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The Impact of Fluid Inertia on In-Vivo Estimation of Mitral Valve Leaflet Constitutive Properties and Mechanics

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Abstract

We examine the influence of the added mass effect (fluid inertia) on mitral valve leaflet stress during isovolumetric phases. To study this effect, oscillating flow is applied to a flexible membrane at various frequencies to control inertia. Resulting membrane strain is calculated through a three-dimensional reconstruction of markers from stereo images. To investigate the effect *in vivo*, the analysis is repeated on a published dataset for an ovine mitral valve [Journal of Biomechanics 42(16): 2697–2701]. The membrane experiment demonstrates that the relationship between pressure and strain must be corrected with a fluid inertia term if the ratio of inertia to pressure differential approaches 1. In the mitral valve, this ratio reaches 0.7 during isovolumetric contraction for an acceleration of 6 m/s². Acceleration is reduced by 72% during isovolumetric relaxation. Fluid acceleration also varies along the leaflet during isovolumetric phases, resulting in spatial variations in stress. These results demonstrate that fluid inertia may be the source of the temporally and spatially varying stiffness measurements previously seen through inverse finite element analysis of *in vivo* data during isovolumetric phases. This study demonstrates that there is a need to account for added mass effects when analyzing *in vivo* constitutive relationships of heart valves.

Keywords

Added mass; mitral valve; isovolumetric; stress; acceleration; heart valve; membrane; strain; inertia

Introduction

Heart valves involve the interplay between structural mechanics and fluid dynamics^{8, 18, 29, 31}. Through alterations in valve dynamics, these relationships can impact disease^{14, 33}, medical device design^{11, 23, 27}, and are important to surgical practices in valve repair^{1, 7, 19, 24, 28}. Valvular dynamics are largely dictated by the constitutive equation relating stress and strain in the valve leaflets. Classically this relationship has been determined through biaxial and uniaxial tests on explanted tissue^{4–6, 9, 10, 13, 20, 25, 30}. Links between these *in vitro* studies and the integrative, more complex relationships seen for *in vivo* studies could elucidate additional mechanisms influencing heart valve biomechanics.

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In vivo studies have demonstrated temporal and spatial variations in strain that cannot be predicted by simple transvalvular pressure boundary conditions and simple mechanical models. In one notable example, the mitral valve increases in stiffness by 40–58% during isovolumetric contraction (IVC) relative to isovolumetric relaxation (IVR), as determined through inverse finite element models of *in vivo* data with transvalvular pressure boundary conditions^{8, 29}. This change in stiffness may correspond to active cardiac muscles in the atrialis layer of the anterior mitral leaflet⁸. Strain also varies spatially across the valve and this spatial variation changes in time, possibly owing to microstructure and prestrain^{15, 22, 29, 32}. Although these developments depict a rich spatio-temporal dependence of constitutive properties of the mitral leaflets, the contribution from fluid mechanics remains ill-defined and is typically neglected in these *in vivo* studies.

We revisit the fundamental assumptions made when relating mitral valve leaflet kinematics and measured pressure differentials to constitutive properties by investigating the temporal and spatial role of fluid inertia on these valve leaflets. These concepts have been posed previously in a theoretical form using bulk parameters, but here we demonstrate the phenomena using stream tubes for internal flow pertinent to the mitral valve and for an *in vivo* model^{17, 21}. The new theoretical formulation is useful for demonstrating the temporal and spatial interplay between leaflet tension and fluid inertia. The impact of the added mass effect (fluid inertia) on leaflets is first demonstrated with a synthetic material in oscillating flow, thus isolating this study to added mass effects independent of the complex constitutive properties associated with the native valves. Its implications on isovolumetric contraction and relaxation are further investigated for previously published *in vivo* data provided to us from Dr. Neil Ingels group¹⁸.

