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Impact of Acute Moderate Elevation in Left Ventricular Afterload on Diastolic Transmitral Flow Efficiency: Analysis by Vortex Formation Time

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Abstract

Background—Formation of a vortex alongside a diastolic jet signifies an efficient blood transport mechanism. Vortex formation time (VFT) is an index of optimal conditions for vortex formation. We hypothesized that left ventricular (LV) afterload impairs diastolic transmitral flow efficiency and, therefore, shifts the VFT value out of its optimal range.

Methods—In 9 open-chest pigs, we elevated LV afterload by externally constricting the ascending aorta and increasing systolic blood pressure to 130% of baseline value for 3 minutes.

Results—Systolic LV function decreased, diastolic filling velocity increased only during the late (atrial) phase from 0.46 ± 0.06 to 0.63 ± 0.19 m/s ($P = 0.0231$), and end-diastolic LV volume and heart rate remained unchanged. VFT decreased from 4.09 ± 0.27 to 2.78 ± 1.03 ($P = 0.0046$).

Conclusion—An acute, moderate elevation in LV afterload worsens conditions for diastolic vortex formation, suggesting impaired blood transport efficiency.

Keywords

blood flow velocity; vortex formation; diastolic filling

Left ventricular (LV) diastolic filling and mechanical function are important indicators of overall cardiac health status [1-4] and aid in early diagnosis of cardiovascular disease [1,5]. Clinical evaluation of diastolic filling with Doppler ultrasound is, however, angle-dependent and limited both in detecting flow alterations in early stages of cardiac disease [6] and spatial characterization of intraventricular flow patterns.

We have shown by echocardiographic particle imaging velocimetry [7], or echo PIV [8] - and other investigators demonstrated by magnetic resonance imaging [9] - that transmitral flow

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can produce an intraventricular rotational body of fluid referred to as a vortex ring [10-12], which supports a more efficient fluid transport compared to a straight jet alone [13,14]. Gharib et al. [15] derived a dimensionless index for quantitatively characterizing the optimal conditions for vortex formation from the duration of flow through an orifice with known diameter and, thus, referred to the index as vortex formation time (VFT), and proposed that the process of vortex ring formation during diastole could serve as an indicator of cardiac health.

Acute changes in afterload, such as those induced by a sudden increase in blood pressure due to activation of the adrenergic system during stress [16] or paroxysmal hypertension [17], can negatively impact diastolic filling [18]. We hypothesized that an acute moderate increase in LV afterload, accomplished by mechanical aortic constriction, would alter transmitral blood transport efficiency and, therefore, the VFT value as compared to the baseline condition.

Methods

Animal Preparation

The study was approved by the Mayo Clinic Institutional Animal Care and Use Committee. Pigs weighing 40 to 45 kg were fasted overnight, sedated with Telazol (5 mg/kg), Xylazine (2 mg/kg), and Buprenex (0.005 mg/kg), intubated, and anesthetized by isoflurane inhalation. Heart rate, cardiac rhythm, and arterial oximetry were continuously monitored. Blood pressure was monitored by manometer-tipped catheters (Millar Instruments, Inc, Houston, TX) placed under ultrasound guidance [19] into the LV, aorta (upstream to the constricted segment described below), and LA. Following midsternotomy, the heart was suspended on a pericardial cradle.

Experimental Intervention

An experimental increase in LV afterload was induced by briefly (approximately 3-minute) constricting a short segment of ascending aorta by umbilical tape (Ethicon, Piscataway, NJ) placed as a tourniquet. The corresponding level of vascular resistance (VR) was estimated as [20]:

$$VR = \frac{BP_m}{CO} \times 80,$$

where BP_m (mmHg) is mean blood pressure, CO (L/min) denotes cardiac output, and the constant 80 is a conversion factor so that VR is measured in $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ [21].

Hemodynamic Measurements

Basic hemodynamic measurements are summarized in Table 1. LV end-diastolic pressure (LVEDP) was determined at the peak of the R-wave on the synchronous ECG tracing. Besides peak positive and peak negative dP/dt (ie, $+dP/dt$ and $-dP/dt$, respectively), the time constant of LV pressure decay during the isovolumic relaxation period (ie, τ) was ascertained by using a zero-asymptote model [22].

