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CEREBRAL BLOOD FLOW AND PREDICTORS OF WHITE MATTER LESIONS IN ADULTS WITH TETRALOGY OF FALLOT

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Abstract

Long-term outcomes for Tetralogy of Fallot (TOF) have improved dramatically in recent years, but survivors are still afflicted by cerebral damage. In this paper, we characterized the prevalence and predictors of cerebral silent infarction (SCI) and their relationship to cerebral blood flow (CBF) in 46 adult TOF patients. We calculated both whole brain and regional CBF using 2D arterial spin labeling (ASL) images, and investigated the spatial overlap between voxel-wise CBF values and white matter hyperintensities (WMHs) identified from T2-FLAIR images. SCIs were found in 83% of subjects and were predicted by the year of the patient's first cardiac surgery and patient's age at scanning (combined r^2 0.44). CBF was not different in brain regions prone to stroke compared with healthy white matter.

Index Terms

Tetralogy of Fallot; deep white matter lesion; cerebral blood flow; arterial spin labeling

1. INTRODUCTION

Tetralogy of Fallot (TOF) is a type of congenital heart disease (CHD), characterized by anterior deviation of the conal septum, creating subpulmonary obstruction, ventricular septal defect, right ventricular hypertrophy, and an overriding aorta [1]. In some patients, surgical palliation with a systemic to pulmonary artery shunt is required in the neonatal period. Definitive repair is usually delayed until close to a year of age, leaving the children cyanotic for many months. Although cardiac surgery has dramatically improved overall patient outcome, the age of the first and corrective operation were closely related to cerebral

damage [2]. Brain abnormalities consistent with prior ischemic events were reported on MRI in 42% of adolescent patients with TOF [3]. Infants may be particularly sensitive to hyperperfusion injury. Mahle et. al. demonstrated new or worsening ischemic lesions in 2/3 neonates following cardiac surgery [4].

Frontoparietal white matter (WM) appears to be the most vulnerable to cardiopulmonary bypass [5], characterized by oligodendrocyte dysmaturation, astrogliosis and microglial expansion. On MRI, this manifests as periventricular leukomalacia and silent cerebral infarction (SCI). In recent years, different imaging modalities in newborns and infants with CHD have been used to study WM abnormalities in newborns and children with CHD, including MR spectroscopy, diffusion imaging and perfusion imaging [6]. Yet very few studies have been performed in adult patients with CHD. Thus, our goal was to study the link between brain perfusion and WM lesions in adult TOF survivors, in order to further understand the etiology and significance of SCIs in this population.

Though whole brain and regional cerebral blood flow (CBF) are known to be reduced in normally aging individuals with WM lesions compared to healthy controls [7], no one to date has studied how brain perfusion changes in adults with CHD, nor investigated the overlap between the brain perfusion abnormalities and WM damage in different anatomical regions.

Using magnetic resonance imaging (MRI) techniques such as T2-weighted or fluid attenuation inverse recovery (FLAIR), white matter lesions appear as higher voxel intensities, and hence are referred to as white matter hyperintensities (WMH). Brain perfusion can be characterized using either intravenous contrast or through arterial spin labeling MRI (ASL). ASL has become popular for estimating CBF, because it does not require ionizing radiation or exogenous contrast agents. Pseudo-continuous ASL (PCASL) is a more recently developed MRI technique that utilizes a series of discrete radio frequency pulses to mimic continuous ASL [8], and has enhanced capacity for measuring regional and global CBF in patients with neurological disease and in healthy controls.

In this paper, we calculate both whole brain and regional CBF using 2D PCASL images, and investigate the spatial overlap between voxel-wise CBF values and WMHs identified from T2-FLAIR images in the Sluman patient cohort of 46 adult TOF survivors [2]. We hypothesize that WMHs would co-localize with regions of decreased perfusion.

2. METHODS

2.1. Data Description

The study protocol was approved by the institutional review board of the Academic Medical Center in Amsterdam, the Netherlands. Patients were enrolled from January 2013 to December 2014 and identified through CONCOR (CON-genital CORvitia), the ongoing Dutch national database of adults with CHD. Written informed consent was obtained from all patients. Brain MRI was performed on a Philips 3.0 Tesla Ingenia scanner (Phillips Medical Systems, Best, the Netherlands) using a 16-channel phased-array head coil. 3D T1-weighted images (TR/TE=6.8/3.1 ms, 1 mm³) were acquired for co-registration, using a

magnetization prepared rapid gradient echo sequence. A 3D T2 FLAIR scan (TR/TE=4800/290 ms, 1 mm³) was obtained to identify WM lesions, with inversion time of 1650 ms. Finally, perfusion weighted images were acquired using background-suppressed 2D PCASL images (TR/TE=320/14 ms, 3 × 3 × 7 mm³) with echoplanar readout, a labeling duration of 1650 ms and a post-label delay of 1525 to 1925 ms.

