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Regional biomechanical and histological characterization of the mitral valve apparatus: Implications for mitral repair strategies

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ABSTRACT

The aim of this study was to investigate the regional and directional differences in the biomechanics and histoarchitecture of the porcine mitral valve (MV) apparatus, with a view to tailoring tissue-engineered constructs for MV repair. The anterior leaflet displayed the largest directional anisotropy with significantly higher strength in the circumferential direction compared to the posterior leaflet. The histological results indicated that this was due to the circumferential alignment of the collagen fibers. The posterior leaflet demonstrated no significant directional anisotropy in the mechanical properties, and there was no significant directionality of the collagen fibers in the main body of the leaflet. The thinner commissural chordae were found to be significantly stiffer and less extensible than the strut chordae. Histological staining demonstrated a tighter knit of the collagen fibers in the commissural chordae than the strut chordae. By elucidating the inhomogeneity of the histoarchitecture and biomechanics of the MV apparatus, the results from this study will aid the regional differentiation of MV repair strategies, with tailored mitral-component-specific biomaterials or tissue-engineered constructs.

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1. Introduction

Stenosis and regurgitation are the most significant and frequent causes of mitral valve (MV) dysfunction (Hayek et al., 2005). Regardless of the nature and underlying cause, MV dysfunction is manifested through leaflet thickening or thinning, calcification, annular dilatation, and/or structural chordal impairment. Conventional therapies focus on MV repair or replacement. The complex MV geometry, comprising the annulus, leaflets, chordae tendinae and papillary muscles, makes repair a more attractive option. MV repair preserves the gross natural geometry of the ventricle, and has a reduced need for anticoagulation, good long-term prognosis and decreased risk of endocarditis (Savage et al., 2003). Repair usually employs synthetic biomaterials, such as ePTFE for chordal reconstruction and annuloplasty rings for annular reconstruction (Vetter et al., 1996), or autologous and chemically-treated xenograft tissues, such as pericardium for annular (Bevilacqua et al., 2003), cuspal or chordal reconstruction (Fleisher et al., 1987).

Although MV repair is considered to be the gold standard and has high success rates in the adult patient population (Alvarez et al., 1996; Braunberger et al., 2001), current repair approaches are associated with a high incident of reoperations in the pediatric population (Walter et al., 2010). The shortcomings of current repair strategies are mainly due to the fact that they only deliver inert or biocompatible material solutions that cannot regenerate or grow with the patient, whereas glutaraldehyde-treated tissue with cell remnants will calcify, become rigid and degenerate. Moreover, current approaches usually employ one-type-fits-all materials, with the same material used to repair different components, such as pericardium for annular, cuspal and chordal reconstructions, and ePTFE for different classes of chordae. Ideally, materials for MV repair should be biomechanically and histoarchitecturally tailored to match the replaced MV component. If the repair materials are not sufficiently compatible, they might induce abnormal stress concentrations, which have been linked to calcification, accelerated failure, and abnormal haemodynamics, leading to blood cell damage and valve incompetence. Abnormal stress concentrations can also lead to abnormal cell stimulation

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both in the surrounding tissue and the repair material itself, in the case that it can support cellular colonization, inhibiting cellular growth and tissue integration.

Although the MV is almost equally as prone to disease as the aortic valve, it has received relatively little attention, mainly due to its complex geometry and function. Studies have mainly focused on the stress–strain behavior of the anterior leaflet (Ghista and Rao, 1973; May-Newman and Yin, 1995; Sacks et al., 2002; Chen et al., 2004; He et al., 2005; Sacks et al., 2006; Grashow et al., 2006a; Grashow et al., 2006b) without reference, however, to its histoarchitecture. A limited number of studies have also examined the underlying structural reasons for the gross mechanical phenomena observed in the MV components (Kunzelman et al., 1993; Sato, 2002; Liao and Vesely, 2003, 2004; Ritchie et al., 2005; Liao et al., 2007). To date, there have been no studies investigating the regional structure-function relationships in the whole MV apparatus. The majority of previous studies have focused on either the leaflets or the chordae, without considering the regional differentiation and specificity of the biomechanics and histoarchitecture of the MV components. The aim of the present study was to investigate the biomechanical and histoarchitectural inhomogeneity of the MV apparatus with a view to creating a benchmark for tailoring biomaterials and tissue-engineered strategies for mitral leaflet and chordae reconstructions.

2. Materials and methods

2.1. Biomechanical testing

The MVs were excised from 12 hearts, weighing between 400 and 500 g, of 6–9 month-old British Large White pigs obtained from a local abattoir within 6 h of slaughter. The posterior and anterior leaflets, together with the commissural and strut chordae were dissected from the MV apparatus and tested under uniaxial tensile loading to failure. Strips measuring $5 \times 20\ mm^2$ were isolated along the radial ($n=6$) and circumferential ($n=6$) direction of the leaflets (Fig. 1), whereas 20 mm-long segments were isolated from the strut ($n=6$) and commissural ($n=6$) chordae. From each leaflet, either one circumferential or one radial sample was isolated due to the limited leaflet size. Prior to testing, the thickness of the samples was measured at 3 points along their long axis using a gauge with a resolution of 0.01 mm (Mitutoyo, Andover, UK), and their average thickness (t) was recorded. The variation (standard deviation) in the 3 thickness measurements along the length of each sample ranged between 0.06 and 0.15 mm for the leaflets and 0.25–0.50 mm for the chordae. Subsequently, the samples were mounted onto a bespoke titanium holder (Korossis et al., 2009). The holder defined the gauge length of the specimens at 10 mm, and ensured that no load was imposed on the specimen until the test start. The testing was conducted using an Instron 3365 (Instron, UK) uniaxial tensile testing machine.