LV afterload was quantitated in relative (%) values using the following formula: $[(\text{peak systolic blood pressure at increased afterload})/(\text{peak systolic blood pressure at baseline})] \times 100$. The afterload severity in our setting was then determined using the following scale: (low afterload) $< 125\% \leq$ (moderate afterload) $\leq 140\% <$ (high afterload) [23].

Data Acquisition with 2D and Flow Doppler Echocardiography

Echocardiographic images were acquired using a Vivid 7 system (GE Healthcare, Milwaukee, WI) and a hand-held 3.5 MHz transducer placed epicardially for scanning through a bulk of acoustically-coupling gel. Apical 4-chamber, 3-chamber, and 2-chamber and short-axis basal, mid-level, and apical scans of the LV were recorded for subsequent offline analyses. Measurements included peak transmitral flow velocities at mitral tip during early (E-wave) and atrial (A-wave) phases of LV filling, LV end-diastolic volume (EDV) [24], end-systolic volume (ESV), stroke volume (SV), and ejection fraction (EF) [20].

VFT Definition

Gharib and colleagues [15] mathematically derived the VFT formula based on LV function, mitral orifice diameter, and diastolic filling flow velocities, ie, utilizing easily obtainable physiological and echocardiographical measures, as follows:

$$\text{VFT} = \frac{4(1-\beta)\alpha^3}{\pi} \times \text{EF},$$

where β is the fraction of SV contributed from the atrial component of LV filling and is calculated from Doppler spectra of the E- and A-waves. The symbol α is a dimensionless index

of LV geometry defined as $\alpha = \frac{\text{EDV}^{1/3}}{D}$, where EDV is measured in cm³ (or mL) and D is the mitral valve diameter in cm. D has been obtained by averaging the largest mitral orifice diameters measured during early diastolic filling in the 2, 3, and 4-chamber apical views. Although in this study we used the VFT formula derived by Gharib et al. to be able to assess the effect of each of its component variables on the results, the definition can be simplified, by incorporating the α term into the previous equation and considering that $\text{EF} = \text{SV}/\text{EDV}$, as follows:

$$\text{VFT} = \frac{4(1-\beta)}{\pi D^3} \times \text{SV}.$$

Data Analysis

Data are expressed as mean $\pm$ standard deviation (SD). Hemodynamic, 2D, and Doppler echocardiographic measurements, as well as VFT values were obtained at baseline and during intervention and compared by using a 2-tailed paired t-test. The relation between the increase in VR and decrease in VFT was also assessed by linear regression analysis. A P value less than 0.05 was considered statistically significant.

Results

Eleven pigs were entered into the study; severe hypotension in one animal and first-degree atrioventricular block in another animal affected baseline hemodynamic conditions, and those 2 were therefore excluded. Complete measurements were obtained from all 9 of the remaining animals.

Systemic Hemodynamic Analysis

At baseline, the hemodynamic data were within the usual ranges (Table 1). Experimentally increased afterload, signified by elevation of systolic and mean blood pressures, was accompanied by a decrease in CO and an increase in the calculated VR. By careful adjustment of the compressive aortic tourniquet, a relative LV pressure load of 130% was approximated

in each animal and resulted in the consistent moderate afterload severity within the testing group.

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

Echocardiographic Analysis

Peak mitral flow velocities during the early (E-wave) filling phase did not change, but velocities at the atrial (A-wave) phase increased significantly (Table 2). Consequently, the E/A ratio showed a decreasing trend. EDV did not change but ESV had an increasing trend and impact, resulting in a significant reduction in SV and EF.

Vortex Formation Analysis

The mean values of D and α , when compared between baseline and moderately elevated afterload, remained nearly identical (Table 3). β and VFT significantly decreased during the intervention. There was a trend of an inverse linear correlation between the percent change of VFT compared with that of VR (Figure 1).

Discussion

The main finding of our experimental study is that even a brief, moderate elevation in LV afterload negatively affects transmitral flow efficiency as expressed by a shift of VFT values out of their optimal range.

Another finding of our study is that the mean VFT values at baseline and during moderately increased LV afterload are within and out of the normal range, respectively, of VFT values that are found both in natural and experimental jet propulsion systems [13]. That is, our results further support the notion that VFT index is a setting- and species-independent measure [15, 25].

