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Increase in the Late Diastolic Filling Force is Associated With Impaired Transmitral Flow Efficiency in Acute Moderate Elevation of Left Ventricular Afterload

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Abstract

Aims—Analysis of intraventricular flow force and efficiency is a novel concept of quantitatively assessing left ventricular (LV) hemodynamic performance. We have parametrically characterized diastolic filling flow by early inflow force (EIF), late inflow force (LIF), and total inflow force (TIF) and by vortex formation time (VFT), a fundamental parameter of fluid transport efficiency.

The purpose was to determine what changes in inflow forces characterize a decrease in diastolic blood transport efficiency in acute moderate elevation of LV afterload.

Methods and Results—In 8 open-chest pigs, the flow force and VFT parameters were calculated from conventional and flow Doppler echocardiography measurements at baseline and during brief (3-minute) moderate elevation in afterload induced by increasing systolic blood pressure to 130% of baseline value. Systolic LV function decreased significantly during elevated afterload. EIF did not significantly change, whereas LIF increased from $5,822.09 \pm 1,656.50$ to $13,948.25 \pm 9,773.96$ dyn ($P = 0.0490$) and TIF increased from $13,783.35 \pm 4,816.58$ to $21,836.67 \pm 8,635.33$ dyn ($P = 0.0310$). VFT decreased from 4.09 ± 0.29 to 2.79 ± 1.10 ($P = 0.0068$), confirming suboptimal flow transport efficiency.

Conclusions—Even a brief moderate increase of LV afterload causes a significant increase in the late diastolic filling force and impairs transmitral flow efficiency.

Keywords

Blood flow velocity; diastolic filling; particle image velocimetry

Introduction

Left ventricular (LV) diastolic filling and mechanical function are important indicators of overall cardiac health [1–4] and aid in early diagnosis of cardiovascular disease [1,5]. Clinical evaluation of diastolic filling with Doppler ultrasound imaging represents a noninvasive method for quantitation of transmitral flow velocities and pressure gradients [6–8]. However, evaluation of filling flow velocity does not convey information about forces driving the fluid into the LV and efficiency of transmitral blood transport.

We propose to characterize early and late (atrial) components of diastolic blood transport by physical parameters, including early inflow force (EIF), late inflow force (LIF), and total inflow force (TIF). Efficiency of blood transport can be assessed by vortex formation time (VFT) [9], a parameter with a universal timescale [10]. Formation of a vortex supports a more efficient fluid transport compared to a straight jet alone [11,12] due to minimization of energy dissipation during fluid ejection through an orifice [13]. Using ultrasound particle imaging velocimetry [14], we have previously shown intracardiac vortex formation by an advanced contrast echocardiography approach [15,16] and demonstrated alterations in intracardiac vortices during asynchronous isovolumic phases of the cardiac cycle [17].

In the present study, diastolic blood transport was experimentally altered by an acute moderate increase in afterload. A sudden moderate increase in blood pressure can occur due to activation of the adrenergic system by stress [18] or during paroxysmal hypertension [19], and can impede diastolic function by altering myocardial relaxation [20].

The objective of this study was to determine 1) whether a significant increase in flow force is required to drive transmitral blood transport during moderate LV afterload, 2) whether both early and late components of diastole contribute to the elevated flow force, and 3) whether the experimental intervention represented by a short moderate pressure loading can affect blood transport efficiency, as assessed by VFT.

Materials and Methods

Animal Preparation and Experimental Increase in Afterload

The study was approved by the Mayo Clinic Institutional Animal Care and Use Committee. Pigs weighing 40 to 45 kg were fasted overnight, induced to anesthesia with intramuscular

Telazol (5 mg/kg), Xylazine (2 mg/kg) and Glycopyrrolate (0.02 mg/kg), intubated, and anesthetized by inhalation of 2% isoflurane. Heart rate, cardiac rhythm, and arterial oximetry were monitored. Blood pressure was measured by manometer-tipped catheters (Millar Instruments, Inc, Houston, Texas) placed under ultrasound guidance [21] into the LV, aorta, and left atrium (LA). Following mid sternotomy, the heart was suspended on a pericardial cradle. Toradol (60 mg) and Solu-Medrol (40 mg) prevented a thromboxane-mediated pulmonary hypertension that can develop in the pig following contrast microbubble administration [22].

