Peer Review File

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Reviewer A

Comment 1

1. Regarding flow energy loss (EL), described on Page 6, there have been many studies discussing native aortic valve stenosis and evaluating prosthetic valve. Nonrecoverable energy results from heat generation from turbulence and friction, shearing in the distal jet and valve inertia. The blood flow velocity/pressure exchange in convective acceleration assumes the presence of nonturbulent laminar flow and a flat blood flow velocity profile at the aortic valve. Especially, it is noted that more pressure recovery, associated with EL, causes overestimation of the echocardiography-measured trans-valve gradient compared with catheterization-measured gradient. The authors should review the application of the concept of EL to evaluation of the aortic valve and aortic root. Also, the authors should review the correlation between flow visualization/simulation and echocardiographic/catheter variables, regarding EL.

Response 1:

We appreciate the reviewer for this valuable comment and the opportunity to review more information about energy loss (EL). Following the reviewer's suggestion, we agree that EL has an important relevance to the assessment of hemodynamic severity of aortic stenosis (AS). We have incorporated a discussion on the association between EL and the diagnosis of AS and have cited relevant studies.

Changes in the text:

We have added the sentences in Main text (Page 11, Line 179-191) as follows:

This concept of kinetic energy dissipation has been emphasized the assessment of hemodynamic severity of aortic stenosis (AS). It is well known that there can be discrepancies in the assessment of hemodynamic severity in AS between echocardiography and catheterization because echocardiography does not account for the extent of pressure recovery that occur downstream of the stenosis by dissipation of energy (31). When significant pressure recovery occurs, the echocardiography-measured trans-valve gradient can markedly exceed catheterization-measured gradient (32). This irreversible gradient, which is calculated taking into account pressure recovery, is currently best estimated by catheterization; however, this is invasive which limits its routine use. In contrast, 4D flow MRI permits noninvasive estimation of EL with flow visualization. Previously, several studies reported that EL measured by 4D flow MRI correlated strongly with irreversible pressure gradient (33,34). These studies concluded that EL can provide complementary information to well-established method, helping assess AS severity in patients whose diagnosis is challenging due to subtle examination findings.

Comment 2.

Regarding oscillatory shear index (OSI), described on Page 7, what is the index? Since the index is defined, what is the calculation equation to obtain OSI? The author should clarify the definition of OSI.

Response 2:

We appreciate the reviewer for this valuable comment and for the opportunity to give more information about the oscillatory shear index (OSI). OSI measures the degree of fluctuation in the shear force orientation over a cardiac cycle, therefore, it is an index of the fluctuation of WSS in one cardiac cycle (5) (Figure 5). It is mathematically defined as follows.

$$\mathrm{OSI} = \frac{1}{2}\left(1 - \frac{\left|\int_0^T \overrightarrow{\mathrm{WSS}}\mathrm{dt}\right|}{\int_0^T \left\lceil\overrightarrow{\mathrm{WSS}}\right\rceil \mathrm{dt}}\right)$$

where, WSS is the wall shear stress vector, and T is the time interval of interest, typically the cardiac cycle duration.

Changes in the text:

We have added the below information to the main text of the manuscript (see Page 12, Line 206-210) as follows:

OSI measures the degree of fluctuation in shear stress orientation over a cardiac cycle (5) (Figure 5). An OSI value close to 0.5 indicates that WSS experienced a 180° change in its orientation during the cycle, while an OSI value of 0 indicates that the WSS vector didn't change its direction throughout the cycle. It is defined as,

$$\mathrm{OSI} = \frac{1}{2}\left(1 - \frac{\left|\int_0^T \overrightarrow{\mathrm{WSS}}\mathrm{dt}\right|}{\int_0^T \left|\overrightarrow{\mathrm{WSS}}\right|\mathrm{dt}}\right)$$

Comment 3.

Regarding Ascending Aorta on page 9, the authors described the positive effects of 4D flow MRI visualization on prediction of prognosis of the patients with aortic disease. However, the authors did not state the positive effects on the surgical strategies for the aortic disease.

Response 3.

This is an excellent suggestion. We agree that at present 4D flow MRI may not be utilized in guiding the surgical strategy while it certainly provides important information on the mechanism of ascending aneurysm. Previous studies, including one from our collaborators, showed relevance of CT-based CFD analysis. We have added this study that utilized CFD analysis to show the difference in systemic and cerebral perfusion flow patterns between subclavian artery cannulation and ascending aorta cannulation during ascending aorta or arch replacement.

Changes in the text:

We have added the relevant sentences as follows (see Page 15, Line 256-261):

Previously, Numata et al. investigated the difference in systemic and cerebral perfusion flow patterns between subclavian artery cannulation and ascending aorta cannulation during ascending aorta or arch replacement using CFD analysis; they reported that right subclavian artery cannulation produced a protective effect on the brain, especially on the right side (60). Thus, blood flow assessment may play an important role on the surgical management of aortic disease.

Comment 4.

