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Using hemodynamic parameters quantified with computational fluid dynamics to explore potential mechanisms of occurrence and progression in Alzheimer Disease

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Abstract

Background: It has gradually recognized that the patients with Alzheimer's disease (AD) have cerebral hemodynamic disorders. The purpose of the present study was to exploit a novel computational fluid dynamics (CFD) model, which could be used to measure intracranial hemodynamics quantitively in AD patients and to further explore how the hemodynamic changes are involved in progression of AD.

Methods: A novel CFD model was constructed by personal magnetic resonance angiography (MRA), vessel ultrasound and blood pressure value of all subjects, of whom included AD patients, vascular dementia (VaD) patients and well-matched

healthy controls (HCs). Demographic, clinical and imaging data of all subjects were recorded and analyzed. Quantitative total cerebral blood flow (CBF) and cerebrovascular resistance (CVR) were compared among three groups, in order to ascertain the potential hemodynamic disorders in AD patients.

Results: Total CBF and CVR of AD patients were significantly different from those of HCs (both $P<0.01$), but not different from patients with VaD (both $P>0.5$), despite the cerebral arteries in AD patients were anatomically intact. Total CBF was negatively correlated with total CVR (r_s=-0.822, $P<0.001$) in AD patients. Comparing with HCs, Elevated CVR (OR=2.25, P=0.004) and age (OR=2.06, P=0.021) were independent risk factor of AD.

Conclusions: CFD can be applied to non-invasively and conveniently quantify and visualize biomechanical changes of cerebral blood flow. Patients with AD have dysfunction of cerebral hemodynamic, including lower CBF and higher CVR, and the CVR was an independent risk factor of AD. These findings provide quantitative evidence to support that increase of cerebrovascular resistance may involve in development of AD.

Key words: Computational fluid dynamics, Hemodynamics, Cerebral blood flow, Cerebrovascular resistance, Alzheimer's disease.

Introduction

Dementia is a disorder characterized by the impairment of cognitive function with attenuated daily activity and psychiatric symptoms. Dementia is the third contributor of neurological disability-adjusted life-years (DALYs) [1]. More than 50 million people are

affected by the dementia globally, it has been estimated that the total number of dementia patients worldwide will reach 76 million by 2030 and 135 million by 2050[2]. AD and VaD are the most common causes of dementia[3]. As acknowledged by clinicians, lifestyle and vascular risk factors accelerate VaD progression[4]. However, recently studies indicated that cardiovascular risk factors correlate with the occurrence and development of AD[5]. For example, previous studies have confirmed higher vascular risk and lower physical activity are associated with burden of β-Amyloid and cognitive decline [6, 7].

The circulatory pathophysiological changes mediated by vascular risk factors were always accompanied by intracranial hemodynamic disorder, which was involved in mechanisms of cognitive decline[5-7]. For instance, patients with cardiac dysfunction manifest hemodynamic disorders and decreased cerebral perfusion, which subsequently lead to injury or death of neurons[8, 9]. Moreover, remodeling and cerebral vasomotor disorders of intracranial or extracranial vessels reduce cerebral perfusion and increase resistance of cerebral arteries, which impair metabolism of nervous tissue and clearance of A-β amyloid, further exacerbate cognitive decline[10-12]. Therefore detection of hemodynamic disorders may contribute to identification potentially pathophysiological changes in dementia patients.

Hemodynamic parameters can be measured indirectly through some medical imaging techniques, including arterial spin labeling (ASL) MRI, transcranial doppler ultrasonography (TCD), oxygen-15-labelled water positron emission tomography (PET), four dimensional (4D) flow MRI. Using ASL, the CBF ratio of gray