Materials and Methods

Theoretical development

During the isovolumetric contraction and relaxation phases, the mitral valve leaflets are closed while the pressure difference between the left atrium and ventricle respectively loads and unloads the leaflets. During IVC, the leaflet is strained as a finite volume of blood is displaced toward the atrium, which can expand the compliant atrial wall to accommodate the displaced volume. Conversely, blood is displaced towards the ventricle during IVR as leaflet strain decreases until the valve opens. Incompressibility of blood transfers these volume displacements exactly to the displacement of atrial and ventricular walls. During the isovolumetric phases, this flow from the leaflets to the chamber walls may be represented as fluid stream tubes that connect the leaflet to the chamber walls on either side of the leaflets. Fig. 1A depicts one such stream tube separated by the mitral valve in its closed state that will be the basis for the theoretical development. Heart valve leaflets are modeled, here, as an interface between the separated atrial and ventricular fluid domains with a tension, T , Fig. 1B. Considering the stream tube as a control volume, V , and applying the Reynolds transport theorem for momentum balance, the equation representing conservation of momentum is given as:

$$\rho \int_V \frac{D\vec{u}}{Dt} dV = \int_S [\vec{t}] \cdot \hat{n} dS + \int_C T \hat{s} dl. \quad (\text{Eq. 1})$$

The first term is the inertial force or the material time derivative of velocity, $\vec{u}$, in the volume element, V . The second term is the difference in hydrodynamic force exerted normal to the interface based on the difference in stress vectors, $\vec{t}$, over a differential surface, S . Tension acts along the arc length dl over contour C , $\hat{s}$ is the unit vector normal to C along the interface, and $\hat{n}$ is the unit outward normal vector. For this model, the volume element is modeled as a stream tube, the fluid is assumed incompressible, interfacial tension is uniform, body forces are negligible, and there is no gradient in the velocity field along the stream tube (simplifying the stress vector to pressure). With these assumptions, the model depicted in Fig 1 reduces to:

$$2\kappa T = \underbrace{(P_1 - P_2)}_{\text{Pressure Contribution}} - \underbrace{\rho L \vec{a} \cdot \hat{n}}_{\text{Acceleration Contribution}}, \quad (\text{Eq. 2})$$

where κ is the local curvature of the leaflet resulting from the divergence of the normal unit vector, ρ is the fluid density, L is the total length along the stream tube with a corresponding pressure differential, $P_1 - P_2$, across the stream tube (i.e. pressure differential between the left ventricle and atrium), and $\vec{a} \cdot \hat{n}$ is the fluid acceleration component normal to the leaflet surface. Notice that the acceleration contribution term in equation 2 is neglected in the current state of inverse finite element modeling^{4, 8, 29}.

Areal stretch is also computed through the area of triangular elements linking material (marker) points on the leaflet. It is calculated as:

$$\lambda_{\text{area}}^2 = \frac{|\vec{u} \times \vec{v}|}{|\vec{u}_0 \times \vec{v}_0|}, \quad (\text{Eq. 3})$$

where $\vec{u}$ is the vector linking 2 vertices, while $\vec{v}$ links one of these vertices to the 3rd vertex. Strain for the membrane presumes isotropic deformation and is determined as:

$$\varepsilon = 1 - \sqrt{\lambda_{\text{area}}^2}. \quad (\text{Eq. 4})$$

Lastly, the Cauchy stress is calculated from Eq. 2. Assuming an incompressible membrane, the instantaneous membrane thickness can be related to the initial thickness, t_0 , through the areal stretch. Resultantly, Cauchy stress is calculated using:

$$\sigma = \frac{\Delta P \lambda_{\text{area}}^2}{2\kappa t_0} \left[1 - \frac{\rho L \vec{a} \cdot \hat{n}}{\Delta P} \right]. \quad (\text{Eq. 5})$$

Based on the above theoretical considerations of momentum balance across the leaflet, particularly during isovolumetric phases, it is clear that the term $\rho L \vec{a} \cdot \hat{n} / \Delta P$ is a non-dimensional number (that we may refer to as the added-mass number) that gauges the relative importance of fluid inertia on the “apparent stiffness” of the leaflet. It is clear that a

quasi-static assumption, in order to ignore fluid inertia, is valid only if $|\rho L a / P| \ll 1$. In the following sections, we show proof that this number is significant in in-vitro mock experiments as well as *in vivo* mitral valve experiments during IVC and IVR.

