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Quantification of intracranial arterial blood flow using non-contrast enhanced four-dimensional dynamic magnetic resonance angiography

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Abstract

Purpose: Non-contrast enhanced dynamic magnetic resonance angiography delineates the pattern of dynamic blood flow of the cerebral vasculature. A model-free solution was proposed to quantify arterial blood flow (aBF) by utilizing the monotonic property of the residual function.

Methods: Analytical simulations and in-vivo studies were performed to evaluate the performance of the proposed method by comparing the aBF values generated from the proposed and conventional singular value decomposition (SVD) methods. The aBF values were compared with blood flow velocity measured by 2D phase contrast (PC)-MRI, and compared between bSSFP based radial and spoiled GRE based Cartesian acquisitions. Hemodynamic parametric maps were generated in one patient with arteriovenous malformation (AVM).

Results: The proposed method generates reliable aBF measurement at different SNR levels, whereas overestimation/underestimation of aBF was observed when a high/low threshold was applied in the SVD method. Average aBF in large vascular branches was 214.4 and 214.5 ml/ml/min with radial and Cartesian acquisitions, respectively. Significant correlations were found between aBF and blood flow velocity measured by PC-MRI ($P=0.0008$), and between Cartesian and radial acquisitions ($P<0.0001$). Altered hemodynamics were observed at the lesion site of the AVM patient.

Conclusion: A robust analytical solution was proposed for quantifying aBF. This model-free method is robust to noise, and its clinical value in the diagnosis of cerebrovascular disorders awaits further evaluation.

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Keywords

Cerebrovascular hemodynamics; arterial blood flow (aBF); arterial spin labeling (ASL); dynamic magnetic resonance angiography (dMRA)

INTRODUCTION

Characterization of intracranial hemodynamics provides insights into the pathophysiological changes in cerebrovascular diseases. Although digital subtraction angiography (DSA) and computed tomography angiography (CTA) are gold standards for evaluating intracranial vasculature, both require ionizing radiation and potentially toxic exogenous contrast agents. Furthermore, DSA only provides qualitative flow dynamic information and flow information on CTA must be inferred (1). Phase-contrast (PC) magnetic resonance angiography (MRA) allows direct measurement of blood flow velocity, which utilizes bipolar gradients to encode velocity through flow-induced phase shift along the gradient direction. PC-MRI can be applied along a plane perpendicular to each of the main branches of the circle of Willis – a technique dubbed quantitative MRA (QMRA) (2). The advantage of QMRA is high reliability, however, it requires lengthy acquisition time (~30 minutes) for each examination. The newly introduced four-dimensional (4D) flow MRI technique is capable of generating quantitative maps of hemodynamic parameters, e.g. a velocity distribution map. However, this technique has been mainly limited to research purposes due to the long acquisition time (10–20 minutes) and sophisticated post-processing procedures. The application of 4D flow MRI in studying intracranial hemodynamics remains challenging since it is difficult to quantify the full range of flow velocities in vessels with different sizes (3). Recently, arterial spin labeling (ASL)-based non-contrast enhanced dynamic MRA (NCE-dMRA) was introduced to qualitatively delineate the pattern of dynamic blood flow through the cerebral vasculature with high spatiotemporal resolution (4,5). In combination with golden-angle stack-of-stars radial acquisition and advanced reconstructions, such as k-space weighted image contrast (KWIC) (6) and compressed sensing (7), NCE-dMRA can significantly shorten the scan time by approximately three-fold while maintaining high temporal and spatial information, greatly facilitating its potential clinical applications. Particularly, quantitative hemodynamic parameters can be derived from the dynamic time series of ASL based dMRA signals. Similar to dynamic susceptibility contrast (DSC) MRI (8), the concentration of labeled blood in an artery can be modeled by the convolution between the arterial input function (AIF) and residual function according to the indicator dilution theory (9). Blood flow can be estimated by deconvolution, as the maximum of the residual function, without any assumptions about the kinetic model or exchange mechanism (9).

Deconvolution methods have been widely studied in DSC MRI (8). Solving the residual function can be simply achieved by division in the frequency domain, which is not sensitive to the delay of AIF, but is very sensitive to noise (10). Hence, a common approach is applying a low-pass filter in the Fourier transform (FT)-based methods, which suppresses the high-frequency information before the inverse FT (11). However, smoothing of the true signal in the time domain due to the low-pass filter in the frequency domain underestimates

the initial point of the tissue residual function, causing about half signal reduction even in the absence of noise, as previously reported (12).