matter/white matter has been shown to decline globally in the poststroke dementia patients[13], AD patients also exhibit increased CVR index (CVRi) and diminished CBF in inferior parietal and temporal cerebral[14, 15]. However, ASL has poor noise to signal ratio and only reflects changes in a small portion of hemodynamic parameters. Flow velocity and the pulsatility index can be evaluated by TCD, in which, increased CVRi were found in aged adults[16] and AD patients [17]. A meta-analysis indicated that hemodynamic disturbance in VaD was more severe than that of AD[18] . However, TCD cannot accurately detect hemodynamic parameters of distal arterial branches, furthermore, the accuracy of TCD relies on an experienced operator and interpreter. PET only measures the CBF and is applied limitedly. The 4D flow MRI is an emerging imaging paradigm and capable to quantify the temporal evolution of complex blood flow patterns within an acquired 3D volume, by which AD patients have been found to have decreased mean flow in the internal carotid and middle cerebral arteries [19]. However, there is a trade-off between the spatial and temporal resolution of 4D-flow MRI, it is suitable either for the large arteries with fast velocity or the narrow vessels with slow velocity, such as measurements of blood flow velocity in the aorta or veins, thereby limiting the applications of 4D-flow MRI in cerebral arteries.

CFD is a well-established technique that provides comprehensive information of hemodynamics non-invasively. Various 3D CFD models using routinely available medical imaging had been proposed and applied to evaluate hemodynamic parameters, for example, fractional flow reserve (FFR) was calculated by CFD based on computed tomography angiography (CTA) , which has been approved to assess the risk of

coronary stenosis, and CFD derived FFR is highly comparable with the FFR measured by a interventional pressure wire[20, 21]. CFD technique can reduce unnecessary interventional angiography effectively and help doctors to diagnose pathological conditions[22, 23]. Moreover, CFD can be applied to assess the risk of rupture and pressure of the intracranial aneurysm, thereby improving the understanding of the biomechanics of the aneurysms[24].

To our knowledge, there is lack of study on hemodynamic alterations in AD patients using CFD. The present study would use self-constructed CFD model to quantify the hemodynamic parameters and compared among three groups: (1) AD patients, (2)VaD patients as positive controls and (3)HCs as negative controls, so as to explore potential mechanisms of occurrence and progression in Alzheimer Disease.

Methods

Participants

The present cross-sectional study included AD patients (n=30), VaD patients (n=29), and HCs (n=34). Probable AD diagnosis was determined in accordance with the criteria of the National Institute of Neurological and Communicative Disorders and Stroke, and the AD and Related Disorders Association (NINCDS-ADRDA). Probable VaD was diagnosed in accordance with the criteria of the International Classification of Diseases-10 (ICD-10). Individuals who were cognitively normal were also included to be HCs. All participants received MRI+MRA and ultrasound of cervical arteries.

Subjects were excluded from the study if they suffered from heavy organ dysfunction, or a history of cognitive disorders. The study was approved by the ethics committee of

111 the affiliated ZhongDa hospital of Southeast University.

112 **Collection of demographic data**

113 All participants underwent comprehensive medical and neurological evaluations,
114 fasting venous blood samples were collected for routine blood testing and blood
115 biochemical parameters (Table 1 and Supplementary Table S1). The 10-year risk of
116 heart disease or stroke was determined using the ASCVD algorithm (website:
117 http://www.cvriskcalculator. com/), which was used to evaluated the risk factor burden
118 of cardiovascular and cerebrovascular diseases, ASCVD scores were categorized as low,
119 moderate and high risk depending on the risk stratification. Mean arterial pressure
120 (MAP) was calculated by formula: MAP=DBP+(SBP-DBP)/3.

121 **Protocols of imaging**

122 The systolic and diastolic BP of participant were measured prior to examination
123 of cervical vessel ultrasound in the same morning. Doppler ultrasonography was
124 performed to measure velocities of the left and right internal carotid and vertebral
125 arteries (CCA/VA) using high-resolution ultrasound (GE, LOGIQ E9) at 8-15 MHz, in
126 which, peak systolic velocity (PSV) and end diastolic velocity (EDV) acted as two
127 important indexes to build CFD model. All patients were scanned using a 3T clinical
128 MRI system (Siemens) with a 12-channel head and neck coil array. The MR scan
129 included parenchymal brain imaging sequences (axial DWI, T2 FLAIR, and T1), MRA
130 was performed on axial 3D TOF MRA (TR = 15.0 ms, TE = 3.45 ms, flip angle = 25,
131 NEX = 1, field of view = 242 x 242 mm, matrix size 512 x 512, 24 slices x 3 sections,
132 slice thickness 1 mm).