Regarding Aortic Dissection on page 9, the authors the authors reviewed their report of CFD analysis on CT images of patients with acute type A aortic dissection (AAAD) to elucidate the mechanism of primary entry occurrence in the AAAD, as shown in Figure 6. Although they found that shear stress fluctuations were closely associated with the future occurrence of AAAD, the OSI data and imaging were obtained after the onset of AAAD. We should know the OSI data and imaging before the onset of AAAD to conclude the site with high OSI is the primary entry site. We can not conclude based upon the OSI data and imaging after the primary entry occurred.

Response 4.

We appreciate the reviewer for the comment. In our study, we in fact performed CFD analysis ***using a CT before the AAAD occurrence***. By using pre-onset CT, we demonstrated that the pre-onset high OSI area was closely associated with the subsequent primary entry site.

Changes in the text:

We have added further sentences (see Page 15-16, Line 265-267) as follows:

Our group performed CFD analysis on pre-onset CT images of patients with acute type A aortic dissection (AAAD) to elucidate the mechanism of primary entry occurrence in the AAAD (45).

Comment 5.

Also, regarding Aortic Dissection on pages 9 and 10, the authors stated the usefulness of flow visualization, especially of CFD, to perceive the anatomy of aortic dissection. However, the authors did not state the usefulness of CFD to perceive the triple-lumen aortic dissection and distal residual dissection after central aortic repair, presenting multiple entries and complex flow channels. The authors should review application of CFD in such complex clinical settings.

Response 5.

We appreciate the reviewer for this valuable comment and for the opportunity to give more information about CFD analysis applied to aortic dissection. We have included a study that showed that the pressure difference between the true and false lumens could predict progressive residual native aortic dilatation after primary surgery in patients with AAAD.

Following the reviewer's suggestion, we have added another study that investigated the effect of multiple entry locations on flow velocity and wall pressure distributions in patients with type B aortic dissection. They highlighted that type B aortic dissection with two entry tears tends to squeeze the true lumen and expand the false lumen with higher wall pressure, resulting in a new entry tear and deterioration into multiple entry type B aortic dissection. Therefore, this study demonstrated that the closure of the proximal entry tear was considered an ideal solution for type B aortic dissection with two entry tears.

Changes in the text:

We have added this information (see Page 16-17, Line 280-286) as follows:

Moreover, Liu et al. investigated the differences in flow velocity and wall pressure (the force on the vessel wall caused by blood flow) between patients with two and multiple entry tears in patients with type B aortic dissection (TBAD). They showed that TBAD with two entry tears squeezes the true lumen and expands the false lumen with higher wall pressure, resulting in a new entry tear and deterioration into multiple entry-TBAD. Therefore, they concluded that the closure of the proximal entry tear was deemed ideal solution for TBAD with two entry tears (70).

Comment 6.

Regarding Future Perspective of Blood Flow Assessment in Aortic Surgery on Page 11, the authors jumbled together anatomical visualization and functional visualization. 3D printed models contributes to anatomical visualization, while CFD does functional visualization. Although the authors presented Figure 7, the computer-based virtual postoperative models provide anatomical information only, not flow information. In addition, when the CFD data is based upon the 3D printed models, it will be not reliable because the 3D printed models vary with many interactive variables.

Response 6:

We appreciate the reviewer for this comment. When combined with 3D computer graphics, CFD analysis may help surgeons predict the postoperative hemodynamics and determine a surgical strategy. As we showed in Figure 7, in this case, CFD analysis was used to predict the postoperative coronary flow volume in various graft patterns. The result of the flow volume predictions was shown in Figure 7. As you suggested, when the CFD data is based upon the 3D printed models, it is not reliable because the 3D printed models vary with many interactive variables. Therefore, we decide to remove content about CFD analysis based on 3D printed models.

Changes in the text:

We have removed relevant sentences from previous draft as below:

Future Perspective of Blood Flow Assessment in Aortic Surgery

"Virtual Surgery"

~~3D printed models for CFD analysis have been used to evaluate hemodynamics in~~

~~cardiovascular disease (71,72). In particular, 3D-printed models can demonstrate realistic fabric folds and wrinkles in prosthetic grafts for aortic disease (71). Moreover, immersive computational techniques, such as Virtual Reality (VR), may allow for improved visualization and understanding of cardiac anatomy in CHD (73,74). Baheri Islami et al. reported that simulated flow can be displayed in VR environments to allow physicians to understand the complex blood flow patterns within arteries: while "taking a walk" inside the aneurysm, the viewer can observe the velocity, pressure, and stress fields (75).~~
When combined with 3D computer graphics, CFD analysis can enable aortic surgeons to perform "virtual surgery" (6,76). Virtual surgery predicts postoperative blood flow, which can supplement preoperative surgical planning based on an individual's hemodynamics in aortic disease. In this method, the patient-specific geometry acquired from preoperative CT imaging is morphed into a predicted postoperative anatomy, and blood flow is computed following the simulated repair (6). For example, Fujisue et al. utilized virtual surgery to guide preoperative planning in patients with aortic coarctation. They compared the postoperative hemodynamics between three surgical approaches: ascending-abdominal aorta bypass, descending-descending aorta bypass, and descending aorta replacement; their calculations helped guide the approach ultimately pursued in the operating room (77). We used this technology to decide whether to pursue concomitant coronary revascularization during aortic root replacement for a patient with supravalvular aortic root stenosis. After comparing postoperative coronary flow volume following a Bentall procedure with and without concomitant CABG, a preoperative decision to perform an isolated Bentall was made (Figure 7) (78). Virtual surgery with CFD analysis can help determine the optimal surgical procedure personalized to an individual during preoperative planning.

