Investigation of Cerebral Ischemic Disease in the Aged with Aortic Stenosis

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Introduction:

Patients undergoing aortic valve replacement for aortic stenosis (AS) incur an exceptionally high risk for perioperative cerebral ischemia. Patients undergoing cardiac surgery also have a high frequency of pre-existing white matter and ischemia-like lesions (WML-ILL) [1, 2], the presence of which appears to predict postoperative cognitive dysfunction (POCD) and the development of new ischemic lesions [1]. The extreme risk in this group may arise from the interaction of aspects of cardio-pulmonary bypass with the pre-existing cerebrovascular disease. Assessment of risk factors for cerebrovascular small vessel disease within those with AS may assist in stratifying risk and better understanding the pathophysiology of perioperative cerebral ischemia. In this study, we investigated the predictive value of aging, sex, and AS degree for the severity of WML-ILL.

Methods:

This study was approved by the Institutional Review Board (IRB) of the University of Pennsylvania and all participants were appropriately consented prior to participation. Ninety five subjects (age ≥ 65 years) were included with mild, moderate, or severe-critical AS. Subjects were imaged on 1.5 Tesla Siemens Magnetom Avanto or GE Signa Excite MRI scanners to acquire the T1-weighted, T2-weighted, proton density-weighted (PD), and fluid attenuation inversion recovery (FLAIR) scans. These MR modalities were normalized to a study specific template with the following steps: 1) each subject's T2, PD, and FLAIR were co-registered to this individual's T1 with FLIRT - FMRIB's Linear Image Registration Tool (http://www.fmrib.ox.ac.uk/fsl/flirt/index.html) [3]; 2) each subject's T1 volume was then normalized to a study specific template by using FNIRT - FMRIB Non-Linear Image Registration Tool (http://www.fmrib.ox.ac.uk/fsl/fnirt/index.html). For normalizing other sequences (T2, PD, and FLAIR) to the template space, the affine transformations from FLIRT and the deformation fields from FNIRT were concatenated and applied to the original sequences, thus making all the sequences normalized in the same template space. After spatial normalization, BALSAM (Bayesian Automatic Lesion SegmentAtion in MRI) [4] was employed for lesion segmentation which combined the intensity information of multimodal MR sequences (T1, T2, PD, and FLAIR) and the spatial information. The original codes/scripts of BALSAM are available at Dr. Herskovits's laboratory (https://www.rad.upenn.edu/sbia/braid/balsam_web/), we made some adjustments/modifications on the scripts to match our study. Finally, statistical analysis was performed using JMP 8.0 (SAS Institute Inc., Cary, NC), the dependence of WML-ILL volume upon the variables age, sex, and AS severity was tested with univariate approaches. Lesion volume data were log transformed to improve normality of distribution prior to analyses.

Results:

Figure 1 (A) shows the global lesion distribution along axial, coronal, and sagittal orientations of this study population, colorbar indicates the occurrence frequency of lesion. Most lesions are peri-ventricular or deep, while few are subcortical. Figure 1 (B) – (D) are the univariate analyses of the dependence of Ln(Lesion Volume) upon age, sex, and AS Severity: Mild, Mod (Moderate), Sev-Crit (Severe-Critical).

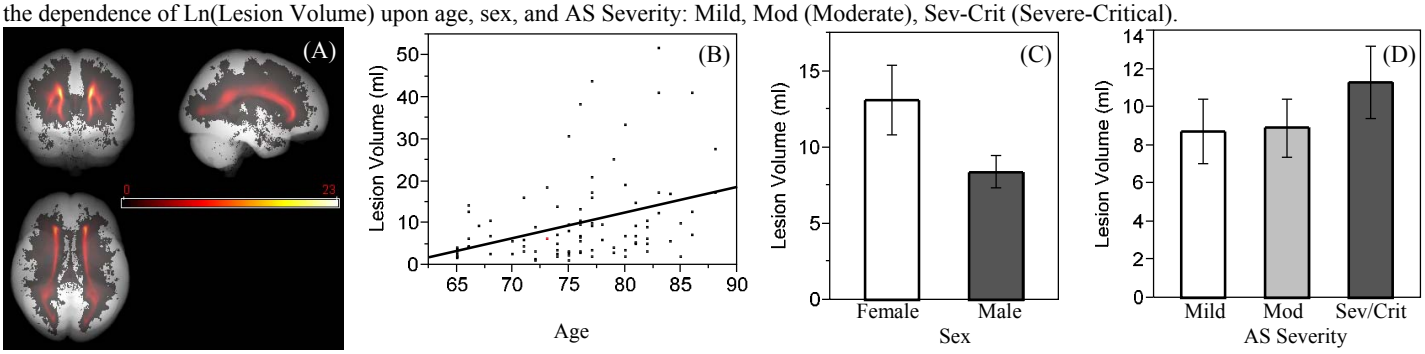

Figure 1. (A) Global lesion distributions. (B), (C), and (D) are the univariate analyses of the Ln(Lesion Volume) upon age (p=0.0001), sex (p=0.058), and AS Severity: Mild, Mod, Sev-Crit, p=0.72. The bars represent mean ± SE (standard error).

Conclusions:

Aging in our AS population was associated with rapidly progressive cerebral ischemic disease. Subjects in the current study ranged in age from 65 to 88 years, and over this period of time experience a dramatic 11-fold increase in lesion volume. Female sex accounted for a 56% increased in lesion volume over men and may account for the increased frequency of POCD in women after coronary artery bypass grafting previously reported by Hogue *et al* [5]. While the severity of AS did not demonstrate statistical significance in influencing lesion volume, univariate analysis demonstrated an important trend of increasing lesion volume with increasing severity of AS. Progression from mild to moderate AS was associated with only a slight increase in lesion volume whereas progression from moderate to severe-critical AS was associated with a marked acceleration in the degree of cerebral ischemic disease, as WML-ILL volume increased by nearly 30%.

This is the first attempt to study the impact of aging and cardiovascular co-morbidities upon cerebrovascular ischemic disease in an aged population with progressive aortic stenosis, severe-critical AS can probably safely be considered an imaging biomarker for the presence and severity of cerebrovascular disease.

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