A standard approach of deconvolution in the time domain is truncated singular value decomposition (t-SVD), which truncates the diagonal matrix based on a pre-defined threshold to remove the high-frequency components that originate from the arterial input function (12). A threshold of 20% of maximal singular value was considered as the optimal cut-off value based on Monte-Carlo simulations (12). However, a high threshold can lead to underestimation of the blood flow. An optimal threshold is highly dependent on SNR and characteristics of AIF according to simulation studies (13,14). Analytical function modeling (e.g. exponential decaying residual function (15); gamma-variate shaped tracer concentration signal (11)), regularization (16), and statistical approaches (17–19) were also proposed to increase the reliability of blood flow estimation with assumptions about the signal property. However, an error often arises in the blood flow estimation if the underlying assumption is violated.

The purpose of this study was to introduce a novel analytical solution by taking advantage of the monotonic property of residual function to achieve reliable arterial blood flow (aBF) quantification in NCE-dMRA. A set of comprehensive hemodynamic parametric maps including arterial blood volume (aBV), arterial transit time (ATT) and arterial time-to-peak (TTP) can be also simultaneously generated from NCE-dMRA. The proposed method was evaluated in seven healthy subjects and one AVM patient. The aBF values from healthy subjects were compared with velocity measurements using PC-MRI. The proposed quantification method was further evaluated in NCE-dMRA with both radial and Cartesian acquisition trajectories.

THEORY

aBF quantification with monotonic property of residual function

The dynamic time series of labeled blood signal can be expressed by:

$$S(t) = AIF(t) \otimes (aBF \cdot R(t)) \quad [1]$$

where $S(t)$ is the dynamic time series of labeled blood signal, arterial input function $AIF(t)$ is measured in M1 segment of middle cerebral artery (MCA), and $R(t)$ is un-known residual function which describes the fraction of contrast that remains in the system after a given time t . Theoretically, $R(t)$ is a positive, decreasing function with $R(0)=1$, thus $aBF = R'(0)$ when setting $R'(t) = aBF \cdot R(t)$ (20). [Eq. 1] can be expressed in discretized form and expanded into matrix notations:

$$\begin{bmatrix} S(t_0) \\ S(t_1) \\ \vdots \\ S(t_{N-1}) \end{bmatrix} = \Delta TI \begin{bmatrix} AIF(t_0) & 0 & \cdots & 0 \\ AIF(t_1) & AIF(t_0) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ AIF(t_{N-1}) & AIF(t_{N-2}) & \cdots & AIF(t_0) \end{bmatrix} \times \begin{bmatrix} R'(t_0) \\ R'(t_1) \\ \vdots \\ R'(t_{N-1}) \end{bmatrix} \quad [2]$$

where N is the number of frames of dMRA acquisition, and TI is the time interval between frames. We propose to regularize the $R'(t_i)$ by a monotonicity constraint: $R'(t_i) \geq R'(t_{i+1})$, which equals to $P(t_i) \geq 0$ when substituting $R'(t_i)$ by $P(t_i)$:

$$\begin{cases} P(t_i) = R'(t_i) - R'(t_{i+1}) & (0 \leq i \leq N-2) \\ P(t_i) = R'(t_i) & (i = N-1) \end{cases} \quad [3]$$

Then [Eq. 2] can be reformatted as:

$$\begin{bmatrix} \Delta S(t_0) \\ \Delta S(t_1) \\ \vdots \\ \Delta S(t_{N-1}) \end{bmatrix} = \Delta TI \begin{bmatrix} AIF(t_0) - AIF(t_1) & -AIF(t_1) & \cdots & -AIF(t_1) \\ AIF(t_1) - AIF(t_2) & AIF(t_0) - AIF(t_2) & \cdots & -AIF(t_2) \\ \vdots & \vdots & \ddots & \vdots \\ AIF(t_{N-1}) & AIF(t_{N-2}) & \cdots & \sum_{i=0}^{N-1} AIF(t_i) \end{bmatrix} \times \begin{bmatrix} P(t_0) \\ P(t_1) \\ \vdots \\ P(t_{N-1}) \end{bmatrix} \quad [4]$$

[Eq. 4] describes the linear relationship between $\Delta S(t_i)$ and $P(t_i)$. Solving $P(t_i)$ can be considered as a least-squares problem with boundary conditions. Due to the delay between measured AIF and $\Delta S(t)$, boundary conditions of $P(t_i)$ can be expressed as:

$$\begin{cases} P(t_i) \leq 0 & (t_i \leq \tau_d) \\ P(t_i) \geq 0 & (t_i > \tau_d) \end{cases} \quad [5]$$

where τ_d is the bolus arrival time, i.e., ATT. [Eq. 5] ensures underlying $R'(t_i)$ to be a positive unimodal function, which peaks at τ_d , and $aBF = R'(\tau_d)$. Solving $P(t_i)$ was implemented in Matlab using 'active-set' algorithm.