Experimental Procedures

A flow chamber is designed to validate the effect that fluid inertia has during isovolumetric phases of the cardiac cycle by cyclically loading a mock leaflet material at controlled frequencies, Fig. 2A. To experimentally model a closed heart valve, a latex membrane is placed between two chambers $2 \times (1.5'' \times \phi 2.0'')$, representing the ventricle and atrium for a mitral valve leaflet, Fig. 2B. The initial thickness of the latex membrane is determined through ASTM-D3577 and is $\sim 200 \mu\text{m}$. Both atrial and ventricular sides are connected to compliance chambers. Compliance chambers dampen pressure waves in the flow system and further represent the natural compliance of the atrium and ventricle. Ventricular flow is raised and lowered as a sinusoid using a computer controlled linear actuator (Model P01-37x120F/300x380-HP, Linmot, Inc., Elkhorn, WI) that is attached to a custom built piston designed to displace fluid with a diameter of 33.09 mm. Polyvinyl chloride (PVC) pipe connects all of the flow chamber components. Trans-membrane pressure is measured using high temporal response Model DP15 pressure transducers (Validyne Engineering Corporation, Northridge, CA). Transducers are located 17 inches on either side of the membrane, corresponding to length L . The entire flow chamber is filled with reverse osmosis water.

Ink-based markers were placed on the membrane to make a grid pattern with points spaced $\sim 1/8''$ apart along the entire membrane in perpendicular directions. Stereo images were recorded onto a Photron Fastcam SA3 high-speed video camera (Photron, San Diego, CA) by dividing the optical plane with a series of first surface mirrors, Fig. 2C. The aperture, imaging distance, and lighting was setup to achieve maximum contrast between markers and the membrane. Images were taken at a frame rate of 1000 frames per second (fps) when the frequency of the chamber was greater than 2 Hz. 500 fps was used for lower frequencies. Images were recorded using Photron FASTCAM Viewer. Recordings were triggered by a LabVIEW (National Instruments Corporation, Austin, TX) program so that pressure data collection could be aligned with marker locations.

Three-dimensional reconstruction of markers—A calibration cylinder was placed in the flow chamber during experiments. The cylinder contains a checkerboard pattern on a sloped surface facing the camera, Fig. 2D. The pattern involves straight lines originating at the center of the chamber, separated by 5 degrees, and a series of perpendicular arcs that are separated by 0.07'' in the radial direction. The checkerboard is angled at 65 degrees and starts at a radius that is 0.55'' from the center of the chamber. Each inner vertex on the checkerboard is mapped from each stereo view to a known three-dimensional location using a linear least squares analysis to solve an overdetermined set of linear equations. 20 vertices are required for the projection matrix that maps camera translation and 2 sets of image coordinates into 3 world coordinates with an additional component to normalize the world coordinates. The checkerboard provides 144 vertices. The calibration cylinder remains in the flow chamber throughout the experiment.

Image processing for markers—Images are registered using Fiji-based program called TrakEM2. Registration is based on a region of interest outside of the moving membrane to minimize the influence of vibrations on world coordinates mapped from image coordinates. Only translational registration is performed, which would allow some influence from rotation occurring from vibration of the flow chamber during image recordings. However, negligible rotation is found during the experiments, since reference points moved less than 1 pixel during recordings. Matlab R2013a (The MathWorks, Inc., Natick, MA) is used to find 16 markers located near the center of the membrane based on an automated technique that locates dots in an image. The projection matrix is subsequently used to convert image coordinates into world coordinates.

Post-Processing

Global coordinates of markers placed on the membrane for the experiment and on the leaflets for the *in vivo* data are used to determine a number of parameters in post-processing. Data points are loaded into Matlab R2013a and are temporally aligned with pressure and flow measurement data. An ensemble average is taken for the coordinates, flow data, and pressure data over the cardiac cycle (sinusoid for membrane). Eq. 2 and Eq. 5 require the radius of curvature and the local acceleration of the leaflets (membrane). For this, a surface is fitted to the scattered data to obtain the local average radius of curvature and to calculate normal vectors relative to the surface. Acceleration vectors for each marker are computed by taking the double derivative of a fitted-cubic smoothing spline with respect to time through the marker world coordinates. For the latex membrane, the reference configuration in Eq. 3 is based on triangular areas in its stress-free state. The areal stretch (Eq. 3) of the leaflets from the *in vivo* experiments is based on the smallest area between markers, since we do not have data for the stress-free state.