An experimental increase in LV afterload was induced by a brief (approximately 3-minute) tightening of umbilical tape (Ethicon, Piscataway, NJ) placed as a tourniquet around the ascending aorta, while continuously monitoring blood pressure.

Echocardiographic Scans

Echocardiographic scans were obtained in rapid succession during the brief aortic tightening using a Vivid 7 system (GE Healthcare, Milwaukee, Wisconsin) and a handheld 3.5 MHz transducer placed epicardially for scanning through a bulk of acoustically coupling gel. Standard apical 2, 3, and 4-chamber views and parasternal short axis views of the basal, mid-level, and apical portions of the LV were stored in cine-loop format for subsequent offline analyses. Measurements of LV end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and ejection fraction (EF) was obtained with 2D echocardiography, whereas peak transmitral flow velocities at mitral tip during early (E-wave) and atrial (A-wave) phases of LV filling and their E/A ratio were measured using pulsed-wave Doppler echocardiography.

Hemodynamic Measurements

Basic hemodynamic measures, including peak positive and peak negative dP/dt (ie, $+dP/dt$ and $-dP/dt$, respectively), are summarized in Table 1. LV end-diastolic pressure (LVEDP) was determined at the peak of R-wave on the synchronous ECG tracing.

LV afterload severity was assessed based on systolic blood pressure as $(\text{systolic blood pressure at elevated afterload})/(\text{systolic blood pressure at baseline}) \times 100$. Moderate afterload was defined as 125% and 140% [23], and all pigs in this study fell within this range.

Vascular Resistance

Change in vascular resistance that corresponded to experimental intervention were estimated as $VR = (BPm/CO) \times 80$, measured in $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ [24,25]. In this equation, BPm is mean blood pressure and CO denotes cardiac output calculated from echocardiographically measured stroke volume (SV).

Flow Force Measurements

Flow force (F) is defined as $F = \rho AV^2$ [26], where ρ is the density of blood, ie, 1.06 gm/cm^3 at 37° C [27], $A = (\pi/4) \times D^2$, and D is the largest mitral valve (MV) orifice diameter in cm at the MV tip level during early (De) and late (atrial) (Da) diastolic filling phases to calculate area of MV at leaflet tips during early (E-area) and late (A-area) diastolic filling, EIF and LIF, respectively. Measurement of D in a 4-chamber view is averaged with that obtained in either a 2- or 3-chamber view at the appropriate times of peak E-waves or A-waves. V is transmitral flow velocity (cm/s) derived from the maximum pulse wave Doppler velocity measurement during early (Ve) and late (ie, atrial-phase) inflow (Va) for EIF and LIF calculations, respectively. TIF is defined as the summation of EIF and LIF.

VFT Measurement

VFT is calculated based on work by Gharib and colleagues [9] as follows:

$$\text{VFT} = \frac{4 \times (1 - \beta) \times \text{SV}}{\pi \times (\text{De})^3}, \quad (1)$$

where β is the fraction of stroke volume contributed from the atrial component of LV filling and is estimated from a peak magnitude of the A-wave divided by the sum of the A-wave and E-wave peak magnitudes. SV is measured in mL and De is the MV diameter measured between the tips during the peak of the E-wave.

Data Analysis

Data are presented as mean $\pm$ standard deviation. Hemodynamic, echocardiographic, flow force (ie, EIF, LIF, TIF), and efficiency (ie, VFT) measurements are obtained at baseline and during afterload intervention and compared by a 2-tailed paired t test. The relation of a percent change in LIF and TIF to that in VR is assessed by linear regression. A *P* value <0.05 is considered statistically significant.

Results

Complete measurements were obtained from 8 animals. Two additional animals were not entered into the study because of severe hypotension in one and first degree atrioventricular block in the other, which altered the baseline hemodynamic status.