Prior to loading to failure, the specimens were preconditioned for 30 cycles under cyclic loading using a double-ramp wave function at a rate of 10 mm/min. Following preconditioning, the samples were sequentially stretched to failure at a rate of 10 mm/min. All testing was conducted in phosphate buffered saline (0.9%(w/v) NaCl) at 37 °C. During testing, load data from the load cell and specimen extension data from the stroke of the cross-head of the tensile testing machine was acquired at a rate of 20 Hz. In order to obtain an accurate measure of the tissue gauge length, the tensile machine was set to produce a specimen preloading of 0.02 N before the operating program started to acquire any data. Therefore, zero extension was taken at the point where a load of 0.02 N was detected. The final gauge length (L_o) of the specimen was calculated as the initial gauge length (10 mm) plus the extension required to producing the specified preloading. Failure was taken to occur when the first decrease in load was detected during extension.

The recorded load (F) and specimen extension data (ΔL) for the final loading ramp to failure and of each specimen was converted to stress and strain. Stress (σ) was defined as F/CSA (engineering stress), with CSA representing the unloaded cross-sectional area of the specimen. The CSA was assumed rectangular for the leaflet specimens and circular for the chordae ones. The in-plane axial engineering strain (ε) was defined as $\Delta L/L_o$ (Korossis et al., 2005). The calculated stress–strain responses for the specimens of each group were averaged over the number of specimens in each group using a mathematical analysis software package (Origin v6.0, Microbal). Moreover, the stress–strain behavior of each specimen was analyzed by means of six parameters, which included the elastin (El-E) and collagen (Col-E) phase slopes, transition stress (σ_{trans}) and strain (ε_{trans}), ultimate tensile strength (σ_{uts}) and failure strain (ε_{uts}) (Korossis et al., 2002). The calculated biomechanical parameters were averaged over the number of specimens in each group and analyzed by one-way analysis of variance (ANOVA) and the minimum significance difference (MSD) method at the 95% confidence level. The difference between the means of the paired comparison groups was compared to the MSD. Statistical significance was accepted when the difference between means was greater than the MSD. The results are presented as means $\pm$ 95% confidence intervals.

2.2. Histological staining

Circumferential and radial samples from posterior and anterior leaflets (Fig. 1), and axial samples from strut and commissural chordae, were dissected from porcine hearts within 6 h of slaughter. The samples were fixed in 10%(v/v) neutral buffered formalin (NBF) for 24 h, dehydrated, and then embedded in paraffin wax blocks. Subsequently, 5 μm sections were dissected from the blocks, which were placed on microscope slides and secured with coverslips. The slides were then stained with either Miller's elastin (Raymond A. Lamb) and Sirius Red (WWR International), or Masson's Trichrome (Raymond A. Lamb). The stained slides were viewed and photographed under Koehler illumination or polarized light using a BX40 Olympus upright microscope (Olympus UK Ltd.) and an Evolution MP5 digital camera in conjunction with Image-ProPlus 5.1 (Media Cybernetics).

3. Results

3.1. Biomechanics

The anterior leaflet demonstrated a noticeable anisotropy between the radial and circumferential directions, with the radial specimens demonstrating a much more extensible behavior and achieving significantly reduced failure stresses compared to the circumferential group (Fig. 2). A directional anisotropy was also

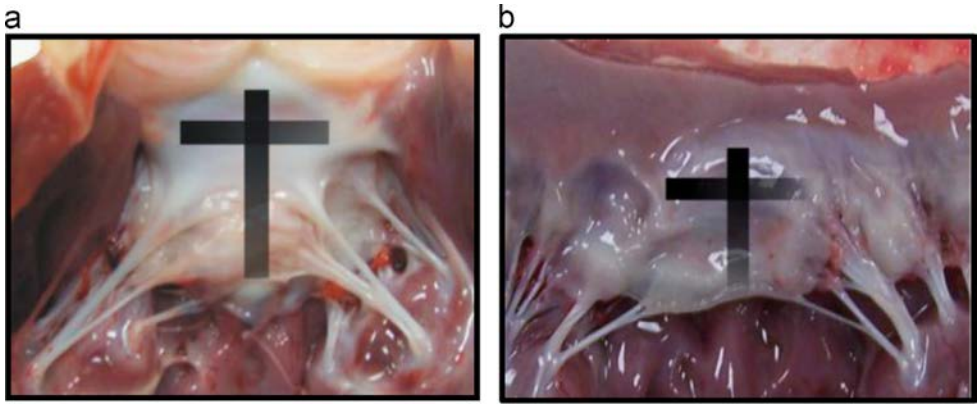

Fig. 1. Leaflet specimen orientation, used for histological and biomechanical testing, along the circumferential (horizontal rectangles) and radial (vertical rectangles) directions; (a) anterior leaflet; (b) posterior leaflet.

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