Results

In what follows, results are presented first for the flexible membrane experiments followed by the same analysis performed on *in vivo* data obtained from Dr. Neil Ingels group¹⁸.

Flexible Membrane Experiments

Pressure and flow measurements—Fig. 3A shows the displacement of the driving piston for a 200, 300, 500, and 1000 ms periods. The piston follows a sinusoidal waveform with a peak displacement of 10 mm. As shown in Fig. 3B, the piston displacement results in a peak pressure differential across the membrane of 18–19 mmHg for periods of 500 and 1000 ms, while it reaches a pressure of 24 mmHg for 200 and 300 ms. Higher frequency oscillations (low periods) result in the peak pressure differential that occurs earlier in time than the maximum piston displacement. Whereas, the peak pressure for the lowest frequency (highest period) is in phase with the peak piston position. Correspondingly, flow entering the test chamber oscillates during each piston cycle, exhibiting a flow rate that is naturally 90° out of phase with the sinusoidal piston position, and is shown in Fig. 3C. Flow rates reach larger values, approaching 15 ml/s, for higher frequency oscillations (lower period) relative to the low frequency oscillations, with the lowest peak flow rate of <1 ml/s.

Marker position accuracy and computed kinematics—The membrane remains positively displaced for the entire flow cycle, as demonstrated for a period of 500 ms in Fig. 3D. Displacement is integrated along cross-section of the chamber to calculate the total displaced fluid volume at a point in time. To assess the accuracy of marker world coordinates, the fluid volume derived from marker coordinates is compared with the integrated measured flow rate into or out of the test chamber of Fig. 3C, with volume comparisons shown in Fig. 3E for a period of 500 ms. A regression between the integrated flow rate curve to the marker data results an r^2 value of 0.99. Membrane and fluid acceleration are also derived from the marker positions relative to time. Representative curves are shown in Fig. 3F for a cycle period of 500 ms with a plot of peak membrane displacement relative to the 180° out-of-phase membrane acceleration. The membrane reaches peak acceleration as it begins to deflect. As the membrane continues to extend, acceleration is reduced until peak deceleration is reached. In this particular example, deceleration decreases as the membrane approaches its peak displacement relative to time. Acceleration is mirrored for the half of the flow cycle.

Stress and strain—The role for added mass (fluid inertia) in stress derivations is assessed through Eq. 2 by adding the acceleration component, $-\rho L a \cdot \vec{n}$, to the pressure contribution,

P . Fig. 4 shows plots of areal stretch (Eq. 3) relative to corrected stress contributions from added mass and measured pressure contributions previously shown in Fig. 3B. At high frequency (low period) oscillations, i.e. 200 ms and 300 ms, the acceleration component augments pressure as can be seen in Fig. 4A and 4B. Fluid acceleration decreases the stress, while decelerating fluid increases the stress. Acceleration and deceleration occurs during both forward and backward membrane movement. The intersection between the pressure curve and corrected pressure curve corresponds with the transition between acceleration and deceleration. At low “quasi-static” frequencies, the acceleration contribution to stress is relatively small compared to pressure, as shown in Fig. 4C and 4D. Overall, areal stretch follows the corrected pressure curves. Conversely, as shown in Fig. 4A and 4B, areal stretch does not follow the uncorrected measured pressure curves at high frequency, demonstrating the role that fluid inertia has on the membrane.

To relate the added mass effect to potential effects on stiffness measurements derived through inverse computational modeling approaches that do not account for inertial effects, we plot the Cauchy Stress (Eq. 5) relative to strain (Eq. 4), as shown for a period of 200 ms in Fig 5A. A linear regression is performed with the resulting lines also shown in the figure. “Pressure Differential” data is a plot with 0 acceleration in Eq. 5, while the “Corrected Pressure” data accounts for added mass (Eq. 5). The corrected data aligns better with the linear regression ($r^2=0.98$) compared with the stress determined only from the pressure differential ($r^2=0.91$). Correspondingly in the experiments, fluid accelerates at low strain causing a decrease in membrane stress, while it decelerates at high strain causing an increase in membrane stress. As a result, the corrected data exhibits a steeper slope on the stress-strain plot. The uncorrected slope is artificially shallower. Cauchy stress is also plotted relative to strain for a “quasi-static” period of 1000 ms in Fig. 5B. The data points largely overlap. For a large period, the regression analysis results in a line that fits well for both the pressure differential data ($r^2=0.95$) and for the corrected pressure ($r^2=0.96$). Fig. 5A and 5B

