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Can isolated annular dilatation cause significant ischemic mitral regurgitation? Another look at the causative mechanisms

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ABSTRACT

This study was to investigate the mechanisms of ischemic mitral regurgitation (IMR) by using a finite element (FE) approach. IMR is a common complication of coronary artery disease; and it usually occurs due to myocardial infarction. The pathophysiological mechanisms of IMR have not been fully understood, much debate remains about the exact contribution of each mechanism to IMR. Two patient-specific FE models of normal mitral valves (MV) were reconstructed from multi-slice computed tomography scans. Different grades of IMR during its pathogenesis were created by perturbation of the normal MV geometry. Effects of annular dilatation and papillary muscle (PM) displacement (both isolated and combined) on the severity of IMR were examined. We observed greater increase in IMR (in terms of regurgitant area and coaptation length) in response to isolated annular dilatation than that caused by isolated PM displacement, while a larger PM displacement resulted in higher PM forces. Annular dilation, combined with PM displacement, was able to significantly increase the severity of IMR and PM forces. Our simulations demonstrated that isolated annular dilatation might be a more important determinant of IMR than isolated PM displacement, which could help explain the clinical observation that annular size reduction by restrictive annuloplasty is generally effective in treating IMR.

1. Introduction

Ischemic mitral regurgitation (IMR) is a common complication of coronary artery disease and may develop in the acute or chronic phase (Agricola et al., 2008; Bouma et al., 2010; Donal et al., 2006; Krishnaswamy et al., 2011; Magne et al., 2009; Otsuji et al., 2008; Timek and Miller, 2012; Unger et al., 2012). Chronic IMR occurs due to myocardial infarction or chronic ischemia, which leads to left ventricle (LV) remodeling and significant alterations in the geometry of the mitral valve (MV) apparatus. Although the knowledge about IMR has increased over the years, many questions remain unanswered and no consensus exists on the optimal surgical treatment for IMR (Murphy et al., 2011; Nishimura et al., 2008).

The main pathophysiological mechanisms of IMR are believed to include LV remodeling with papillary muscle (PM) displacement and leaflet tethering, annular dilatation, and PM dysfunction and dyssynchrony. Much debate remains about the exact contribution of each mechanism to IMR. For instance, studies (Carpentier, 1983; He et al., 1997) have implicated that the systolic tethering of mitral leaflets caused by PM displacement is a major causative mechanism of IMR. In the meantime, it is still widely accepted that annular dilatation as an isolated lesion is suggested to be insufficient to cause significant IMR (Bouma et al., 2010; Krishnaswamy et al., 2011; Otsuji et al., 2002). Conversely, the immediate postoperative clinical results (Adams and Anyanwu, 2006; Fattouch et al., 2009; Mihaljevic et al., 2007; Murphy et al., 2011; Serri et al., 2006) have shown that restrictive annuloplasty, *i.e.*, by correcting and restoring annulus without relieving leaflet tethering, is an effective procedure to treat IMR. If restoring annulus alone can eliminate MR, isolated leaflet tethering resulted from PM displacement might not be a predominant factor in inducing significant IMR for patients with normal mitral annulus.

Mechanisms of IMR have been studied by *in vivo* imaging and *in vitro* experiments (He et al., 1997, 2003; Kono et al., 1992; Otsuji et al., 2002; Tibayan et al., 2003), although several limitations exist. For *in vivo* imaging studies, it is difficult to assess various mechanisms independently; and to quantify the pathogenesis of IMR for individual patients over time. The findings of *in vitro* experiments are usually limited by the use of animal models, since they are significantly different from human heart tissues (Martin et al., 2011; Martin and Sun, 2012). Moreover, for the *in vitro* experiments where MVs are dissected from the whole hearts, the natural configuration of the MVs and the active contraction of the LV are difficult to preserve and replicate.