Hemodynamic measurement of subjects using CFD

Image processing and CFD mesh generation

MRA images were exported from computing the server of the MRI scanner in standard Digital Imaging and Communication in Medicine (DICOM) format. The cerebral artery was segmented from each DICOM image using 3D region-growing provided by Mimics (Materialise NV, Belgium), in which results were inspected and refined by two radiologists. The 3D surface of the cerebral artery was then reconstructed. The computational domain of CFD was defined by a mesh generated by ANSYS ICEM CFD software (ANSYS, Inc., USA). Due to the complexity of the geometry, an unstructured tetrahedral cell was used for domain discretization. The total number of elements was greater than 1 million with a minimum volume of approximately $1.0*10^{-8}$ cm^3 in order to capture features of flow dynamics in small-scale, to provide more detailed computation of the hemodynamics, especially within the stenotic artery.

Modelling of blood flow in 3D

The blood flow was assumed to be a viscous and incompressible Newtonian fluid, the heat transfer and compressibility effects of the vascular wall were neglected in this process. The blood flow were defined as a constant density $\rho = 1.06 \times 10^3 kg.m^{-1}$ and dynamic viscosity $\mu = 3.5 \times 10^{-3} kg.m^{-1}.s^{-1}$, as the simulated blood flow was not sensitive to these parameters[25, 26]. A typical carotid artery diameter $D = 6.0 \times 10^{-3}\, m$ and its corresponding velocity of blood flow $v = 0.4\, m.s^{-1}$ were assumed in order to calculate the Reynolds number: $Re = \rho v D/\mu \approx 121$, which suggested that the blood flow was laminar. A 3D unsteady incompressible Navier-

Stokes equation was then utilized to describe the blood flow, as follows:

$$\mathrm{U}\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v}\cdot\boldsymbol{\nabla})\mathbf{v} = -\frac{1}{\rho}\boldsymbol{\nabla}p + \frac{\mu}{\rho}\boldsymbol{\nabla}^{\mathbf{2}}\mathbf{v} + \mathbf{f}, \tag{1.1}$$

The equation for conservation of mass was defined as:

$$\boldsymbol{\nabla}\cdot\mathbf{v} = \mathbf{0}, \tag{1.2}$$

where $\mathbf{v}$ was the velocity vector, p was the pressure, and $\mathbf{f}$ was force of the body, assumed equal to 0.

To solve equations (1.1) and (1.2), a finite volume approach using ANSYS CFX software version 14.5 (ANSYS, Inc., USA) was used. CFD simulations were conducted on an AMAX server with dual 22-core Intel Xeon E5-2699 v4 CPUs running at 2.20GHz with 256GB memory. Mesh partitioning was performed using a k-way Metis algorithm with a message passing interface (MPI) unutilized for multi-core communication. A five second period of blood flow in each cerebral artery was simulated with a time step of $0.01\ s$. A second-order backward Euler scheme was used for the transient term. The criteria for convergence was set at a root mean square error (RMSE) for the relative levels of 1.0×10^{-5} .

Determination of Boundary conditions

Both PSV and EDV at each internal carotid artery (ICA) and vertebral artery (VA) were used as the inlet boundary conditions to estimate the respective mean velocities, as $V_{mean} = \frac{1}{3}V_{PSV} + \frac{2}{3}V_{EDV}$. The mean velocities were assumed to be present at the centerline of the vessels, the flow was further assumed to be laminar with pulsatility neglected at all inlets. Inlet blood flow was then approximated by $Q_{in} = \frac{1}{2}V_{mean} \cdot A_{in}$,