Assessment of LV Systolic and Diastolic Function during Elevated Afterload

Elevated afterload can influence LV systolic function by blunting contractile reserve, increasing cardiac energy required to provide blood flow, and raising myocardial oxygen consumption for a given SV [26]. LV diastolic function can become abnormal due to impaired relaxation in the ventricle with elevated systolic pressure [18]. In our setting, the elevated resistance to LV ejection (reflected by a significant increase in the VR parameter) was controlled by maintaining the systolic blood pressure at approximately 130% of its baseline value (Table 1), which yielded a moderate elevation in afterload. The hemodynamic impact of such an intervention was expressed in systole by a drop in SV accompanied by decreases in EF and CO, and by elevation in ESV. In diastole, the impact of moderately increased afterload on relaxation was demonstrated by an E/A ratio less than 1, resulting primarily from a significant increase in A-wave velocity (Table 2). The E-wave velocity did not change, which can occur despite impairment in LV relaxation if left atrial pressure has increased [27] or if early relaxation is controlled by an early transmitral pressure gradient, primarily driven by diastolic untwisting [7,28,29].

Consistent with results by others [23], the rate of LV pressure increase [30], was not affected by the moderate elevation in afterload. However, the magnitude of the rate of LV pressure fall (ie, the magnitude of $-dP/dt$), significantly decreased and such findings can be explained as follows [23]: At low afterload, the onset of LV pressure fall is delayed and the rate of LV pressure fall is, therefore, accelerated (ie, the $-dP/dt$ magnitude increases). However, with

moderate or high afterload, the onset of LV pressure fall occurs earlier, and the $-dP/dt$ magnitude decreases.

Tau, when calculated by a zero-asymptote model, has been shown to correlate with $-dP/dt$ for Tau ranging from 50 to 130 ms [31]. However, with a consistent and only moderate elevation in afterload, the values of Tau obtained at baseline and during the intervention accumulated around the lower values of that range, without showing a significant increase (Table 1).

A range of VFT from 3.3 to 4.5 characterizes optimal hemodynamic conditions for vortex ring formation. Outside this range, a vortex ring may be limited in its growth or duration [25,32].

Gharib and colleagues [15] initially employed the simplified formula, time-velocity integral divided by the diameter of the mitral annulus, in their analysis of vortex formation in healthy subjects and in patients with dilated cardiomyopathy. While LV dysfunction in dilated cardiomyopathy caused a shift of VFT values clearly out of the optimal range, we speculate that the use of the mitral valve annulus is not a good generally usable measure, because mitral annular diameter would not reflect the actual exit orifice in mitral stenosis and other clinical cases with altered valvular geometry and orifice.

Hemodynamic Implications of Vortex Ring Formation

The diastolic vortex ring acts as a kinetic energy reservoir that facilitates propulsion of blood in systole [33], contributes to blood redirection into the outflow tract and aorta [34,35], and helps in preventing blood stagnation within the LV apex [35]. In addition, the vortex ring is supposed to exert a force that contributes to timely closure of the mitral valve [36]. Premature disintegration of the vortex and dissipation of the stored energy eliminates the beneficial effects of vortex formation and may necessitate an increase in the physical work generated by the cardiac muscle, thus augmenting the consumption of the oxygen, and in turn reducing efficiency of the heart pump [33].

Changes in VFT and its Component Parameters with Moderately Increased Afterload

The acute moderate increase in afterload not only impairs LV systolic and diastolic function, but our study shows that this condition also negatively impacts vortex ring formation. The latter finding is signified by the mean VFT value below the optimal range. 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 of diastolic filling. The augmented atrial contraction could be an adaptive functional mechanism activated in response to elevated LV afterload. However, as we show, this mechanism, in turn, impairs formation of a diastolic vortex suggesting reduced hemodynamic efficiency during LV filling [27].

The parameter α has not significantly changed in response to increased afterload in our acute setting. It can be anticipated, however, that in chronically increased afterload with impact on LV geometry, the value of α would change significantly.

We found a linear trend between percent increase in vascular resistance and percent decrease in VFT (Figure 1). If confirmed by further studies, the utility of this relation could be in grading the severity of LV pressure loading and its impact on diastolic filling efficiency.

Study Limitations

We obtained values of the β parameter from maximum mitral tip-to-tip diameter recordings and from peaks of E- and A-wave Doppler spectra rather than by utilizing time integrals. These simplifications have not impacted the consistency of our results with VFT analyses by others [15,25].

We used an open-chest pig setting, which was necessary for controlling the acutely induced afterload elevation by the aortic tourniquet, but could have theoretically affected cardiac filling due to cancellation of negative intrathoracic pressure during inspiration. However, the baseline hemodynamic data as well as VFT values were well within the normal ranges and all paired comparisons were done at the same experimental setting.

