dysfunction peak E'-wave velocity decreases indicating impairment in longitudinal motion and in turn a decrease in longitudinal volume accommodation capacity. In the initial stages of dysfunction this decrease in longitudinal volume accommodation is compensated by an increase in radial filling. However due to chamber geometry which places a limit on radial extension, the ventricle has to do more work when filling in radial direction.

Directional impedances have the capability to characterize the relative directional filling attributes of the LV. Our results show that as predicted from physiology, the longitudinal impedance (Z_L) is much lower (2 orders of magnitude) than the transverse impedance (Z_T). This quantifies in impedance terms the ease of filling in the longitudinal direction relative to the transverse.

We computed directional impedances in two groups of subjects dichotomized based on their longitudinal (mitral annular peak velocity, E'-wave) motion. Comparing Z_L between the two groups we found that with impaired longitudinal motion (decreased E'-wave peak) Z_L increased. In addition, when Z_T was compared between groups we found that the Z_T decreased with impaired longitudinal motion. Although Z_c, Z_L and Z_T values were not significantly different between normals and subjects with DD, these results were consistent with the hypothesis that the relative volume accommodation capabilities of the chamber change with impaired diastolic function. The non-significant differences in impedance values can be attributed to the small size of the study and subject selection. However, the goal of this study was to understand the trends in Z_L and Z_T variation with pathophysiologic changes.

Directional impedances reflect chamber kinematic properties since global chamber stiffness and viscoelasticity/relaxation determine pressure decay rate and the atrioventricular pressure gradient, which in turn powers filling. Hence directional impedances provide novel insight into global LV chamber kinematic properties. Impedance analysis helps to elucidate and characterize the physiology via a more comprehensive understanding of the causal role by which chamber kinematic properties ultimately influence the fluid mechanics associated with diastolic function.

Z_L and Z_T have the potential to be used as diagnostic indexes for quantitative DF assessment and to quantify the outcomes of therapeutic procedures which are aimed at improving cardiac function such as resynchronization therapy etc. Impedance analysis can also help to evaluate therapeutic efficacy of pharmacologic agents (ACE inhibitors, ARBs, etc) as affecting beneficial remodeling and improvement in DF. The relationship between Z_L and Z_T and ventricular torsion in diastole remains to be elucidated.

V. CONCLUSION

In this study, we evaluated directional flow impedances in the LV during early, rapid filling (Doppler E-wave component) using simultaneous hemodynamic-echocardiographic data obtained during cardiac catheterization. Our hemodynamic results show for the first time, that LV longitudinal impedance is much lower than transverse impedance, in concordance with cine-MRI data [11] that the preferred spatial mode of filling volume accommodation is longitudinal. We also found that with progressive decline in diastolic function, there was an increase (worsening) in longitudinal impedance and a decrease (improvement) in transverse impedance. Our analysis shows that directional impedances can quantify diastolic LV chamber properties and that, relative to normal, diastolic dysfunction can be defined and quantitatively assessed as a state of impedance mismatch.

REFERENCES

1) A.W. Bowman, S.J. Kovács. "Assessment and consequences of the constant-volume attribute of the four-chambered heart." *Am J Physiol Heart Circ Physiol*. 2003;285(5):H2027-33.
2) M.F. O'Rourke. "Vascular Impedance in Studies of Arterial and Cardiac Function." *Physiol. Rev*. 1982;62;1;570-623.
3) FCP Yin, ML Weisfeldt, WR Milnor. "Role of aortic input impedance in the decreased cardiovascular response to exercise with aging in dogs." *J. Clin. Invest.* 1980; 68: 28- 38.
4) NK Sweitzer, M Palta, M Shenoy, T LeCaire, JH Stein, GF Mitchell, S Keles. "Increases in central aortic impedance precede alterations in arterial stiffness measures in Type 1 diabetes." *Diabetes Care*. 2007; 30(11): 2886- 2891.
5) NM Pahlevan, M Gharib. "Low pulse pressure with high pulsatile external left ventricular power: Influence of aortic waves." *J Biomechanics*. 2011; 44: 2083- 2089.
6) Y Wu, AW Bowman, S.J. Kovács. "Frequency- based analysis of diastolic function: The early rapid filling phase generates negative intraventricular wave reflections." *Cardiovasc. Engg.* 2005; 5(1): 1- 12.
7) S.J. Kovács, R. Sester, A.F. Hall." Left Ventricular Chamber Stiffness from Model-based Image Processing of Transmitral Doppler E-waves." *Coron. Artery Dis*. 1997; 8:179-187.
8) S.F. Nagueh, C.P. Appleton, T.C. Gillebert, P.N. Marino, J.K. Oh, O.A. Smiseth, A.D. Waggoner, F.A. Flachskampf, P.A. Pellikka, A. Evangelista. "Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography." *J. Am. Soc. Echocardiogr*. 2009; 22(2):107-133.
9) L Shmuylovich, SJ Kovács. "Stiffness and relaxation components of the exponential and logistic time constants may be used to derive a load-independent index of isovolumic pressure decay." *Am J Physiol Heart Circ Physiol*. 2008; 295(6): H2551-2559.
10) WR Milnor. Hemodynamics. Baltimore MD: Williams & Wilkins, 1982.
11) Carlsson M, Cain P, Holmqvist C, Stahlberg F, Lundback S, Arheden H. Total heart volume variation throughout the cardiac cycle in humans. *Am J Physiol Heart Circ Physiol*. 2004; 287: H243-250.
12) Carlsson M, Ugander M, Mosén H, Buhre T, Arheden H. Atrioventricular plane displacement is the major contributor to left ventricular pumping in healthy adults, athletes and patients with dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol*. 2007; 292: H1452-1459.