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Towards the improved quantification of *in vivo* abnormal wall shear stresses in BAV-affected patients from 4D-flow imaging: Benchmarking and application to real data

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ABSTRACT

Bicuspid aortic valve (BAV), i.e. the fusion of two aortic valve cusps, is the most frequent congenital cardiac malformation. Its progression is often characterized by accelerated leaflet calcification and aortic wall dilation. These processes are likely enhanced by altered biomechanical stimuli, including fluid-dynamic wall shear stresses (WSS) acting on both the aortic wall and the aortic valve. Several studies have proposed the exploitation of 4D-flow magnetic resonance imaging sequences to characterize abnormal *in vivo* WSS in BAV-affected patients, to support prognosis and timing of intervention. However, current methods fail to quantify WSS peak values.

On this basis, we developed two new methods for the improved quantification of *in vivo* WSS acting on the aortic wall based on 4D-flow data.

We tested both methods separately and in combination on synthetic datasets obtained by two computational fluid-dynamics (CFD) models of the aorta with healthy and bicuspid aortic valve. Tests highlighted the need for data spatial resolution at least comparable to current clinical guidelines, the low sensitivity of the methods to data noise, and their capability, when used jointly, to compute more realistic peak WSS values as compared to state-of-the-art methods.

The integrated application of the two methods on the real 4D-flow data from a preliminary cohort of three healthy volunteers and three BAV-affected patients confirmed these indications. In particular, quantified WSS peak values were one order of magnitude higher than those reported in previous 4D-flow studies, and much closer to those computed by highly time- and space-resolved CFD simulations.

1. Introduction

Bicuspid aortic valve (BAV) consists in the congenital fusion of two of the three aortic valve (AV) leaflets. BAV is the most common congenital cardiac disease and affects about 2% of newborns (Michelena et al., 2014). BAV is a recognized risk factor for calcific aortic valve stenosis and for ascending aorta dilation: approximately one half of the patients undergoing surgery to treat calcific aortic stenosis are affected by BAV (Roberts and Ko, 2005), and more than 50% of BAV patients develop ascending aorta aneurysm (Fedak et al., 2002; Nistri et al., 1999). Alterations in aortic root structural mechanics (Conti et al., 2010a, 2010b) and fluid-dynamics (Hope et al., 2014) induced by BAV abnormal morphology have been identified as key factors determining or accelerating these degenerative processes. These alterations include abnormal fluid-dynamic wall shear stresses (WSS) acting on the endothelial cells covering the inner surface of the aortic wall and the aortic valve leaflets, respectively. Although through mechanisms that are not fully understood, altered WSS can trigger mechanotransduction pathways leading to altered gene and protein expression, to inflammatory processes, and to altered regulation of interstitial cell phenotypes (Butcher and Nerem, 2006; El-Hamamsy et al., 2010). Currently, BAV risk stratification, prognosis and decision for surgery largely rely on purely geometrical criteria, as the measurement of the aortic diameter (Della Corte et al., 2014) and of the tilting angle

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characterizing the fused leaflets (Della Corte et al., 2012). These criteria are empirical and sub-optimal; biomechanically-driven ones could complement them allowing for more reliable prognosis and aid the decision process.

In this scenario, phase-contrast magnetic resonance imaging (PC-MRI), and in particular its latest evolution, i.e. 4D flow, has been proposed as a tool to quantify *in vivo* fluid-dynamic alterations affecting BAV patients (Bissell et al., 2013; Hope et al., 2014). 4D-flow sequences offer the ability to capture complex 3D time-resolved velocity patterns, without any restriction to predefined 2D imaging planes (Markl et al., 2012), allowing for retrospective investigations of any location of the acquired volume. 4D-flow sequences' value is yet still hampered by low spatial-temporal resolution, long-lasting acquisitions and lack of standardized protocols (Markl et al., 2014). However, published studies have clearly shown that some hemodynamic markers (e.g. peak velocity, flow jet angle, helicity) can be reliably quantified to assess alterations in BAV (Lorenz et al., 2014; Sigovan et al., 2011; Stalder et al., 2008). By contrast, the reliability of WSS patterns estimations is still debated: differences in spatial trends of WSS between healthy subjects and BAV patients can be captured (Bissell et al., 2013), even though the corresponding numerical results are not valuable. In fact, there are evidences that underestimations in WSS values can occur primarily due to spatial resolution and noise issues of the acquired datasets (Petersson et al., 2012). Hence, currently the gross fluid-dynamic alterations affecting WSS in BAV patients can be assessed based on 4D-flow acquisitions, but reference values for healthy and disease states are yet undefined (Potters et al., 2014) and cannot be used for risk stratification.

To address these limitations, we developed and tested two new methods to improve the reliability of WSS computation from 4D-flow discrete velocity field. These are based on a fully volumetric and a local planar analysis, respectively. To test these methods, computational fluid-dynamics (CFD) models of the thoracic aorta with healthy and bicuspid aortic valve were created, accounting for the complex anatomy of the domain. To mimic MR acquisitions, the computed velocity fields were down-sampled to obtain artificial 4D-flow datasets. The sensitivity of our methods to data spatial resolution and noise was assessed. Finally, we applied our methods on 4D-flow datasets of three healthy subjects and three BAV patients, assessing consistent hemodynamic differences and shear stress patterns.

