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Effects of valve geometry and tissue anisotropy on the radial stretch and coaptation area of tissue-engineered heart valves

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ABSTRACT

Tissue engineering represents a promising technique to overcome the limitations of the current valve replacements, since it allows for creating living autologous heart valves that have the potential to grow and remodel. However, also this approach still faces a number of challenges. One particular problem is regurgitation, caused by cell-mediated tissue retraction or the mismatch in geometrical and material properties between tissue-engineered heart valves (TEHVs) and their native counterparts. The goal of the present study was to assess the influence of valve geometry and tissue anisotropy on the deformation profile and closed configuration of TEHVs. To achieve this aim, a range of finite element models incorporating different valve shapes was developed, and the constitutive behavior of the tissue was modeled using an established computational framework, where the degree of anisotropy was varied between values representative of TEHVs and native valves. The results of this study suggest that valve geometry and tissue anisotropy are both important to maximize the radial strains and thereby the coaptation area. Additionally, the minimum degree of anisotropy that is required to obtain positive radial strains was shown to depend on the valve shape and the pressure to which the valves are exposed. Exposure to pulmonary diastolic pressure only yielded positive radial strains if the anisotropy was comparable to the native situation, whereas considerably less anisotropy was required if the valves were exposed to aortic diastolic pressure.

1. Introduction

Heart valve disease remains a major problem worldwide (Takkenberg et al., 2008). Approximately 280,000 heart valve replacements are performed each year (Pibarot and Dumesnil, 2009) and this number still increases (Dunning et al., 2011; Takkenberg et al., 2008). Currently, diseased valves are replaced by either mechanical or bioprosthetic valves. Both types of prostheses significantly enhance the quality of life, but also have several limitations. For example, mechanical valves require life-long anticoagulation therapy to prevent thromboembolism, and bioprosthetic valves have a limited durability (Kidane et al., 2009; Pibarot and Dumesnil, 2009). Most importantly, both valve substitutes are unable to grow, repair, and remodel in response to changing demands. This represents a major problem for pediatric patients, who need multiple surgical interventions during their life due to valve deterioration or to accommodate somatic growth (Ackermann et al., 2007; Lee et al., 2011).

Tissue engineering represents a promising technique to overcome the limitations of the current valve replacements, since this approach allows for creating living autologous heart valves that have the potential to grow and remodel. Indeed, previous studies have demonstrated the in vivo functionality of tissue-engineered heart valves (TEHVs) in animal models (Flanagan et al., 2009; Gottlieb et al., 2010; Hoerstrup et al., 2000; Schmidt et al., 2010). However, also this approach faces a number of challenges. For example, mild to severe regurgitation due to retraction of the leaflets has been reported in several studies (Flanagan et al., 2009; Gottlieb et al., 2010), which may even progress with time (Gottlieb et al., 2010). Long-term regurgitation is unacceptable because it will ultimately lead to ventricular failure. Therefore, leaflet retraction is a critical problem that needs to be solved.

TEHVs have different structural properties compared to native valves. This may result in nonphysiological deformation patterns in the tissue when the valve is loaded, and consequently have an influence on both short-term and long-term valve function. In the short term, different deformation patterns in the TEHV can alter the closed configuration of the valve and thereby lead to sub-optimal coaptation during diastole. In the long term, as cells remodel the extracellular matrix in response to mechanical stimuli, nonphysiological deformation patterns may lead to altered collagen remodeling compared to native valves. We hypothesize that leaflet retraction leading to regurgitation is, at least partly, caused by this mismatch in structural properties between TEHVs

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and their native counterparts. Therefore, it may be essential to mimic the deformation profile of native valves in TEHVs to ensure proper valve closure and induce physiological tissue remodeling. In this study, we investigated the influence of the structural properties of TEHVs on the deformation profile and closed configuration of TEHVs.

The geometry of the valve leaflets is one of the factors that influences the deformation profile of TEHVs. The geometry of native valves can be described by the well-known design of Thubrikar (1990), where the load-bearing surfaces of the leaflets are approximated by nearly cylindrical shapes with a curvature in circumferential direction. Using this design, Labrosse et al. (2006) reported that a range of valve dimensions exist for normal aortic heart valves that lead to proper valve function. However, it is not known whether this geometrical range also leads to optimal performance in TEHVs. Moreover, it remains to be questioned whether the Thubrikar design as such provides the ideal shape for TEHVs. In fact, it has been proposed that native leaflets also have a curvature in radial direction (Anderson, 2007; Hamid et al., 1986), which may considerably influence valve performance.

The material properties of TEHVs also affect the mechanical behavior of the valve. Since collagen is the main load-bearing structure in the tissue, particularly the anisotropy of the collagen network is important for its overall function. Native aortic valves exhibit a clear anisotropic material behavior because most collagen fibers are aligned in the circumferential direction (Billiar and Sacks, 2000a; Martin and Sun, 2012). Consequently, extension is limited in this direction, and the tissue will mainly extend in radial direction when the valve is loaded (Billiar and Sacks, 2000a, 2000b; Martin and Sun, 2012). Finite element (FE) models that incorporated this material behavior have also shown that this anisotropic deformation profile affects the stress distribution in the tissue (Li et al., 2001; Luo et al., 2003; Sun et al., 2005), and the opening and closing times during the cardiac cycle (Saleeb et al., 2013). Unfortunately, TEHVs generally have a less distinct collagen anisotropy (Mol et al., 2006), and are therefore exposed to smaller radial strains which can even become negative (Driessen et al., 2007). This contributes to suboptimal coaptation during the diastolic phase, and maybe also leads to adverse tissue remodeling in the long term. Clearly, this insufficient anisotropy of the collagen network should be improved to enhance the performance of TEHVs. However, it is not clear how much anisotropy is needed to ensure proper valve closure.