Finally, we were unable to determine from the current study whether the VFT formula would work in conditions with abnormal direction of flow during diastole such as aortic regurgitation.

Clinical Perspectives

The VFT parameter contributes to a conceptually novel interpretation of cardiac function. While ventricular EF, regional strain, and transmitral flow velocities are only a few of many examples of association of quantitative functional measurements to certain aspects of tissue or blood motion, VFT is a multifactorial parameter characterizing whether the ultimate goal of LV functional performance - blood transport - is achieved efficiently. Moreover, VFT may supersede conventional parameters of cardiac function in that it is a dimensionless index defined on a universal timescale [25] and, thus, VFT measurements can be interpreted without considering patient-specific effects. For example, no correction of VFT with respect to body surface is needed or, unlike with E-wave and A-wave analyses, there is no “pseudonormalization” of VFT with progressive diastolic dysfunction [15,37].

In patients with diastolic dysfunction related to cardiac dyssynchrony [38], quantitative evaluation of cardiac efficiency by VFT before and after resynchronization could be a useful indication of the clinical severity and success of therapy, respectively.

Studies relating vortex ring formation to the functionality of native and prosthetic mitral valves [39-41] suggest that VFT could have a role in functional evaluations of the valves and in optimization of prosthetic valve design.

Conclusions

An experimental acute moderate increase in ventricular afterload impairs hemodynamic conditions for vortex ring formation alongside the diastolic filling jet and, thus, for efficient transmitral blood transport. Implementation of the VFT parameter as a noninvasively measurable, fundamental fluid dynamic index of the presence or absence of efficient intracardiac blood transport could contribute to clinical evaluations as a measure of cardiac health that is disease stage- and patient effects-independent.

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Figure 1.
Relation between percent change of vascular resistance (VR) and percent change of vortex formation time (VFT).

Table 1**Hemodynamic Parameters**

Variable	Baseline	Afterload	P value
BP _s (mm Hg)	103.00 ± 11.73	133.36 ± 10.07	0.0014
BP _d (mm Hg)	74.64 ± 11.73	80.82 ± 26.23	0.3253
BP _m (mm Hg)	84.10 ± 10.19	98.33 ± 17.04	0.0080
HR (beats/min)	74.65 ± 7.77	79.07 ± 13.49	0.3693
CO (mL/min)	2923.08 ± 610.59	2389.61 ± 517.36	0.0385
VR (dyne·sec·cm ⁻⁵)	2358.31 ± 411.85	3395.17 ± 701.84	0.0020
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 (mmHg/sec)	-2297.75 ± 492.18	-1944.75 ± 580.56	0.0097
Tau [42]	39.49 ± 10.54	44.49 ± 17.86	0.5005

Abbreviations: +dP/dt, maximum positive LV pressure change; -dP/dt, maximum negative LV pressure change BP_s, BP_d, and BP_m, blood pressure systolic, diastolic, and mean, respectively; CO, cardiac output; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; Tau, the time constant of isovolumic relaxation; VR, vascular resistance.

Table 2

Echocardiographic Parameters

Variable	Baseline	Afterload	P value
E (m/s)	0.52 ± 0.10	0.52 ± 0.11	0.8962
A (m/s)	0.46 ± 0.06	0.63 ± 0.19	0.0231
E/A	1.13 ± 0.13	0.88 ± 0.28	0.0721
EDV (mL)	67.50 ± 5.41	67.50 ± 6.02	1.0000
ESV (mL)	28.50 ± 5.11	36.78 ± 11.13	0.0562
SV (mL)	39.00 ± 5.82	30.72 ± 7.28	0.0071
EF	0.58 ± 0.07	0.46 ± 0.12	0.0193

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

Vortex Formation Parameters

Variable	Baseline	Afterload	<i>P</i> value
D (cm)	1.86 ± 0.09	1.88 ± 0.09	0.2145
α	2.20 ± 0.07	2.17 ± 0.12	0.2200
β	0.47 ± 0.03	0.55 ± 0.10	0.0806
VFT	4.09 ± 0.27	2.78 ± 1.03	0.0046

Abbreviations: α , LV geometry parameter; β , the fraction of the stroke volume contributed from A-wave filling; D, diameter of mitral valve orifice; VFT, vortex formation time.