where A_{in} represents the cross-sectional area of the artery at the inlet, as the hemodynamic assumption resulted in a Poiseuille velocity profile, which is parabolic[27]. The cross-sectional area was calculated by $A_{in} = \pi \cdot (\frac{D_{in}}{2})^2$, where D_{in} was the diameter of the inlet artery, measured from the MRA images. Total CBF was preliminarily obtained from the sum of internal carotid and vertebral Q_{in}. For the outlet boundary conditions, pressure P_{out} was estimated at each outlet. A resistive boundary condition was applied to each outlet of the distal artery to mimic the downstream resistance, assumed to be inversely proportional to the diameter of the outlet. In order to achieve this, total CVR R_{total} was calculated from the total inflow $Q_{total} = Q_{in}^{ICA} + Q_{in}^{VA}$ and mean arterial pressure (MAP), approximated by brachial blood pressure. Initial R_{total} was then calculated from $R_{total} = MAP/Q_{total}$. R_{out} at each outlet was estimated from R_{total} depending on the diameter of the outlet (D_{out}) as calculated from MRA images. Finally, the outlet pressure P_{out} was calculated by $P_{out} = Q_{out} \cdot R_{out}$, where Q_{out} was the flow rate at each outlet, estimated from the integral of the outlet velocity V_{out} at the outlet area.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp.). Normality of continuous data was confirmed using a Shapiro-Wilk test, and homogeneity of variance assessed using Levene test. Data are presented as means ± standard deviation (SD). Categorical data are expressed numerically. Analysis of differences in demographic, clinical characteristics, and CFD among the three groups were conducted using a one-way analysis of variance (ANOVA), and Kruskal-Wallis

test or χ^2 test. Where a significant difference was found, Dunnett's, Pairwise Comparisons and Bonferroni methods were used to adjust for each two groups respectively. Differences in CBF or CVR between gender, with or without a history of stroke were analyzed by independent sample t tests and Kruskale-Wallis test respectively. The correlation between CBF, CVR and age were explored using Spearman correlation analyses. To elucidate the independent contributions of hemodynamic parameters to dementia, binary logistic regression analyses were performed for patients and HCs groups, statistically significant independent variables in univariate analysis were included in a binary regression. In these analyses, AD or VaD was the dependent variable, gender, age, history of stroke, CBF and CVR were independent variables. According to the interquartile range of all subjects, CBF and CVR were divided into four continuous levels (supplementary Table 2), with entry and removal criteria of 0.05 and 0.1, respectively. For significant findings, odds ratios (*OR*) were calculated to interpreted the effect on "dementia". *P*-values of <0.05 were considered statistically significant.

Results

Comparison of baseline demographic and clinical characteristics among three groups

The baseline demographic and clinical characteristics are summarized in Table1 for the three groups. There were significant differences in age (F=14.713, P<0.001), gender distribution($\chi 2$ =13.449, P=0.001) and percentage of stroke history (χ^2=12.041; P=0.002) among three groups. As compared to HCs, average age of VaD patients

(P<0.001) and AD patients (P=0.005) were older than HCs, however, no significant difference for age was founded between AD and VaD patients (P=0.058). As compared with AD and HCs groups, the proportion of male and history of stroke in VaD group were significantly increased (both P<0.05). Additional information for all subjects is displayed in Supplementary Table S1.

Comparison of Hemodynamic parameters among groups

Three typical color maps of pressure and velocity throughout the arterial tree are displayed in Figure 1 for three subjects: AD (a, b), VaD (c, d),and HCs (e, f). both AD and VaD patients had diminished blood supply even if the arterial trees of AD patient were anatomically intact. CBF and CVR in arteries that were larger than 0.2cm in diameter could be estimated by the CFD model (Supplementary figure S1). The hemodynamic parameters of all subjects were calculated by the 3D CFD model (Table 2). As compared with HCs, there were significant reduced total CBF or increased total CVR in AD group(CBF:P=0.008; CVR: P=0.009) and VaD group (CBF: P=0.002; CVR: P=0.001), however no significant difference in the CBF and CVR were founded between AD and VaD patients (CBF: P=0.905; CVR: P=0.524). other hemodynamic parameters of all subjects are displayed in Supplementary Table S2

Figure1 Three typical examples of pressure distribution and stream lines of blood flow velocity are displayed in the first and the second row, respectively. The first column(fig a and b)is for an AD patients, the second column (fig c and d)is for a VaD patients, and the third column (fig e and f) is for a healthy subject. It is evident that the AD patient and the healthy subject are with intact arterial trees, whereas VaD the patient is with scarce arterial branches. However, according to computation,

the total blood flow in the models was 692 ml/min (AD patient), 647 ml/min (VaD patient), and 998 ml/min (healthy subject) respectively.