2. Material and methods

2.1. Artificial 4D-flow datasets

Two geometrical models of the thoracic aorta with open physiological tricuspid (TAV) and bicuspid aortic valve (BAV), respectively, were borrowed from previous work (Conti et al., 2010a, 2010b; Della Corte et al., 2012) (Fig. 1.a,b). Transient CFD simulations were run with the commercial solver Fluent (Ansys Inc., Canonsburg, PA, USA). Time-dependent flow rates were imposed at the aorta inlet and at the supra-aortic branches (Fig. 1c), zero-pressure was set at the aorta outlet, and no-slip condition at the wall was assumed. Blood was modeled as an incompressible Newtonian fluid ($\mu = 3.7$ cP, $\rho = 1060$ kg/m^3). Artificial 4D-flow datasets were obtained for the two models with reference to peak systole following our previously published approach (Morbiducci et al., 2012). Briefly, CFD-derived velocity fields were downsampled with an isotropic spatial resolution, obtaining a voxel grid. In order to mimic MR spatial regularization, the velocity data associated to each voxel were computed as the weighted average of the CFD velocity data at the points falling within the voxel, where the weights were generated through a Gaussian function of the distance between these points and the voxel center. This procedure was implemented with a spatial resolution (Δx) of 1, 2, 3 and 4 mm.

On the TAV and BAV datasets with a 2 mm spatial resolution, which is consistent with current clinical practice (Dyverfeldt et al., 2015), we emulated the definition of sub optimal encoding velocity (VENC) values to account for MR noise. Gaussian noise with a variance related to the VENC was added to the dataset, thus worsening the signal-to-noise ratio (Petersson et al., 2012). For each dataset, three noisy variants were obtained, by adding noise consistent with VENC values exceeding the actual maximum velocity by 5%, 10% and 20%, respectively.

2.2. Real 4D-flow datasets

Three BAV-affected patients without complex congenital heart diseases (2 males, age 19,28,31) were recruited prospectively. Three healthy volunteers (3 males, age 17,23,25) were enrolled as controls. 4D-flow acquisitions were performed at John Radcliffe Hospital (Oxford, United Kingdom). Flow-sensitive gradient-echo pulse sequences were acquired with prospective ECG-gating during free-breathing, using a respiratory navigator, on a 3.0 T Magnetom Trio MR system (Siemens, Erlangen, Germany). The acquisition volume was oriented along an oblique-sagittal plane encompassing the whole thoracic aorta, as well as the ascending aorta and the aortic arch. 4D-flow sequences were set with the following specifics: i) voxel sizing $= 1.67 \div 2.2$ mm^3; ii) VENC $= 150 \div 370$ cm/s; iii) Flip Angle $= 7°$; iv) Echo Time $= 2.3 \div 2.5$ ms; v) Repetition Time $= 40$ ms. The Institutional Review Board approved the study and informed consent was obtained from each participant. The time-frame with the highest velocity-to-noise ratio was chosen as the most representative of peak systole and selected for post-processing.

2.3. Definition of the region of interest (ROI)

The region of interest (ROI) in the datasets consisted in the aortic lumen. On CFD-derived artificial 4D-flow datasets, voxels within the ROI were automatically

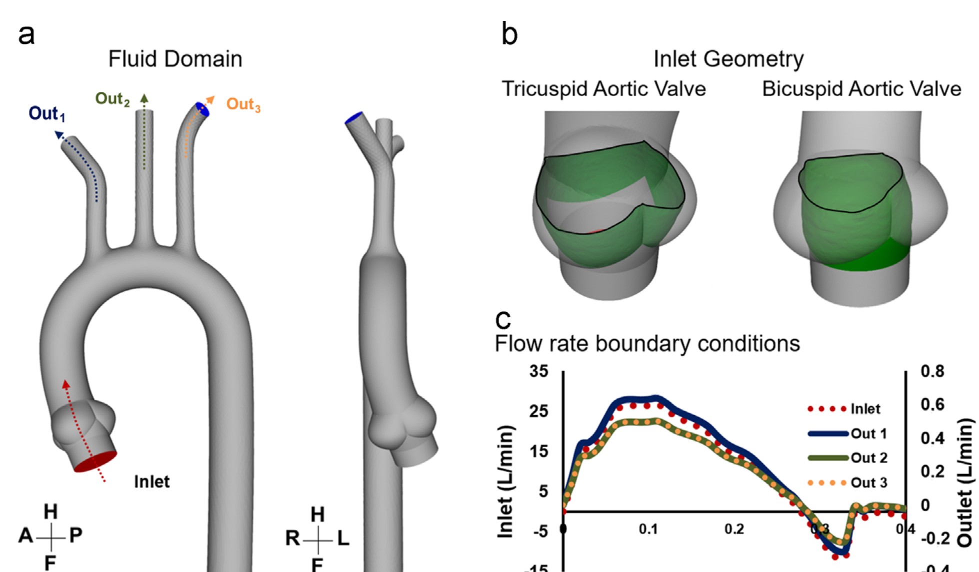

Fig. 1. a) Geometrical models of the thoracic aorta used to perform numerical simulations and to feed the generation of synthetic 4D-flow datasets, b) characterized by physiological tricuspid (TAV) and bicuspid aortic valve (BAV). c) Flow rate waveforms applied as boundary conditions.