consist of plots that depend on the local membrane curvature, as can be seen from Eq. 5. This term is the inverse of the radius of curvature, which varies with respect to time (Fig. 5C), resulting in a minimal radius as the membrane extends outward and a maximal radius for minimal membrane displacement. The slope of membrane Cauchy stress relative to strain is plotted for each period (200, 300, 500, and 1000 ms) and is denoted as stiffness in Fig 5D. Each period results in relatively the same corrected stiffness, while the uncorrected stiffness appears to increase with an increasing period. In the latter case, when added mass is neglected, the stiffness plateaus at high periods.

Fluid Inertia in Ovine Mitral Valve Leaflets

Data is further processed to determine the potential influence of fluid inertia on the ovine mitral valve stress environment *in vivo*. Fig. 6A shows the pressure in the left ventricle, the left atrium, and the aorta during the cardiac cycle taken from Krishnamurthy et al.¹⁸. Position markers sutured to the anterior leaflet of the mitral valve are used to calculate the marker acceleration normal to the leaflet surface throughout the cardiac cycle from the same dataset. The magnitude is plotted in Fig. 6B, for a marker on the Central Free Edge, the Central Meridian, and the Saddlehorn. Acceleration increases from the Saddlehorn to the coaptation region. The Central Meridian of the leaflet can accelerate to 6 m/s² and can decelerate by more than 5 m/s² during IVC. During IVR however, the maximum acceleration magnitude is <1 m/s² and maximum deceleration is ~2 m/s².

In addition to temporal variation, acceleration also varies spatially along the valve, as shown in Fig. 6C during IVC and IVR. As the valve closes, there is a large fluid acceleration in the direction of the mitral annulus. The largest acceleration occurs in the coaptation region during closure. At the next measurable time point 1/60th of a second later, the acceleration vector reverses direction in the coaptation region, corresponding with a large deceleration as the valve enters a closed state. During this time, the saddlehorn continues to accelerate. At the next measurable time, deceleration transfers from the coaptation region to the belly and the saddlehorn, agreeing with Fig. 6B. The spatial importance of added mass is depicted

contours of the ratio of inertia over pressure $\left(\frac{\rho L \vec{a} \cdot \hat{n}}{(P_1 - P_2)} \right)$, which is the rightmost term of Eq. 5. During the IVC and IVR phases, the most spatial variation occurs when the valve immediately closes or opens. The magnitude of deceleration decreases as time progresses and is relatively low during the IVR phase. The spatial variation in the ratio of inertia over pressure is relatively smaller during IVR compared with IVC. Supplementary video 1 demonstrates the spatial and temporal changes in acceleration along the anterior leaflet.

The contribution of fluid acceleration to stress is accounted for through Eq. 2. During IVC, the stress component from the fluid inertia exceeds the trans-mitral pressure reducing the effective stress on the leaflet, as shown in Fig 7A, averaged in the belly region near the coaptation zone. Subsequently, the decelerating fluid adds approximately 20 mmHg of stress to a pressure of ~35 mmHg. As plotted in Fig 7B, fluid inertia during IVR does not provide a substantial contribution to the effective stress on the leaflet. The stress contribution with and without a correction for added mass is shown relative to areal stretch (Eq. 3) throughout the cardiac cycle in Fig 7C.

Discussion

We demonstrate that spatio-temporal changes in leaflet stiffness found from *in vivo* studies of heart valve leaflets through inverse finite element analysis^{11, 14} may be in-part due to the added mass effects (fluid inertia) caused by the displacement of fluid by the closed mitral valve leaflets. These results can impact inverse finite element studies used to extract constitutive relations of heart valve leaflets and may be important to consider for heart valve repair or replacement.