In the present study, a computational model that describes the mechanical behavior of cardiovascular tissues (Driessen et al., 2007) was applied to a range of valve shapes to determine the influence of anisotropy on the radial stretch in the valve and the coaptation area for different geometries. In particular, the following questions were addressed: (1) How much anisotropy is needed to prevent negative radial strains? (2) Does the geometry of the TEHV have an influence on this minimum amount of anisotropy? (3) Is this minimum amount of anisotropy different for valves subjected to pulmonary or aortic diastolic pressure?

2. Methods

2.1. Valve geometry

The scaffolds used to culture TEHVs in the host lab have previously been created according to the design of Thubrikar (1990) without any initial coaptation. This geometry is described by five parameters: R_b, R_c, H, H_s, and β (Fig. 1a). Previously, valves with a diameter of 27 mm were created using the following parameters: $R_b=R_c=13.5$ mm, $H=19.15$ mm, $H_s=3.15$ mm, and $\beta=0^\circ$. In the present study, the commissural height H_s and the angle β of the open leaflet with the vertical direction were varied to assess the influence of geometrical variations in the Thubrikar design for valves with the same diameter and overall height (see Table 1, shapes T1–T9, and Fig. 1b).

In addition, the Thubrikar design was compared with the Hamid design, which incorporates the leaflet curvature in both circumferential and radial direction (Fig. 1d). In this case, the initial leaflet geometry is described by one half of an elliptic paraboloid (Hamid et al., 1986):

$$\frac{x^2}{a^2}+\frac{y^2}{b^2}-z=0 \tag{1}$$

where parameters a and b determine the curvature in circumferential and radial direction, respectively. This initial geometry was rotated by an angle of $\tan^{-1}(R/(2H))$ (Fig. 1d), with R the radius of the valve and H the height of the leaflet. Subsequently, points on this surface that cross the planes that separate the leaflet from the other two ($y=\tan(30^\circ)\|x\|$) were mapped onto these planes to obtain the initial coaptation surface (Hamid et al., 1986). Finally, parts of the leaflet where $\sqrt{x^2+y^2}>R$ were removed. Both the radius and height of the valve were

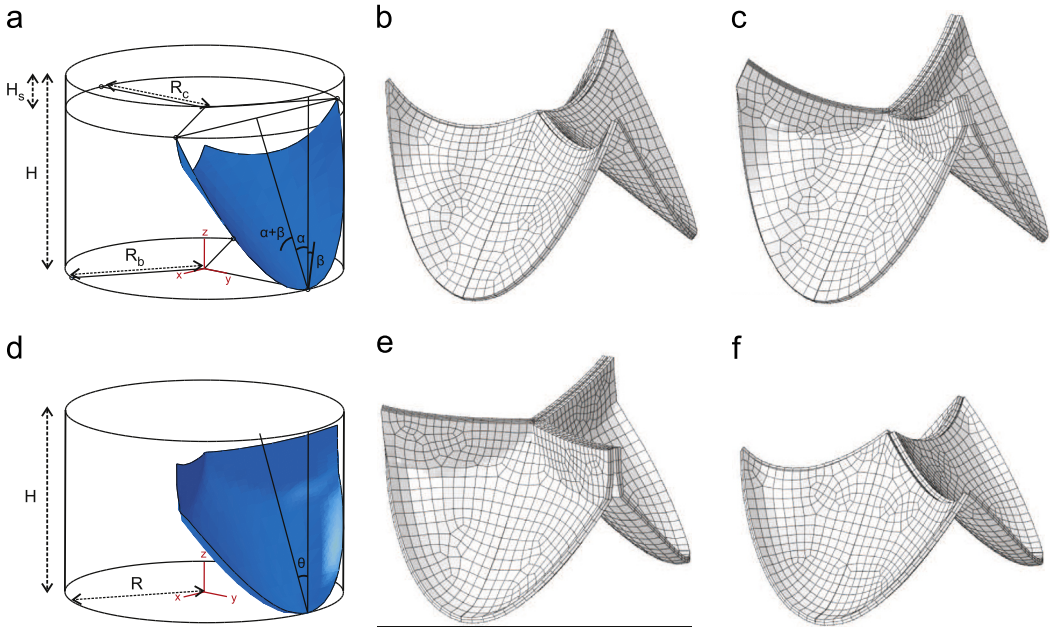

Fig. 1. (a) Valve leaflet geometry defined by Thubrikar (1990), (b) example of the Thubrikar design without initial coaptation (shape T5, see Table 1), (c) example of the Thubrikar design with added initial coaptation (shape T5c), (d) valve leaflet geometry defined by Hamid et al. (1986), (e) example of the Hamid design with initial coaptation (shape H5c) and (f) example of the Hamid design where the initial coaptation area has been removed (shape H5).