Reviewer B

Comment 1.
The section on flow assessment discusses both flow measurement and visualization. The former, including the three measurement parameters (EL, WSS, and OSI), is well explained. However, the latter's explanation, which covers flow patterns such as vortex, helical, and eccentric flow, needs further elaboration for better reader comprehension.

Response 1:
We appreciate the reviewer for the valuable comment. Following the reviewer's suggestion, we added more information on helical, vortical flow, and eccentricity, and

how they relate to cardiovascular disease.

Changes to the Manuscript 1:

We have revised the relevant paragraph (see Page 8-9, Line 137-143 and Page 14-15, Line 248-250) as follows:

Page 8-9, Line 137-143

A helical spiral flow, which is a flow with rotation around an axis while moving forward, was observed in the ascending aorta during the holosystolic phase (23,24). In contrast, a straight transvalvular aortic flow was observed in a bovine pericardial valve in the early systolic phase. Two large vortical flows, which are rotating or swirling flows with streamlines or pathlines that tend to curl back on themselves (23, 24), occurred on both sides of the greater and lesser curvature of the ascending aorta after the mid-systolic period.

Page 14-15, Line 248-250

Eccentric flow, which is an abnormal transvalvular flow caused by bicuspid valvular morphology, is thought to be an important contributor to the aortopathy in patients with BAV (58,59).

Comment 2.

It is necessary to present the reference values, cut-off values, or outliers for EL, WSS, and OSI as mentioned in the cited papers. Clarification on whether these values are maximums or averages, along with the units used, is also needed. The significance of WSS is particularly noted, as it is implicated in aneurysm formation when excessively low or high.

Response 2:

We appreciate the reviewer for this comment and the opportunity to clarify these key details. Previously normal range of WSS was reported between 1 and 7 Pa in the coronary artery. The challenge is that these mechanical stress parameters, including WSS, OSI and EL, vary widely among vessels and ventricular chambers because they depend on mean blood volume, flow velocity, and vessel diameter. For example, EL was reported to be different between left and right ventricles even in healthy volunteers' case (Reference #.75 in manuscript). Therefore, there is no unified reference, cut-off value yet, which is a current limitation of blood flow assessment. Moreover, blood flow assessment is performed using imaging data throughout one cardiac cycle which is separated into numerous slices or segments. The mechanical stress parameters are acquired at each location and at each cardiac phase. When we need information on mechanical stress in the left ventricle during one cardiac cycle, we totalize the measured parameters of the left ventricle during one cardiac cycle.

Changes to the Manuscript 2:

We have added the below information to the main text of the manuscript (see Page 10, Line 172-175, Page 11, Line 193-195, Page 12, Line 207-209 and Page 17, Line 301-305) as follows:

<u>Page 10, Line 172-175</u>

It is calculated as below.

$$\text{EL (mW)} = \int \mu \sum_{i,j} \left(\frac{\partial u_j}{\partial x_i} + \frac{\partial u_i}{\partial x_j}\right)^2 dv$$

where μ is the coefficient of blood viscosity, u is the velocity vector component, and i and j are coordinates on the Cartesian coordinate system (22,23).

<u>Page 11, Line 192-194</u>

WSS is the shear force on the vessel wall caused by blood flow and is calculated from the flow velocity profile within the vessel lumen (6) (Figure 5). Previously, the normal range of WSS was reported between 1 and 7 Pa in the coronary artery.

<u>Page 12, Line 206-210</u>

OSI measures the degree of fluctuation in shear stress orientation over a cardiac cycle (5) (Figure 5). An OSI value close to 0.5 indicates that WSS experienced a 180° change in its orientation during the cycle, while an OSI value of 0 indicates that the WSS vector didn't change its direction throughout the cycle. It is defined as,

$$\mathrm{OSI} = \frac{1}{2}\left(1 - \frac{\left|\int_0^T \overrightarrow{\mathrm{WSS}}\mathrm{dt}\right|}{\int_0^T \left|\overrightarrow{\mathrm{WSS}}\right|\mathrm{dt}}\right)$$

<u>Page 17-18, Line 302-307</u>

Blood flow assessment has several limitations. First, although it can evaluate mechanical stress parameters, including EL, WSS, and OSI, there are no unified reference or cut-off values because these parameters depend on mean blood volume, flow velocity, its variation near the wall, vessel diameter, and blood viscosity, resulting in wide variation among vessels and the ventricular chambers (74). For example, EL was different between left and right ventricles even in healthy volunteers' case (75). Thus, a statistical baseline has yet to be established due to limited data.

Comment 3.
Please clarify the abbreviation: On line 256, CHD is mentioned but not defined.

Response 3:
We appreciate the reviewer for the valuable comment. However, due to the insightful comments by Reviewer A, this abbreviation has been removed.