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Therefore, in the present study, we seek to clarify the mechanisms of IMR by using a finite element (FE) approach. Two patient-specific FE models of normal MVs were reconstructed from multi-slice computed tomography (MSCT) scans. The geometry of the MVs included distinguishable mitral leaflet thickness, chordal origins, chordal insertion points, PM locations, and mitral annulus. Material properties of human MV tissues were obtained from biaxial mechanical tests; and characterized by an anisotropic hyperelastic material model. *in vivo* dynamic closing of MV was simulated; and the MV model was validated by comparing the closed shape of the MV from the FE simulation to the MV geometry reconstructed from MSCT images at middle systole. Subsequently, different pathological IMR conditions were generated by perturbation of the normal MV geometry. Effects of annular dilatation and PM displacement (both isolated and combined) on the severity of IMR were examined. Leaflet coaptation length, regurgitation area, and PM force were obtained from the MV closing simulations to characterize the roles of annular dilatation and PM displacement in patients with IMR.

2. Methods

2.1. Patient-specific MV geometry

Full phase cardiac MSCT scans were collected from patients at Hartford Hospital (Hartford, CT). Institutional Review Broad approval to review de-identified images was obtained for this study. All patients in our database received an MSCT coronary angiography because of suspected coronary artery disease. From our patient database, a 49-year-old female (Patient 1 in Fig. 1a) and a 61-year-old male (Patient 2 in Fig. 1b) patient with normal MVs were identified (Fig. 1). The MSCT examination was performed on a GE LightSpeed 64-channel volume computed tomography scanner. In general, a total of 2000 slices of images with thickness of 0.625 mm were collected for the whole cardiac cycle (Wang et al., 2011). A collimation of $25–30\times0.625$ mm and a rotation time of 375 ms were used resulting in a temporal resolution of less than 200 ms. Typically, 10 phases can be obtained for each cardiac cycle. MSCT images of the MV in middle diastole and middle systole were imported into Avizo 6.3 software (VSG, Burlington, MA) for 3D reconstruction and evaluated using a window width of 950 and −50 Hounsfield units. In the identified middle-systolic frame, MV had the maximum coaptation length under peak physiological pressure. Geometries of the MV, PMs, chordae tendineae, chordal insertion points, and LV (Fig. 1) were identified and separated from the rest of the chest images to create a 3D representation. Initial mid-diastolic geometry of the MV FE model was generated using HyperMesh (Altair Engineering, Inc., MI) software.

Details of the methodology of FE model development and calibration were described in a previous publication (Wang and Sun, 2012). Briefly, an anisotropic hyperelastic material model was adopted to characterize the mechanical behaviors of the mitral leaflet tissues. The model is based on the fiber-reinforced hyperelastic material model proposed by Gasser et al. (2006), Holzapfel et al. (2000). The mitral tissues are assumed to be composed of a matrix material with two families of imbedded fibers. The strain energy function W can be expressed as

$$W = C_{10}\{\exp\ [C_{01}(\overline{I_1}-3)]-1\}+\frac{k_1}{2k_2}\sum_{i=1}^{2}[\exp\{k_2[\kappa\overline{I_1}+(1-3\kappa)\overline{I_{4i}}-1]^2\}-1]+\frac{1}{D}(J-1)^2,$$

$$i=1,2 \tag{1}$$

where, C_{10}, C_{01}, k_1, k_2 and D are material constants. C_{10} and C_{01} are used to describe the matrix material. D is the material constant that introduces the near incompressibility, while k_1 is a positive material constant with the dimensions of stress and k_2 is a dimensionless parameter. The strain invariant $\overline{I_1}$ is used to describe the matrix material; and the strain invariant $\overline{I_{4i}}$ is used to describe the properties of the fiber families. In addition, a dispersion parameter κ was used to describe the distribution of fiber orientation. The anisotropic hyperelastic material model was implemented into Abaqus 6.13 explicit (SIMULIA, Providence, RI) with a user sub-routine VUMAT (Sun and Sacks, 2005).