Hemodynamic parameters

Hemodynamic parameters including aBF, ATT and TTP were generated for the AVM patient and compared between lesion and contralateral sides. aBV was calculated by:

$$aBV = \frac{\int S(t)dt}{\int AIF(t)dt} \quad [6]$$

Details about the estimation of ATT/τ_d were discussed in the method section. TTP was estimated as the time when $S(TTP) = \max(S(t))$.

METHODS

Monte-Carlo simulation

Monte-Carlo simulation was also performed to compare the performance of the conventional t-SVD and the proposed method at different noise levels. All the t-SVD methods were applied with a block-circulant matrix to eliminate bolus-delay sensitivity according to (21). Mathematical model and experimental setup were designed according to (22). A gamma-variate function was used to simulate AIF (12,22):

$$AIF(t) = t^\alpha e^{-t/\beta} \quad [8]$$

where $\alpha = 3$ (shape parameter) and $\beta = 150\text{ms}$ (rate parameter) were used in this study, which gives good accordance between the simulated AIF and average AIF measured in MCA across seven subjects. Assuming the vascular space as a single well-mixed compartment, residual function was simulated by an exponential decay:

$$R(t) = e^{-(t-\tau_d)/D} \quad [9]$$

where D is the decay constant. $\tau_d = 400$ ms for simulation. $S(t)$ was calculated according to [Eq. 1] with $aBF = 100$ ml/ml/min and $TI = 100$ ms. Gaussian noise was added to the time series signal and SNR was defined as average of time series signal divide by the standard deviation of background noise. One thousand Monte-Carlo simulations were also performed to compare the aBF values calculated by the proposed and the conventional t-SVD method at SNR = 5, 10, 15, 20 and 25, respectively.

Estimation of bolus delay τ_d

Estimation of aBF using one global AIF (e.g. measured in MCA) is sensitive to bolus delay in down-streaming vascular branches, which is eliminated for t-SVD methods by employing block-circulant matrix for deconvolution (21). As for the proposed method, τ_d can be estimated as the ATT, when $S(t)$ responses are greater than zero. However, inaccurate estimation of τ_d is usually caused by noise. In this study, τ_d was estimated as the time when $S(t) \geq 3 \times SD_{\text{noise}}$, where SD_{noise} is the standard deviation of the background noise. Voxels with $\max(S(t)) < 3 \times SD_{\text{noise}}$ were considered as background voxels and excluded for further analysis. Venous signal, i.e. superior sagittal sinus, was also manually excluded. $S(t)$

To study the effect of τ_d on the aBF quantification, a sensitivity analysis was performed by Monte-Carlo simulations. Specifically, one thousand simulations were performed to calculate aBF values calculated by the proposed method with under-estimated τ_d (200, 300

ms), accurate τ_d (400 ms) and over-estimated τ_d (500, 600 ms) at SNR = 5, 10, 15, 20 and 25, respectively.

MRI experiments

Seven healthy subjects (2 Male, age = 24.9 ± 2.0 years) and one patient with un-ruptured arteriovenous malformation (AVM) (Male, age = 33 years) were recruited in this study and all participants signed written informed consent approved by the local institutional review board (IRB). Seven healthy subjects were scanned on a Siemens Tim Trio 3T scanner (Erlangen, Germany) with a 12-channel head coil and the AVM patient was scanned on a Siemens Prisma 3T scanner with 20-channel head coil.

Experiment 1: NCE-dMRA aBF quantification using the proposed and t-SVD methods

4-D MRA data were acquired using a pulse ASL prepared golden-angle stack-of-stars (GA-SOS) balanced steady-state free precession (bSSFP) sequence with magnitude subtraction constrained compressed sensing (7). The flow-sensitive alternating inversion recovery (FAIR) scheme was applied for spin tagging. Specifically, a slab-selective (slab thickness = 70mm) and a non-selective hyperbolic secant inversion pulse was applied before the data acquisition in two measurements. Imaging parameters: field-of-view (FOV) = $256 \times 256 \text{ mm}^2$, voxel size = $1.0 \times 1.0 \times 1.5 \text{ mm}^3$, flip angle = $25\text{--}40^\circ$, bandwidth = 558 Hz/pixel, TE/TR = 2.3/4.6 ms, 500 views per shot/slice, 25 time frames (20 views per frame) with a temporal resolution of 92 ms, 32 slices were acquired to cover the circle of Willis and its branches resulting in a scan time of three minutes. NCE-dMRA data was off-line reconstructed using magnitude-subtraction compressed sensing (MS-CS) algorithm. Compared to the conventional CS, an additional term was employed in the MS-CS algorithm by employing the sparsity of the magnitude subtraction between control and label images. Control and label images were subtracted to obtain angiography images. For aBF quantification, the dMRA signal from M1 segment of left and right MCA was extracted across phases as AIF. Three dimensional aBF map was generated using the proposed and t-SVD methods, and maximal-intensity projection (MIP) of 3D aBF volumes was performed towards axial, coronal and sagittal planes.