Interactive associations of the hemodynamic parameters and risk factors

Bivariate Spearman correlation showed that total CBF was negatively correlated with total CVR in whole subjects (fig 2a, r_s=-0.826, P<0.001) and AD groups(fig 2b, r_s=-0.822, P<0.001). There were significant correlations between age and total CBF (fig 2c, r_s=-0.282, P<0.05) or total CVR(fig 2d, r_s=0.278, P<0.05), however there was no significant difference in total CVR (fig 2e, Z=-0.968; P=0.333) or CBF(fig 2f, t=0.759; P=0.450) between male and female subjects. Meanwhile, as compared with subjects without past history of stroke, the subjects with history of stroke have a higher total CVR (fig 2g, Z=-2.179; P=0.029), but not CBF (fig 2h, t=1.793; P=0.076).

Figure 2 Interactive associations of the hemodynamic parameters and risk factors, correlation between total CBF and CVR in all subjects (a) and AD group(b), (c) and (d) showed significant correlations between CBF or CVR and age, fig(e, f) showed there were no significant difference of total CVR or CBF between male and female patients, fig(g) indicated there was significant difference of total CVR in patients with stroke or not, but not total CBF fig(h).ns: no significance, *P<0.05.

Association between hemodynamic parameters and dementia

Binary regression demonstrated that age (10-year increment; P=0.021) and CVR (P=0.004) were independent risk factors for AD (Table 3). Independent risk factors of VaD included age (10-year increment; P=0.001), gender (P=0.014)and CVR (P=0.033).

Discussion

This present study exploited a 3-D CFD model to quantitatively measure the changes of CBF and CVR in AD patients for the first time. The main findings are summarized as follows. Firstly, as compared with HCs, both total CBF and CVR in AD or VaD groups were significantly changed, no differences were observed in total CBF and CVR between AD and VaD groups. Secondly, total CBF was negatively correlated with CVR in all subjects. Finally, elevated CVR and age associated with increased risk of AD, suggesting that changed cerebral hemodynamic are present in AD patients.

It is challenging to measure hemodynamics directly. Previous studies have used other methods to non-invasively quantify the CBF and CVR[15, 28-31]. In current study, a CFD model was constructed individually by the subject-specific medical images, It is non-invasive and not limited by contraindications of imaging examinations , CTA and DSA data can also be used to replace MRA, hence it is accessible to most medical centers. The model has high spatial resolution, and arteries with diameter larger than 0.2cm can be evaluated, allowing hemodynamic parameters even in the distal branches to be available. Furthermore, comprehensive hemodynamic parameters, such as CBF, velocity, CVR, FFR, and arterial wall shear stress can be acquired anywhere of the artery conveniently in the 3D model.

During undertaking cognitive task, healthy subjects and stroke patients exhibited a significant increase both in CBF and blood stream velocity[10, 32], which suggested that cerebrovascular circulation adjusts its hemodynamic response to metabolic requirements. However, the total CBF of the internal carotid and vertebral arteries were decreased in VaD patients[28], Furthermore, a marked decreased CBF in the parietal and

frontal cortex of AD or VaD patients has been observed, which was associated with increased subcortical white matter lesions in VaD patients[33]. Stabilized CBF is dependent on heart function and resistance of intracranial vessels[9], the CVRi of middle cerebral arteries[17], cortex and subcortex were increased in AD patients, particularly within the thalamus and caudate[16, 34]. In addition CVRi was positively correlated with severity of dementia[17]. Hence hemodynamic alterations were involved in the pathophysiology of AD, therefore the alterations of vascular resistance may play an important role progression of AD and VaD.