Hemodynamic Parameters

At baseline, the hemodynamic data were within normal ranges (Table 1). Experimentally increased afterload elevated both the systolic and mean blood pressures. These changes relative to baseline were accompanied by a decreasing trend in cardiac output and an increase in the calculated vascular resistance. The increase in mean systolic blood pressure was 130%, thus generating moderate afterload based on our grading scale.

Diastolic blood pressure and heart rate remained without significant change. LVEDP and $+dP/dt$ did not change with the moderate increase in afterload, whereas the absolute value of $-dP/dt$ decreased significantly.

Echocardiographic Parameters

EDV has not statistically significantly changed, but ESV has an increasing trend and impact on a significant reduction in SV and EF (Table 2). Peak mitral flow velocities during the early (E-wave) filling phase did not change, but velocities during the atrial (A-wave) phase increased significantly although the E/A ratio showed only a trend toward a decrease.

Flow Force and Fluid Transport Efficiency

The mean values of De and Da remained nearly identical at baseline and during moderately elevated afterload (Table 3). E-area, A-area, and Ve did not substantially change during moderately elevated afterload; however, Va increased. The value of α remained nearly identical at baseline and during moderately elevated afterload; however, β increased. These results suggest the impact of intervention on the atrial component of LV filling.

Consequently, the EIF value has not significantly changed, whereas LIF and TIF increased (Figure 1A and 1B, respectively, and Table 4). The intervention was associated with impaired diastolic filling efficiency indicated by a decrease in VFT. Percent changes in LIF

(Figure 2A) and TIF (Figure 2B) with respect to VR suggest an inverse trend, especially in the case of TIF, but no significant correlation was found.

Discussion

The main finding is that an acute moderate elevation in ventricular afterload increases the force required to maintain transmitral flow and eliminates optimal fluid transport conditions. In particular, total inflow force increases due to augmentation in the late inflow force, whereas early inflow force, the other component of TIF, is not significantly changed. The mean VFT values during the acute intervention no longer match the normal VFT range, thus indicating a negative impact of a sudden moderate elevation of LV afterload on transmitral flow efficiency.

Assessment of LV Systolic and Diastolic Function During Elevated Afterload

In our setting, the elevated resistance to LV ejection is reflected by a significant increase in the VR parameter and was controlled by maintaining the systolic blood pressure at approximately 130% of its baseline value (Table 1), which yields a moderate elevation in afterload. In systole, the afterload elevation resulted in reduced SV accompanied by decreases in EF and CO and by elevation in the mean ESV. In diastole, the impact of moderately increased afterload on relaxation results in E/A ratios less than 1 and occurs primarily from an increase in A-wave velocity (Table 2). Consistent with results by others [23], the rate of LV pressure increases (ie, $+dP/dt$) and has not been affected by the moderate elevation in afterload. However, the magnitude of an LV pressure fall (ie, that of $-dP/dt$) significantly decreases, and such findings can be explained as follows [23]: in other studies at low afterload, the onset of LV pressure is delayed and the rate of an LV fall is therefore accelerated (ie, the $-dP/dt$ magnitude increases). However, in our study, with moderately increased afterload, the onset of LV pressure fall occurs earlier, and the $-dP/dt$ magnitude decreases. The decrease in the $-dP/dt$ magnitude occurred without a significant increase of LVEDP, EDV, or E/A ratio (Table 1,2). Considering that $-dP/dt$ index is relatively load-independent [28–30], it is useful in assessing changes in LV function with acute interventions [31], although this index is of a less value in analyses of baseline LV function or differences in LV function among patients or in any given patient at different times [32]. In a clinical setting, it is well known that diastolic dysfunction is common in systolic heart failure [33] and patients with diastolic heart failure show abnormalities in systolic function [34–37]. Furthermore, there is evidence that patients with diastolic dysfunction can progress to systolic heart failure, particularly those with poorly treated (chronic) hypertension [38,39]. Our experimental setting represents acutely increased blood pressure. Thus, it is expectable that EF and SV were significantly decreased following the experimental intervention because there was not enough time to develop a physiological compensatory mechanism. However, it is conceivable that an acute diastolic dysfunction developed and presented itself as a decrease in the $-dP/dt$ magnitude even without an increase in LVEDP or EDV. As a consequence, transmitral blood transfer was impaired in the early diastolic period, which prompted increased LA contraction expressed as increased A-wave velocity to maintain adequate diastolic blood filling. We therefore propose the decrease in the $-dP/dt$ magnitude in the isovolumic relaxation period as a parameter indicating an early response of LV to the increased LIF and TIF in a setting of acute moderate elevation in LV afterload.