Experiment 2: Comparison of NCE-dMRA aBF quantification between radial and Cartesian acquisition trajectories

To demonstrate the proposed quantification method is applicable for NCE-dMRA with different acquisition trajectories, a standard Cartesian-based NCE-dMRA with a cine segmented readout was also performed on six of the recruited healthy subjects (1 Male, age = 24.5 ± 1.9 years). Both segmented cine bSSFP and spoiled gradient-echo (GRE) readouts have been successfully employed in NCE-dMRA (4). To reduce the arterial pulsation-induced motion artifacts especially in large branches, e.g. MCA, a segmented multi-phase GRE with flow compensation was employed for data acquisition. The imaging parameters for GRE based Cartesian acquisition were: field-of-view (FOV) = $220 \times 156 \text{ mm}^2$, voxel size = $1.0 \times 1.0 \times 1.5 \text{ mm}^3$, flip angle = 12° , bandwidth = 720 Hz/pixel, TR/TE = 5.6/3.19 ms, in-plane GRAPPA acceleration factor = 2. 32 slices were collected with 13-time frames at a temporal resolution of 113 ms, leading to a scan time of 10 mins 33 secs. 4D MRA images as well as associated MIP images were generated online in the vendor-provided

reconstruction environment. For comparison between radial and Cartesian acquisitions, average aBF values were calculated from large vascular branches (M1 and P1/2 segments of MCA and PCA).

Experiment 3: Comparison of aBF from NCE-dMRA and blood flow velocity from PC-MRI

To evaluate the association between aBF values and local blood supply at major arteries, the aBF values were compared with blood velocities measured with a standard 2D PC-MRI (resolution = $0.5 \times 0.5 \times 5 \text{ mm}^3$, velocity encoding (VENC) = 80 cm/s). Blood velocities were measured at both sides of MCA and PCA with the imaging plane perpendicular to the selected artery, and averaged within each ROI for comparison with aBF values. ROIs of MCA/PCA were manually drawn by a research fellow.

Statistical analysis

Correlation between aBF values measured with radial and Cartesian acquisitions was evaluated by linear regression assuming no interception. Correlation between aBF and blood flow velocity was evaluated by using Pearson's correlation coefficients. Statistical significance was defined as $P < 0.001$ (2 tailed).

RESULTS

Figure 1 (a) shows the simulated dynamic blood signal curve without noise with $\tau_d = 400$ ms. Simulated signal curves (ten repeated simulations were shown) at five SNR levels are plotted in figure 1 (b–f), respectively. Dashed black lines in figure (b–f) indicates the threshold ($3 \times \text{SD}_{\text{noise}}$) which was used to determine the τ_d . Average $S(t)$ in MCA, PCA and distal small arteries were 413 ± 20.9 , 409 ± 18.7 and 213 ± 15.3 , respectively, while the background noise was 19.8 ± 4.5 across seven healthy subjects. Therefore, SNR in MCA, PCA and distal small arteries were 20.9, 20.7 and 10.8, respectively. Results in figure 1 (c) represents the arterial blood signal measured in distal small arteries, and figure 1 (e) represents the arterial blood signal measured in MCA and PCA.

Figure 2 shows the aBF values simulated with the proposed and t-SVD method with threshold varying from 1.0% to 10.0% respectively. Estimated were 504 ± 66 , 453 ± 56 , 419 ± 64 , 401 ± 54 and 403 ± 51 ms when SNR=5, 10, 15, 20 and 25, respectively. And aBF calculated by the proposed method were 96.1 ± 44.1 , 106.5 ± 28.2 , 104.6 ± 21.9 , 101.9 ± 18.3 , and 99.6 ± 15.5 ml/ml/min when SNR=5, 10, 15, 20 and 25, respectively, which matched well with the reference of 100 ml/ml/min. In contrast, aBF values are highly dependent on the threshold in t-SVD method. About 80% overestimation was found at SNR=5 when a low threshold of 1.0% was used, while about 24% underestimation was found across all SNR levels when a high threshold of 10.0% was used.

