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DEGREE OF RETROGRADE FLOW AND ITS EFFECT ON LOCAL HEMODYNAMICS AND PLAQUE DISTRIBUTION IN AN AORTIC REGURGITATION MURINE MODEL OF ATHEROSCLEROSIS

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INTRODUCTION

Previously, Zhou et al. [1] presented a novel mouse model of aortic valve regurgitation (AR) to explore the effect of altered hemodynamics on atherogenesis. In these *ldlr-/-* mice with AR, extensive atherosclerotic plaque was found along the naturally lesion-free descending thoracic (DTAo) and abdominal aorta (AbAo), with distinct spatial distributions suggestive of a strong local hemodynamic influence (Fig. 1, top). Doppler ultrasound measurement showed that both DTAo and AbAo of the AR mice experienced an oscillatory flow pattern induced by the diastolic retrograde flow, as opposed to the consistent antegrade flow found in the non-AR mice. The study also suggested that the fraction of the DTAo surface covered by lesions tends to increase with the absolute diastolic retrograde Time-Velocity Integral (TVI) as measured from the Doppler ultrasound.

Recently, Hoi et al. [2] used image-based Computational Fluid Dynamics (CFD) to demonstrate that maps of oscillatory shear index (OSI) and relative residence time (RRT) (Fig. 1, bottom: AR100 case) were remarkably consistent with the distribution of plaques along the DTAo of mice with a high degree of AR (e.g., Fig. 1, top: case III), and the absence of plaque in control mice (e.g., Fig 1, top: case C). For that study we considered a single AR and control flow waveform. Here, to further investigate how the *degree* of retrograde flow impacts the plaque burden in this murine model, we systematically varied the AR flow waveform in our CFD model of the mouse aorta.

METHODS

As detailed in [2], the three-dimensional (3D) aortic geometry of a control mouse was reconstructed from micro-CT scans. The smoothed model, which closely resembled the original aortic lumen, was truncated at the celiac artery, thereby including only the aortic arch and DTAo (Fig. 2, left). The model was imported into ICEM-CFD and used to generate a finite element mesh of approximately 400,000 quadratic tetrahedral elements.

Using the AR waveform from [2] as reference, we systematically reduced its diastolic phase in steps of 10% until it reached 50% of its original value (Fig. 2, right). Additionally, a control waveform with 0% diastolic retrograde flow was also included. In accordance with our observations from [2], the systolic phase was fixed for all cases. In total, seven different waveforms were applied as boundary conditions.

For each case, a plug velocity profile was imposed at the aortic inlet and traction-free boundary condition was imposed at the outlet. Rigid wall and constant blood viscosity of 3.5 mm^2/s were assumed. The unsteady Navier-Stokes equations were solved using a previously validated in-house solver. CFD simulations were carried out 4800 time steps per cardiac cycle, and at least 2 cycles were required to damp initial transients. As detailed in [2], the DTAo segment of the CFD model was unfolded to allow for direct comparison with the en face plaque stainings.

RESULTS

According to our simulation results in Fig. 1 (bottom), the extent of both elevated OSI and RRT decreased monotonically with the retrograde flow reduction, as expected. Patterns of OSI and RRT extrema were preserved, reflecting the dominant influence of geometry as shown previously [2]. For the minimum 50% diastolic flow reduction case (i.e., AR50), OSI and RRT levels were well below the levels previously found to be associated with plaque distributions for the AR100 model (i.e., black contours of AR100 CFD results vs. plaque distribution of AR case III). In fact, these levels of nominally pro-atherogenic shear only begin to appear when the diastolic retrograde flow is between 70% and 80% (ie., between cases AR70 and AR80) of its maximum level.

DISCUSSION

Zhou et al. previously showed that the degrees of lesions in the AR mice qualitatively depended upon on the retrograde TVI values [1], as demonstrated in Fig. 1 (top). For the three AR cases shown in this figure, the corresponding diastolic TVI (TVI_d) values are presented in Table 1. Thus, the TVI_d level of 45% for case I corresponds to a much reduced, but still geographically distinctive staining in the DTAo, compared to case III. For case II, the TVI_d level of 60% shows extensive staining more consistent with that at the 100% TVI_d level of case III. These observations are clearly inconsistent with the CFD results, which would suggest an absence of staining for TVI_d levels of 70% and below.

To resolve this inconsistency, we note that unpublished results from our CFD studies [2] indicated that OSI and RRT values and distributions were largely unaffected by the amplitude of the AR flow waveform so long as the *proportion* of diastolic:systolic flow was unchanged. Noting that the amplitude of systolic flow was different in the three AR cases shown in Fig. 1 (top), in Table 1 we also present the ratios of diastolic:systolic TVI (TVI_d:TVI_s) for the three cases. The small but finite degree of staining for case I is now seen to correspond to a TVI_d:TVI_s level of 72%, which is broadly consistent with the OSI and RRT distributions of the AR70 to AR80 CFD models. Case II is now seen to have a TVI_d:TVI_s level almost identical to case III, consistent with their similar degrees of staining.