The isotropic hyperelastic Ogden material model was used to characterize the mechanical properties of porcine basal and marginal MV chordae tendineae based on the experimental data published by Kunzelman and Cochran (1990). The values for the material constants were determined using SYSTAT (Systat Software Inc., Chicago, IL) with the Marquardt–Levenberg algorithm (Wang and Sun, 2012). The material constants listed in Table 3 in Wang and Sun (2012) were adopted for both patient MV models in this study.

2.2. FE simulation of MV closing

A dynamic explicit analysis was completed to simulate the MV closing process. To mimic the mitral annular and PM dynamics due to the contraction of the surrounding LV, nodal displacements of the mitral annulus and chordal origins on the PMs were tracked from the MSCT scans at middle diastole and middle systole, and applied to the FE MV model as kinematic boundary conditions. A time-dependent physiological transmitral pressure of one cardiac cycle was applied on the ventricular side of the mitral leaflets. To validate the MV FE model (Wang and Sun, 2012), the closed shape of the MV from the simulation was compared to the MV geometry at middle systole reconstructed from MSCT images.

2.3. MV geometry with IMR

In this study, MV geometries with symmetric annular dilatation and displacement of both PMs were created to represent the development of human IMR (from normal MV to severe IMR). Displacement fields were prescribed to the nodes that represented the MV annulus so that mitral annulus perimeter was dilated uniformly and symmetrically on the annulus plane by up to 25%, since annulus diameters of the patients with significant IMR were found to be approximately 25% (Daimon et al., 2008; De Simone et al., 2006; Kaji et al., 2005; Kwan et al., 2003) larger than those of the control groups. Chordal origins of both PMs were displaced away from the annulus plane in the apical direction by up to 6 mm, which was the estimated change in PM tethering distance in IMR patients compared with control groups (Agricola et al., 2004; De Simone et al., 2006; Kaji et al., 2005; Veronesi et al., 2008; Yiu et al., 2000).

2.4. Evaluation of IMR severity

Leaflet coaptation length, regurgitation area, and PM force were obtained from the MV closing simulations at middle systole to characterize the role of annular dilatation and PM displacement in IMR. A plane of analysis was defined to be perpendicular to both the line of leaflet coaptation and the annular plane. Anterior leaflet coaptation length at the center of the MV which was perpendicular to both the line of leaflet coaptation and the annular plane (A2-P2 region) was measured. To obtain the regurgitant area of the MVs, the mid-systolic MV orifice area was projected onto the annulus plane. Contour of the projected area was then used to calculate the regurgitant area in HyperMesh. Severe IMR was defined by regurgitant area ≥ 20 mm^2 (Agricola et al., 2008; Bouma et al., 2010). Reaction forces of the chordal origins were output from the simulations to represent forces applied by the PMs on the LV at middle systole. To show the percentage of increase, force values of the MVs with IMR conditions were normalized by dividing the PM forces by those of the original normal MVs.

3. Results

3.1. Patient information

The patients in this study were a 49-year-old female (Patient 1 in Fig. 1c) and a 61-year-old male (Patient 2 in Fig. 1d) with mitral annulus middle-diastolic circumference of 112 mm and 125 mm respectively. It was measured from the initial FE MV models at middle diastole that the areas of the anterior and posterior mitral leaflets of Patient 1 were 534.5 mm^2 and 698.1 mm^2 respectively; they were 690.6 mm^2 and 705.8 mm^2, respectively, for Patient 2. The maximum lengths of the anterior and posterior mitral leaflets in the axial direction of Patient 1 were 18.3 mm and 16.9 mm, respectively; they were 22.5 mm and 11.9 mm respectively for Patient 2.

3.2. FE simulation

The original MV FE models reconstructed from MSCT images were closed completely (zero regurgitant area) at middle systole in the presence of the physiological transvalvular pressure. The anterior leaflet coaptation lengths at A2-P2 at middle systole were 6.4 mm and 4.3 mm for Patient 1 and Patient 2 respectively. Forces that the anterolateral and posteromedial PM groups applied on the LV at middle systole were 5.8 N and 5.1 N respectively for Patient 1; they were 6.4 N and 6.7 N respectively for Patient 2. The higher