Here, we show that fluid inertia is large during IVC, providing a larger contribution to leaflet stress relative to IVR, providing an explanation for the difference seen in perceived stiffness of each^{4, 8, 29}. During IVC, the leaflet decelerates once it closes. Correspondingly, the fluid decelerates, causing an increase in leaflet stress. If added mass is neglected, the stress will appear to be lower than it actually is, as depicted in Fig. 8 at point t_1 . As time continues and as pressure increases (as well as strain), the added mass effect is less dominant, causing the uncorrected and corrected stiffness curves to align, resulting in a quasi-static state, denoted by point t_2 in Fig 8. Since the initial stress appears lower than it is when neglecting added mass, it results in an artificially large perceived stiffness, as illustrated in Fig. 8. As previously suggested, an increase in stress may aid in valve closure during IVC and therefore added mass effects may benefit the mitral valve²⁹.

Both changes in heart rate and contractility can impact the fluid acceleration during IVC and IVR. As the timescale reduces from reduced heart rates, the results here indicate that the role for added mass will increase. Similarly, as contractility increases, it can increase the rate of leaflet acceleration/deceleration as the valve closes. Evidence supporting the role of the heart rate and contractility is demonstrated with the addition of Esmolol.^{8, 29} Esmolol reduces the apparent mitral leaflet stiffness during IVC, while IVR remains relatively unchanged. Due to a reduction in heart rate and contractile forces, this beta blocker increases the timescale for IVC, reducing the added mass effects. These effects are negligible during IVR, therefore a further reduction in timescales or contractility would not be expected to alter the stress in the valve from added mass effects. However, when the heart was electrically stimulated near the mitral valve, there was an increase in stiffness for both IVC and IVR, but relatively little change in heart rate or stroke volume⁸. Although, fluid acceleration may still be affected by the stimulation, these results indicate that muscular contraction may still play a role in valve stiffness during IVC.

Another study has shown an increased perceived stiffness for increased peak ventricular pressures during cardiac contraction induced through a vasopressor agent³¹. The resulting increase in transvalvular pressure would increase the valve and fluid acceleration/deceleration, increasing the added mass effect. These results could impact surgical repair choices, specifically for hypertensive patients.

There is spatial variation in valve strain owing to structural characteristics of the valve, with largest increases in stretch near the coaptation line under quasi-static conditions.^{4, 29} However, spatial variation in strain may also be influenced by fluid inertia as we demonstrate here. In Fig. 8 there is a large fluid deceleration region near the leaflet

coaptation region, while there is acceleration near the annulus as the valve closes. The added mass effect is acting in opposite directions along the valve, demonstrating a spatial change in stress. Furthermore, the small radius of curvature near the coaptation region can increase the stress and therefore the strain of the valve, as demonstrated in Eq. 5.

Leaflet stress is balanced by the tension in the mitral valve annulus and the chordae tendoneae. In terms of the annulus, the tension is ~ 40 N/m at the center of the anterior annulus for a static trans-mitral pressure of 80 mmHg, which is 2–4x greater than the trans-mitral pressure existing during IVC and IVR^{3, 12}. Comparatively, if we assume that the stress contribution from fluid inertia is 20 mmHg during IVC, Eq. 2 shows that the contribution to the annulus tension is 20 N/m. For this calculation, curvature is calculated using a leaflet radius of 1.5 cm and demonstrates that fluid inertia impacts annulus tension during IVC.

Chordae tendineae attach the mitral valve leaflets to the papillary muscles, which can help balance the load on the mitral valve. During systole, the chordae tendineae at the free edge of the leaflet experiences a force of 0.14 N, while a larger force of 0.66 N is felt near the belly for *in vitro* conditions involving a flexible annulus¹⁶. Later studies show that the force along the papillary muscle changes throughout the cardiac cycle. The combined force for both papillary muscles is 2.9 N at the beginning of systole and increases to 7.2 N at the end of systole². To compare the contribution from inertia, we assume a stress contribution of 20 mmHg is applied uniformly along anterior and posterior leaflets, corresponding to a surface area of ~ 7 cm². This analysis results in an overall force from fluid inertia of 1.88 N during IVC, but is ~ 0 during IVR. Therefore, the papillary muscle may not need to balance as much of the load during IVC due to initial fluid acceleration. As flow begins to decelerate, the muscle will need to take more load, which agrees with the subsequent high load experienced by the papillary muscle². Comparatively there is little fluid inertia during IVR. Therefore, the papillary muscle may need to more directly balance the trans-mitral pressure load, corresponding to the large force seen during IVR. These complex relationships are further complicated by the potential active contraction previously noted. However, the relative magnitude of fluid inertia demonstrates its importance for mitral valve closure or opening.