Although the TVI_d:TVI_s appears to predict the pro-atherogenic hemodynamics, a number of limitations make it difficult to render these relationships more quantitatively. All AR cases were stained at the same time point, and it is likely that there is both a time- and dose response, which is not reflected in our CFD results. TVI values were based on Doppler ultrasound spectral values averaged from three locations along a diameter, and do not account for diameter variations between cases. Compliance-induced storage and release of flow also potentially causes attenuation or dispersion of flow waveform along the DTAo, but can not be accounted for by the rigid models used in this study. Our current works focus on introducing the compliance effects, and on comparing local hemodynamics and plaque staining in a more mouse specific manner by using MRI to better capture the flow rate waveform characteristics along the DTAo.

CONCLUSIONS

The degree of disturbed flow is potentially related to the ratio of diastole-to-systole flow, and such ratio is more reflective of the lesion distributions seen in the AR mice than diastolic flow measurement alone. This also suggests that the *presence* of retrograde flow may not induce plaque development, but rather there exists a nominal diastolic:systolic flow ratio above which plaques are prone to develop.

REFERENCES

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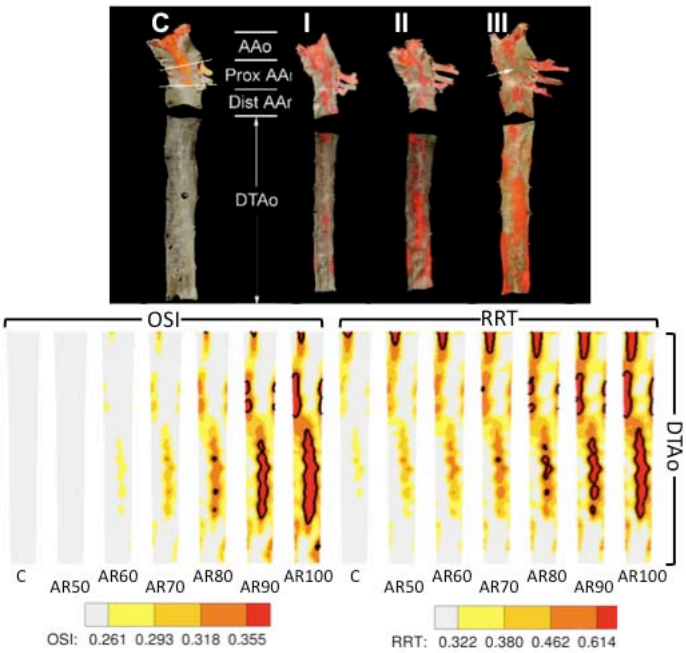

Figure 1. (Top) En face topology of the stained lesions, showing a control mouse (*C*) free of plaque in the DTAo and AR mice aorta (*I - III*) stained with defined regions of plaque at the proximal, middle and distal segments of DTAo. (Bottom) OSI and RRT plotted at levels corresponding to quintiles of AR100 over the mapped surface. Black contour lines highlight regions exposed to OSI>0.355 and RRT>0.614, the 80th percentile values that roughly correspond to the plaque regions of AR case III.

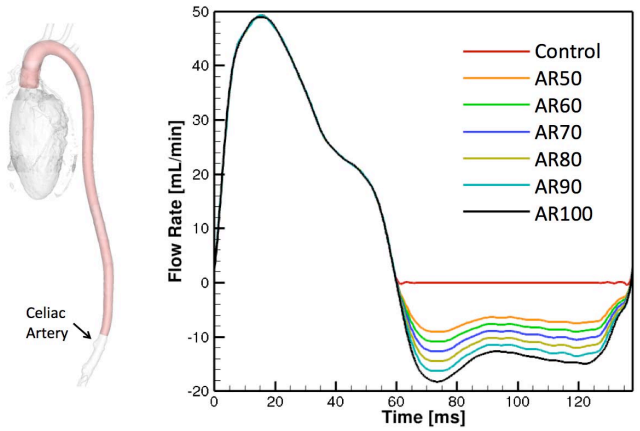

Figure 2. (Left) CFD model (red) overlaid on the micro-CT data. (Right) AR flow waveforms with different degrees of diastolic retrograde flow, were imposed at the aortic inlet of the CFD models.

Table 1: TVI at the proximal DTAo for the three AR cases shown in Figure 1.

	I	II	III
TVI_d *(cm)*	-1.23 (45%)	-1.63 (60%)	-2.74 100%)
TVI_d:TVI_s	0.49 (72%)	0.67 (99%)	0.68 (100%)

TVI_d: Absolute Diastolic TVI; TVI_s: Absolute Systolic TVI. Values in parentheses are after normalizing by the TVI of case III.