However previous studies only analyzed the correlation between AD and CVR or CBF respectively. In present study, the decreased total CBF and increased CVR were observed in AD group, and total CVR was an independent risk factor of AD, more importantly, the total CBF was significantly and negatively correlated with total CVR. Therefore, the CBF may be regulated by CVR. All above results demonstrated that the increase of vascular resistance may affect the perfusion of whole brain and occurrence of AD. Therefore, early discovery of changes in CVR indicates that potential cerebrovascular lesions in AD.

The increases of cerebral resistance in AD patients are caused by other potential mechanisms. Recent research confirmed that capillary constriction caused by Aβ induces energy lack and neurodegeneration in neuron[35], which subsequently elevate the cerebral vascular resistance. Moreover the cerebral vascular resistance may be increased by mixed brain lesions and remodeling of cerebral microvasculature which were mediated by vascular risk factors[6, 7]. Consequently the treatments of AD should

include the alleviation of cerebrovascular lesions, careful control or decreased exposure to risk factors may attenuate cognitive decline, and alleviation of the capillary contraction caused by Aβ may be a new treatment direction of AD.

Limitations

There are some limitations to this study. Firstly, it is a cross-sectional research study, the correlation between hemodynamic parameters and AD need to be verified by follow-up studies. In a future study we will verify the correlation between more hemodynamic parameters and dementia with follow-up investigation, in addition the effect of hemodynamics on progression. Secondly, the diagnosis of AD was based on clinical data and lack of neuropathic markers. Thirdly, due to the small number of patients, which may restrict findings of this study, and the large-scale clinical studies were needed for further verified. Finally, the sensitivity and specificity of CFD require comparation with other non-invasive methods to explore the practicality of CFD.

Conclusions

CFD can be used to distinguish hemodynamic changes between AD patients and healthy subjects. AD patients had lower CBF and higher CVR, and the CVR was an independent risk factor of AD, Early detection of alterations of CVR will help clinicians find potential cerebrovascular lesions, alleviation of CVR may be another direction of treatment in AD.

Supplementary information

Table S1. Supplementary demographics and clinical characteristics of all subjects. Table S2. Hemodynamic parameters of all subjects. FigureS1. Procedure of CFD model.

Abbreviations

AD: Alzheimer's disease, ASL: arterial spin labeling, BMI: body mass index, CFD: computational fluid dynamics, CVR: cerebral vascular resistance, CVRi: CVR index, CBF: cerebral blood flow, CHD: coronary heart disease, DBP: diastolic blood pressure, EDV: end diastolic velocity, FFR: fractional flow reserve, GT: triglycerides, HCs: healthy control subjects, HDL: high-density lipoprotein, Hb: hemoglobin, LDL: low-density lipoprotein, MAP: mean arterial pressure, MRA: magnetic resonance angiography, PSV: peak systolic velocity, SBP: systolic BP, Tc: total cholesterol, TCD: transcranial doppler ultrasonography, VaD: vascular dementia.

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Author's contributions

ZJZ and JL designed the study, analyzed and interpreted of data, and drafted and revised the manuscript, JL Jia contributed to technique writing. JX collected, analyzed and interpreted the data, prepared all statistic figures, drafted the manuscript. ZC and BW contributed to arterial 3D reconstruction and mesh generation. GJZ, GLH and ZW contributed to collected the clinical data, WSS, RLC and XCC contributed to numerical computation, CL contributed to medical image processing, LPW participated in design the study. All authors contributed to the writing and revisions of the paper and approved the final version.

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Availability of data and materials

The dataset used during the current study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Institutional Ethical Committee of Nanjing ZhongDa Hospital, Southeast University and the participants gave written informed consents prior to obtain the data.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