Blood Transport Efficiency Analysis by VFT and Flow Force Parameters

Normal VFT value falls within the range of 3.3 to 4.5 [10]. Outside this range, fluid dynamic physical constraints limit vortex growth and either a flow efficiency-impairing trailing jet occurs behind the vortex ring [10], the vortex disintegrates (as in our study), or

the vortex pinches off from the jet [40]. The law of energy conservation states that the total amount of energy in any isolated system remains constant, but individual forms of energy can change from one to another, such as friction turning kinetic energy into potential or thermal energy [41]. Consistently with work by others [13], our study suggests that the vortex serves as a transitory storage of kinetic energy, contributing to redirection of blood flow to the LV outflow tract prior to aortic valve opening [15,17]. The moderately elevated afterload in our study results in grade 1 diastolic dysfunction, defined by a low early (E-wave) component and an increased late (A-wave) component, which results from augmented atrial contraction [42]. At this stage, the LA generates more force that converts to flow forces, captured by LIF and TIF parameters, and in turn acts against friction in the aorta to maintain homeostasis in the circulation. This process could be a diastolic component of an adaptive functional mechanism activated in response to elevated LV afterload. However, as shown by this study, such mechanism can compromise transmitral flow efficiency.

Our results in Table 3 suggest that of all component parameters of LIF and TIF, only V_a is an influential factor prompting the increase in LIF and TIF values. We have not found a convincing linear relationship between percent increase in vascular resistance and percent change in LIF and TIF (Figure 2). We speculate that besides the relative homogeneity of generated afterload values in our setting, the reason could also be in nonlinearity of transition from the kinetic energy of blood flow to kinetic energy dissipation, as it is acting against the increased afterload.

Study Limitations

We have calculated VFT (specifically, the β value) and flow forces from peak velocities rather than velocity integrals of the E- and A-waves. We found it difficult to separate clearly the areas under the E- and A-waves in Doppler data obtained during the increased afterload because the waves tended to merge. Accordingly, rather than taking a time-averaged mitral valve diameter [9], we used a mean diameter calculated from maximum opening diameters obtained in 2 apical projections. These simplifications have not impacted the consistency of our results with VFT analyses by others [9,10] and may contribute to the practicality of any future clinical implementation of the method. We assumed that the area of the MV orifice was ellipsoidal to calculate the area in the flow jet force formula.

Clinical Perspectives

Flow jet forces are physical measures of transmitral blood flow that can be calculated using existing noninvasive clinical echocardiographic measures. In patients with diastolic dysfunction, the changes in flow jet forces can be useful indicators of the clinical severity and success of therapy.

Conclusions

An experimental acute moderate increase in ventricular afterload substantially increases the late and total inflow forces and, thus, impairs fluid transport efficiency. Clinical implementation of noninvasively measurable, fundamental fluid dynamic indices, such as flow jet forces, can contribute to early detection and therapeutic optimization of diastolic dysfunction.

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Figure 1.
A) Relation between late inflow force (LIF) at baseline and during moderate afterload. B) Relation between total inflow force (TIF) at baseline and during moderate afterload.

Figure 2.

A) Relation between percent change of vascular resistance (VR) and percent change of late inflow force (LIF). **B)** Relation between percent change of VR and percent change of total inflow force (TIF).