The flexible membrane experiment demonstrates the added mass phenomenon. The inertial term provides a stress contribution on the order of 10 mmHg with a pressure differential of 30 mmHg, matching closely to conditions of the mitral valve based on the analysis performed here on the ovine model. In the experiments in the current study, we underpredict the stiffness of membrane when we don't account for added mass because the fluid accelerates for low strain and decelerates for high strain. This underprediction reduces as the membrane approaches a quasi-static state. The membrane stiffness approaches the corrected stiffness value of ~ 4 MPa. Comparatively, latex can exhibit 1–4 MPa, depending on the range of strain values and environmental conditions²⁶. It should also be noted that the linear fit to stress-strain data does not cross strain at a 0 value. This is because we applied a small amount of prestrain to the flexible latex membrane when inserting it into the chamber depicted in Fig. 2. Additionally, corrected Cauchy stress values became slightly negative for the high frequency experiments. This may result from the error in calculating acceleration. The calculation requires the double derivative of displacement and therefore noise and errors

in displacement calculations are amplified for acceleration calculations. A small error in acceleration calculations for a period of 200 ms may also provide an explanation for why the stiffness value is slightly larger than other experimental conditions.

A limitation in the present study is that we have limited experimental *in vivo* data. Additional studies evaluating changes in added mass effects on various heart valves would be required to determine what magnitude added mass effects have on the stress experienced by the valves. Furthermore, a synthetic membrane is used in the present study, as opposed to a heart valve in its native environment. The synthetic membrane was chosen to simplify the study and to demonstrate the added mass effect, without the confounding effects from varied thickness, anisotropy, and complex constitutive relations. Similar results would be seen with a native heart valve, since the added mass effects are a simple consequence of momentum balance only, independent of the membrane or valve material.

Conclusions

Results demonstrate that the added mass effect can play a significant role in heart valve leaflet deformations by augmenting the stress experienced by the leaflets. We demonstrate the added mass effect in a simplified model and extend the analysis to *in vivo* mitral valve data. The effects are pronounced during the isovolumetric contraction phase and are negligible during isovolumetric relaxation. We show that the added mass effect can alter the perceived stiffness of a thin membrane, when acceleration/deceleration is large, but that the impact on stiffness is negligible in a quasi-static state. Overall, the added mass effect can alter spatio-temporal stress over heart valve leaflets and may be an important consideration when designing prosthetic valves or heart valve repair.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A) Diagram of the heart with a stream tube beginning in the left ventricle and ending in the left atrium. The stream tube is physically separated by the mitral valve, which is modeled as either a thin-walled membrane or a fluid-fluid interface. Black arrows represent contraction of the ventricle, expansion of the atrium, and represents the direction of flow along the stream tube, corresponding to isovolumetric contraction. Pressure measurements are made in the atrium and ventricle at either end of the stream tube. B) Schematic of a stream tube with a fluid-fluid interface. P_1 and P_2 are pressure measurements in the ventricle and atrium respectively. κ represents curvature of the leaflet, T the tension in the leaflet, and L the length of the fluid path between the two pressure tap locations. Normal and tangential unit vectors are represented as $\hat{n}$ and $\hat{s}$

Figure 2.

A) Schematic of the experimental flow chamber, with labels on each component. B) Found in the inset of (A), the test chamber holds a membrane that represents the leaflets of a closed heart valve. Flow is directed into and out of the chambers through the large holes, while the smaller holes are used for draining purposes. C) An example stereo image obtained from a series of first surface mirrors and a single camera. D) Schematic of the calibration cylinder seen in (C). A checkerboard grid is placed along the cylinder that is sloped at 65 degrees.