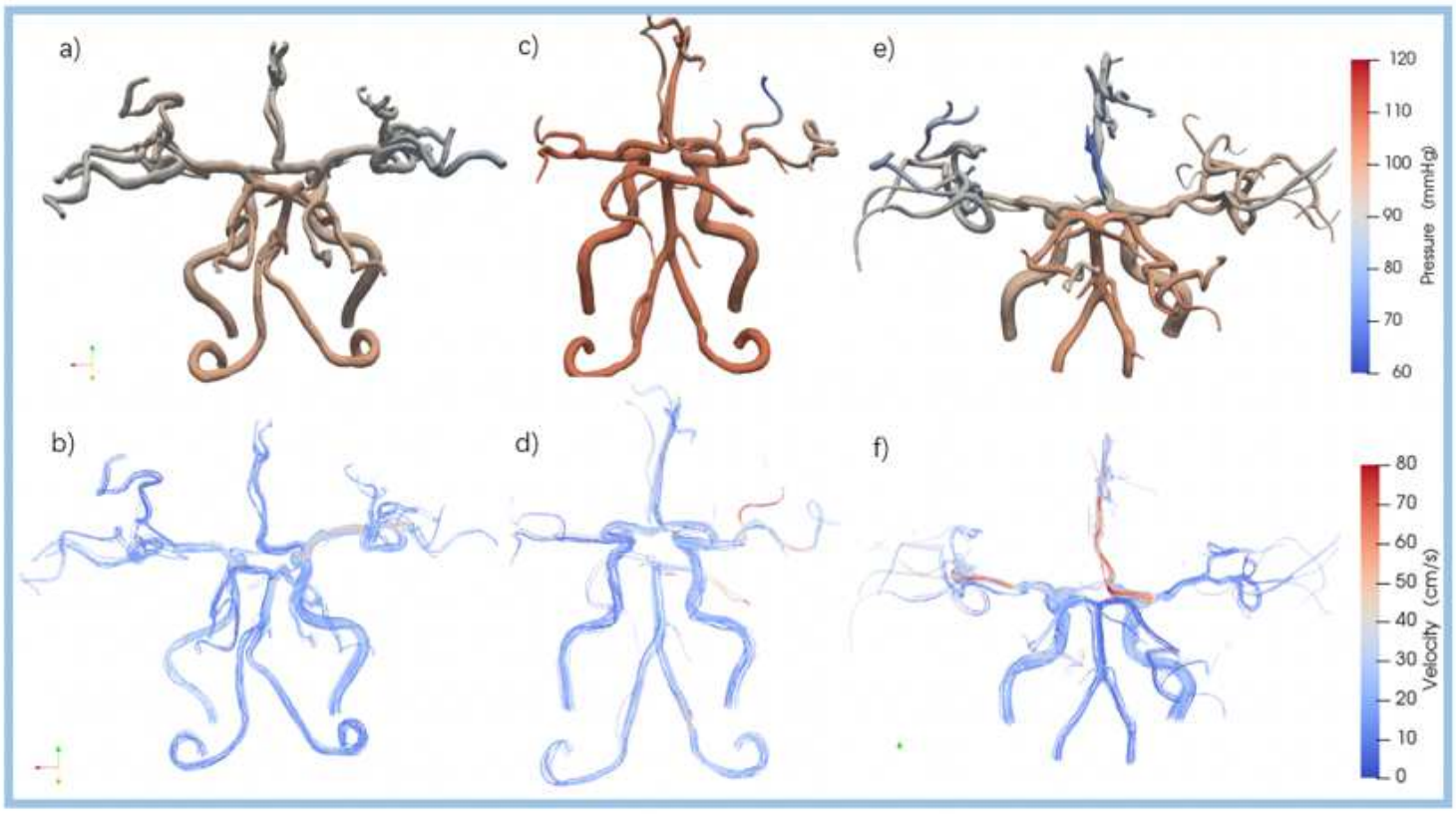

Figure 1

Three typical examples of pressure distribution and stream lines of blood flow velocity are displayed in the first and the second row, respectively. The first column(fig a and b)is for an AD patients, the second column (fig c and d)is for a VaD patients, and the third column (fig e and f) is for a healthy subject. It is evident that the AD patient and the healthy subject are with intact arterial trees, whereas VaD the patient is with scarce arterial branches. However, according to computation, the total blood flow in the models was 692 ml/min (AD patient), 647 ml/min (VaD patient), and 998 ml/min (healthy subject) respectively.