Table 1**Hemodynamic Parameters**

Variable	Baseline	Afterload	P value
BPs (mm Hg)	101.95 ± 12.08	132.90 ± 10.67	0.0035
BPd (mm Hg)	74.36 ± 12.51	81.20 ± 28.02	0.3375
BPm (mm Hg)	83.56 ± 10.76	98.43 ± 18.21	0.0136
HR (beats/min)	73.92 ± 7.96	79.26 ± 14.41	0.3356
CO (mL/min)	2760.05 ± 390.78	2334.31 ± 523.87	0.0843
VR (dyne sec cm ⁻⁵)	2443.98 ± 344.03	3475.17 ± 705.06	0.0055
LVEDP (mm Hg)	13.31 ± 3.21	17.75 ± 6.28	0.1472
+dP/dt (mm Hg/sec)	1302.25 ± 209.73	1309.63 ± 259.33	0.9519
−dP/dt (mm Hg/sec)	−2297.75 ± 492.18	−1944.75 ± 580.56	0.0097

Abbreviations: +dP/dt, maximum positive LV pressure change; −dP/dt, maximum negative LV pressure change; BPd, blood pressure diastolic; BPm, mean arterial blood pressure; BPs, blood pressure systolic; CO, cardiac output; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; VR, vascular resistance.

Table 2

Echocardiographic Parameters

Variable	Baseline	Afterload	P value
EDV (mL)	67.06 ± 5.62	68.13 ± 6.12	0.6999
ESV (mL)	29.75 ± 3.71	38.13 ± 11.09	0.0867
SV (mL)	37.31 ± 3.06	30.00 ± 7.43	0.0178
EF (%)	0.56 ± 0.03	0.45 ± 0.12	0.0419
E (m/s)	0.52 ± 0.11	0.51 ± 0.12	0.8974
A (m/s)	0.46 ± 0.07	0.65 ± 0.19	0.0221
E/A	1.13 ± 0.14	0.85 ± 0.29	0.0746

Abbreviations: A, peak transmitral flow velocities at late filling phases; E, peak transmitral flow velocities at early filling phase; EDV, left ventricular end-diastolic volume; EF, ejection fraction; ESV, left ventricular end-systolic volume; SV, stroke volume.

Table 3

Flow Force and Vortex Formation Parameters

Variable	Baseline	Afterload	P value
De (cm)	1.83 ± 0.06	1.86 ± 0.04	0.3159
Da (cm)	1.80 ± 0.09	1.89 ± 0.09	0.1152
E-Area cm ²	2.64 ± 0.17	2.71 ± 0.12	0.3298
A-Area cm ²	2.55 ± 0.26	2.82 ± 0.27	0.1212
Ve (cm/sec)	52.00 ± 11.00	51.00 ± 12.00	0.8974
Va (cm/sec)	46.00 ± 7.00	65.00 ± 19.00	0.0221
α	2.22 ± 0.03	2.20 ± 0.07	0.4326
β	0.47 ± 0.03	0.56 ± 0.10	0.0827

Abbreviations: α, LV geometry parameter; β, the fraction of the stroke volume contributed from LV A-wave filling; A-Area, area of MV orifice during late diastole; Da, diameter of MV orifice during late diastole; De, diameter of MV orifice during early diastole; E-Area, area of MV orifice during early diastole; Va, transmitral flow velocity during the atrial-phase inflow; Ve, transmitral flow velocity during the early inflow.

Table 4

Fluid Transport Efficiency Parameters

Variable	Baseline	Afterload	P value
EIF (Dyn)	7961.26 ± 3456.26	7888.42 ± 3279.83	0.9740
LIF (Dyn)	5822.09 ± 1656.50	13948.25 ± 9773.96	0.0490
TIF (Dyn)	13783.35 ± 4816.58	21836.67 ± 8635.33	0.0310
VFT	4.09 ± 0.29	2.79 ± 1.10	0.0068

Abbreviations: EIF, early inflow force; LIF, late inflow force; TIF, total inflow force; VFT, vortex formation time.