2.2. Pre-processing and WMH segmentation

We performed skull-stripping and bias field correction for T1 images using BrainSuite. Then GM/WM probability maps were generated using the SPM12 toolbox [9]. The whole brain images were registered to the 1 mm³ Montreal Neurological Institute (MNI) atlas for statistical analysis.

For ASL images, we visually checked all 40 dynamics to remove outliers, and performed motion correction using the standard routines in [10]. Then dynamic median ASL images were rigidly registered to the high resolution T1 images. We used the inverse registration matrix to transfer the tissue probability maps to ASL space for partial volume effect (PVE) correction, using a 3³ regression model [11]. This PVE correction yields an estimation of CBF for grey and white matter independently in native space, with less blurring due to the point spread function and mixing of tissue-specific signals. Lastly, we registered CBF maps to MNI space by applying the transformation matrix of T1 registration using FLIRT [12].

We used our in-house MATLAB® toolbox published previously to semi-manual segment WM lesions [13]. The process was performed by two on-site raters in consensus (two graduate students with biomedical imaging background) and supervised by two board certified and experienced neuroradiologists. When the rater did not agree with the boundary delineated by the toolbox, we used ITK-SNAP to manually edit it. The segmented lesion volumes and centroids were saved separately as binary images to be used for statistical analyses.

2.3. CBF quantification

The one-compartment kinetic tracer model [14] is a popular approach to CBF estimation [8]. However, it assumes that longitudinal relaxation rates are identical across tissue types, making it unsuitable for accurate WM CBF estimation [15]. Therefore, we used a modified two compartment kinetic quantification model proposed by Wang et. al.[16]:

$$CBF = \frac{6000 * \lambda * (SI_{control} - SI_{label}) * e^{\frac{\delta}{T_{1,blood}}}}{2 * \alpha * T_{1,tissue} * PD * (e^{\frac{\delta - PLD}{T_{1,tissue}}} - e^{\frac{\delta - \tau - PLD}{T_{1,tissue}}})}$$

where λ is the brain/blood partition coefficient (0.9 ml/g), $SI_{control}$ is the voxel intensity of unlabeled images, SI_{label} is the voxel intensity of labeled images, PLD is the post-label delay (1525 ms for first slice and adjusted for different slices), τ is the PCASL labeling duration (1650 ms), $T_{1,blood}$ and $T_{1,tissue}$ are the longitudinal relaxation of blood at 3T (1650 ms) and of the specific tissue, respectively, α is the labeling efficiency (0.85) multiplied by a

background suppression constant (0.83), PD is the proton density image intensity and δ is the tissue transit time. Since we did not measure transit time directly, we used δ_{GM} (1400 ms), and δ_{WM} (1500 ms) from [17], $T_{1,GM}$ (1332 ms), $T_{1,WM}$ (850 ms) [18].

2.4. Statistical analysis

The presence of WMH was evaluated using mono and multivariate logistic regression while the number of WMH was evaluated using mono and multivariate linear regression. Potential predictors evaluated included CBF (global and regional), age of the scanning, age and year of the first cardiac surgery, number of cardiac surgeries, smoking/diabetes history, hypertension, and body mass index (BMI). The detailed patients' characteristics were reported in [2]. To determine spatial concordance between WMH and regional CBF, we performed permutation analysis on the spatially registered CBF and lesion maps. The test distribution consisted of CBF values corresponding to each lesion's centroid, generating a distribution of average CBF values in regions known to be at high risk from strokes. To create the corresponding null statistic, we placed each WMH in multiple random locations within the white matter. The shape of the two distributions was compared by Kolmogorov-Smirnov test, while the mean and variance of the distributions were compared by t-test and ratio test, respectively. We also tested the correlation between WMHs, CBF and physiological parameters using JMP®.