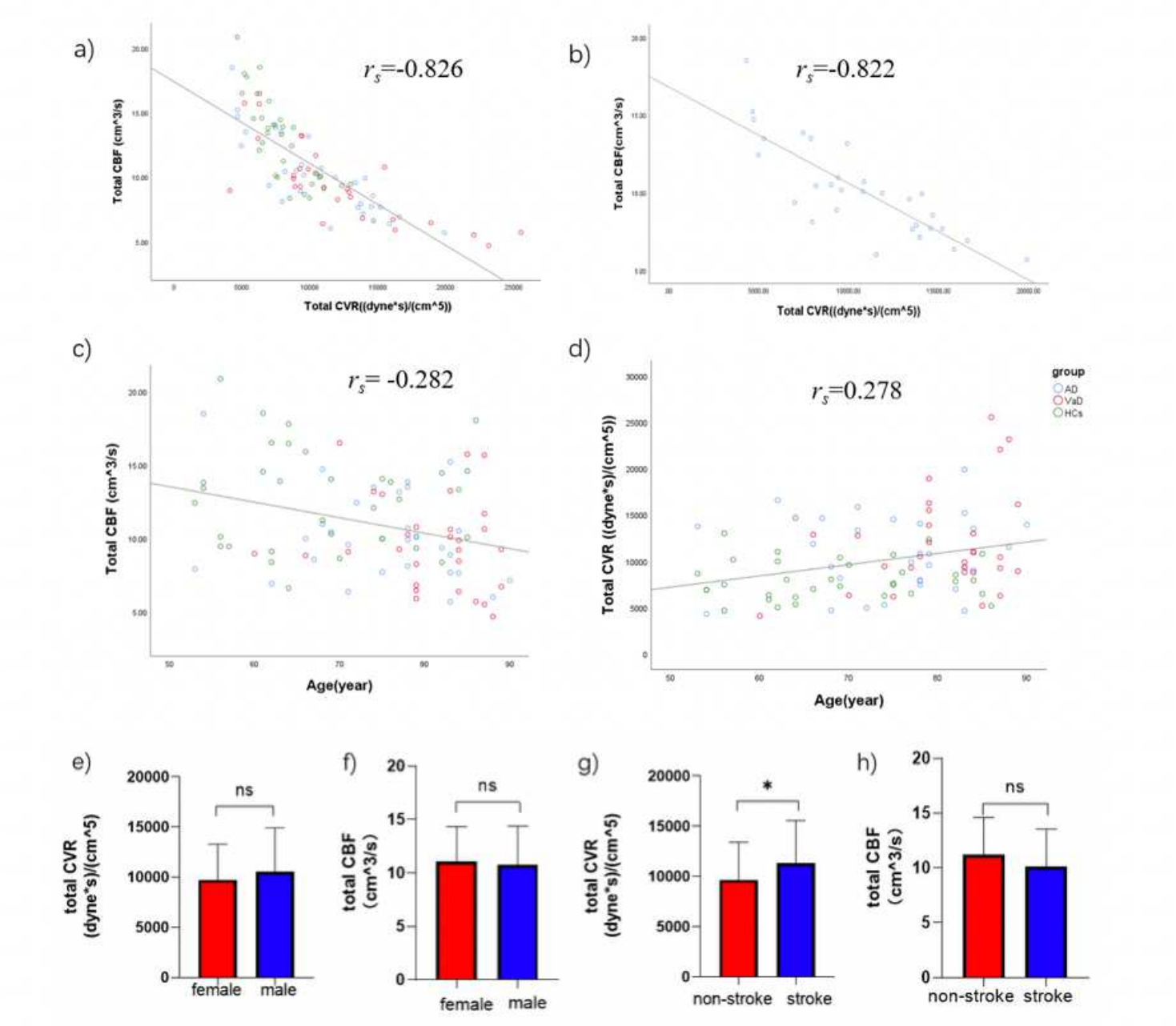

Figure 2

Interactive associations of the hemodynamic parameters and risk factors, correlation between total CBF and CVR in all subjects (a) and AD group(b), (c) and (d) showed significant correlations between CBF or CVR and age, fig(e, f) showed there were no significant difference of total CVR or CBF between male and female patients, fig(g) indicated there was significant difference of total CVR in patients with stroke or not, but not total CBF fig(h).ns: no significance, *P<0.05.

Supplementary Files

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