Figure 3.

Each plot consists of an ensemble average of data over at least 10 periodic cycles. Data is plotted relative to normalized time, t/T . A) Piston position for four different periods with a maximum piston displacement of 10 mm. B) The pressure difference across the membrane, corresponding to piston positions in (A) for each period. C) The flow waveforms of flow exiting the compliance chamber and entering the test chamber where the membrane is placed for piston positions in (A). (D–F) Plots are for a period of 500 ms and are shown in normalized time, t/T . Flow data is ensemble averaged over 53 cycles, while membrane data is ensemble averaged over 8 cycles. D) Membrane displacement relative to radial location and normalized time. E) The fluid volume determined by integrating markers placed on the membrane compared with the fluid volume supporting membrane displacement determined by integrating the flow rate entering the test chamber. F) Acceleration of the membrane and fluid on either side of the membrane during displacement. Acceleration is determined by the double derivative of a cubic smoothing spline for the displacement data.

Figure 4.

Plots of the stress contribution from the pressure differential across the membrane relative to the stress contribution from the pressure and the fluid acceleration (corrected pressure) relative to time. Areal stretch is plotted on another access. Plots are shown for a period of A) 200 ms, B) 300 ms, C) 500 ms, and D) 1000 ms.

Figure 5.

A) Plot of membrane tension relative to areal strain for the pressure differential across the membrane and for the corrected differential that incorporates an additional term for fluid acceleration for a period of 200 ms. Measurements are performed at the membrane inflection point, corresponding to a location furthest from any constrained boundary. A line demonstrating a linear fit to the data is also shown. B) Changes in the mean radius of curvature relative to normalized time for a period of 200 ms and 1000 ms. C) Plot of membrane tension relative to areal strain for a period of 1000 ms. A linear fit to the data is also shown. D) Stiffness of the membrane determined by the slopes shown in (A) and (B). Data is shown for each period, 200, 300, 500, and 1000 ms for values determined for corrected and uncorrected pressure differentials. Error bars correspond to the confidence bounds for the slope of membrane tension relative to areal strain. The r^2 value for each regression account for added mass is 0.91, 0.95, 0.92, and 0.96, while the regression on data where added mass is neglected is 0.55, 0.85, 0.90, and 0.96 for a period of 200, 300, 500, and 1000 ms, respectively. (***) $P < 0.0001$

Figure 6.

Data is provided from Krishnamurthy et al. A) Pressure variations in the left ventricle, left atrium, and the aorta throughout the cardiac cycle in an ovine model. Circles along the left ventricular pressure curve correspond to the images presented in (C). B) Dot product of the acceleration vector and the surface normal vector of the anterior mitral valve leaflet near the Central Free Edge (Free Edge), the Central Meridian (Belly), and the Saddlehorn throughout the cardiac cycle. The light gray bar dictates isovolumetric contraction (IVC) and isovolumetric relaxation (IVR). C) Snapshots of the anterior mitral valve leaflet during IVC (left images) and IVR (right images) are depicted in with vectors corresponding to the local leaflet acceleration magnitude and direction. Contours also correspond to the acceleration magnitude to demonstrate the spatial distribution of acceleration. The dashed line is a reference line corresponding to the annulus of the mitral valve.

Figure 7.

Data is provided from Krishnamurthy et al. Stress contributions are plotted for the trans-mitral pressure and for fluid acceleration (added mass) during isovolumetric contraction (A) and during isovolumetric relaxation (B). C) Corrected stress contributions accounting for the added mass and uncorrected contributions from the trans-mitral pressure are plotted on a separate axis relative to areal stretch during one cardiac cycle.

Figure 8.

Diagram demonstrating the influence of added mass on constitutive equation calculations. The solid line represents the actual stiffness of a material, while the dashed line is the stiffness when added mass is neglected for cases where there is a large amount of fluid deceleration. The last line corresponds to the perceived stiffness when deceleration is large for an initial stress-strain measurement, t_1 , with a second time point, t_2 , occurring when the transvalvular pressure is large and added mass effects are negligible. X markers denote

actual stress values for a specific strain, while circle markers correspond to perceived stress values.