3. RESULTS

Table 1 summarizes patients' demographic information. The patient cohort was gender balanced, had normal average BMI, and ranged in age from 23-69 years old. Number of cardiac surgeries range from 1 to 4 and age of the first surgery ranged from 0-16 years old. After excluding patients without the completed brain MRI scans (T1, FLAIR and PCASL), we studied 46 patients in total. Due to the motion artifacts and registration inaccuracies, we were only able to evaluate the T2 FLAIR images in 36 patients, and WMHs were found in 30/36 (83%). The presence of WMH was strongly correlated with year of the first cardiac surgery ($p < 0.01$), BMI ($p < 0.05$) and patient age ($p < 0.05$) in logistic regression. Year of first cardiac surgery and age remained independent predictors on multivariate analysis with a combined R^2 of 0.44. The step-wise multivariate regression on WMH volumes did not show significant difference than the presence of the WMH. Table 2 summarizes the PCASL perfusion values, expressed as mL/100g/min, across vascular territories for three different age ranges. There was no significant CBF difference between different vascular territories. CBF declined with age across tissue types and vascular territories. Figure 2 summarizes the results of the permutation test. There were no significant differences between CBF values within the WMHs and the ones in the normal WM areas ($p = 0.07$) using a t-test.

4. DISCUSSION AND CONCLUSION

WMH have been described in small case-series of adults with cyanotic CHD [19], but the recent work by Sluman and colleagues was the first to document significant burden of cerebral damage (both grey and white matter) in adults with acyanotic heart disease [2], a much higher prevalence than noted in the general population [7]. The present manuscript explored the cerebral blood flow characteristics in this patient cohort to determine if WM

damage was concentrated in regions of lower perfusion. In the present analysis, the strongest predictor for WMH was year of first surgery, independent of patient age, likely reflecting the improvements in surgical and cardiac bypass techniques that occurred in the 1970s and 1980s. After controlling for year of first surgery, patient age remained an important predictor of WMH, consistent with observations from control subjects [7]. Global, GM, and WM CBF were not associated with WMH, in contrast with prior work [20]. In a population of normal elderly subjects, Brickman et. al. reported that the CBF within WMH areas was 5 mL/100/min lower than the CBF in normal appearing WM [7]. However we did not observe this phenomenon and validate our hypothesis. Our permutation analysis was confined to deep WM lesions because we could not adequately control for PVE in the CBF maps for periventricular lesions. Periventricular WML segmentation is also confounded by pulsatile CSF flow artifacts in the phase-encoding direction, making it difficult to interpret ASL values in these regions [21].

The WMH in our cohorts could be caused by perinatal and preoperative cyanotic disease, operative perfusion insults, or acceleration of chronic cerebral microvascular disease (accelerated vascular aging). Our study does not allow us to distinguish among these possibilities and longitudinal cohorts may be required to reconcile these possible mechanisms. We continue to explore the interdependence between WMH, CBF, and white matter volume loss as well as improved techniques for registration and partial volume correction [22].

In summary, we demonstrate that the presence and number of WMH were independent of global and regional cerebral perfusion. Instead, the year of first surgery and the patient age were the strongest predictors of WM disease in this analysis.

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Fig. 1.

(a): A raw T2-FLAIR image; (b): WMHs superimposed on its T2-FLAIR image

Fig. 2. CBF (in mL/100g/min) map overlaid by WMHs Permutation tests between CBF values in WMHs and the normal WM areas.

Table 1

Patients' demographic information

Sex (Male/Female)	22/24
Age	37.4 ± 14.0
BMI	24.1 ± 3.7
Number of WMH	7.9 ± 14.1
Number of Cardiac Surgeries	2.2 ± 1.0
Age of First Surgery	2.9 ± 3.7
Year of First Surgery	1979 ± 12

Table 2

Global and regional CBF: all in the unit of mL/100g/min. ACA: anterior cerebral artery, MCA: the middle cerebral artery, PCA: posterior cerebral artery.

Age Range	20 – 30	30 – 50	50 – 70
# of Patients	18	19	9
Total	47.9 ± 5.6	44.0 ± 6.1	40.6 ± 6.1
GM	82.0 ± 11.9	78.2 ± 12.5	73.9 ± 11.3
WM	51.6 ± 6.2	47.6 ± 6.0	44.0 ± 7.0
ACA	60.0 ± 6.7	55.0 ± 7.2	50.9 ± 7.4
MCA	50.8 ± 6.5	46.1 ± 6.18	42.9 ± 6.5
PCA	46.7 ± 7.9	42.5 ± 8.14	39.1 ± 6.8