Figure 3 shows the aBF values simulated with the proposed method when τ_d was accurate, under-estimated and over-estimated, respectively. Average aBF = 98.6 ± 0.9 ml/ml/min across five SNR levels with accurate τ_d (400 ms), which is approximately equal to the reference aBF value of 100 ml/ml/min. The proposed method is robust when τ_d is over-estimated. $6.9 \pm 5.3\%$ and $2.3 \pm 4.7\%$ increase of aBF values were observed with 100 and 200 ms over-estimation of τ_d across five SNR levels. However, the proposed method is sensitive to the

under-estimated τ_d . 24.9±0.5% and 35.9±0.7% decrease of aBF values were observed with 100 and 200 ms under-estimation of τ_d across five SNR levels.

Figure 4 shows aBF maps from a representative subject with the proposed (a) and t-SVD (b-d) methods respectively. Significant variation in image intensities was observed in the t-SVD method with different thresholds of singular values, whereas aBF map generated by the proposed method showed desirable contrast. Figure 4 (e) shows the plot of normalized singular values from t-SVD method. Three, four and fifteen components were used for reconstruction with singular value threshold of 20%, 10% and 1%, respectively.

Comparison of radial and Cartesian acquisition trajectories

Three-plane views of three selected frames of the NCE-dMRA MIP images acquired with radial and Cartesian trajectory were shown in Figure 5 (a) and (c), respectively. Satisfactory delineation of arterial vasculature with clear background and no visible pulsation artifacts can be appreciated with both radial and Cartesian trajectories. Corresponding aBF maps generated by the proposed method were shown in (b) and (d), respectively. It was noted that some distal arterial segments became invisible with GRE based Cartesian acquisition, as indicated by white arrows, due to the increased saturation effects on slower moving spins. (23,24).

Average aBF across six healthy subjects in large vascular branches was 214.4±36.6 ml/ml/min with radial acquisition, and 214.5±26.2 ml/ml/min with Cartesian acquisition. Table 1 summarizes the aBF values of each subject with two acquisition trajectories. Significant linear correlation was found between aBF values acquired with radial and Cartesian trajectories ($\beta=0.98$, $P<0.0001$).

Comparison between aBF and blood flow velocity

Figure 6 shows the scatter plot of blood flow velocity versus aBF from seven subjects at both sides of MCA and PCA (each location was indicated by a different marker specifier). Measurements from each subject were distinguished by a different color. Significant correlation was found between blood flow velocity measured by PC-MRI and aBF measured by the proposed method ($\beta=0.09$, $P=0.0008$). Gray dashed line indicates the linear fitting of blood flow velocity versus aBF.

Hemodynamic quantification in patients

Figure 7 displays NCE-dMRA images with GA-SOS radial acquisition and hemodynamic maps (aBF, aBV, ATT and TTP) from the AVM patient. The AVM nidus is indicated by white arrows. Both right MCA and right PCA feeding arteries supplied the nidus. Hemodynamics of feeding arteries demonstrated that decreased ATT and TTP are consistent with increased aBF. The AVM nidus is characterized by increased aBF and aBV as well as prolonged ATT and TTP which are all consistent with the tortuosity of the nidal vessels and the presence of large venous varicosities.

DISCUSSION

Quantitative hemodynamic parameters could provide useful complimentary information to dynamic MRA for the clinical diagnosis and treatment of cerebrovascular disease. In NCE-dMRA, the labeled blood behaves like intracranial vascular contrast agent, which allows for flow hemodynamic quantification according to the indicator dilution theory (9). A novel analytical solution for blood flow quantification was introduced in this study. Both simulation and experimental results suggest the proposed method offers robust flow quantification with reduced sensitivity to background noise compared to conventional t-SVD methods.

T-SVD is the most commonly used method especially in DSC studies although previous studies showed its dependency on the threshold selection at different SNR levels (13,14,22). Consistent with our simulation results, a lower threshold would cause overestimation of blood flow when the peak of the residual function is dominated by noise or spurious oscillations due to amplified leakage frequencies when using the block-circulant deconvolution method (21). In contrast, a high threshold removes high-frequency signal oscillations and produces robust estimation to noise; however, a systematic under-estimation is often present. Although a number of studies have proposed methods for determining the optimal threshold, assumptions about the vasculature model and SNR are usually necessary (8). Compared to the t-SVD method, two advantages of the proposed method are: 1) No assumption about the vascular model or any parameters are required. The proposed method makes assumption of the monotonic property of the residual function, which holds true by definition, and solves linear equations with boundary conditions that can be easily implemented on a stand-alone computer; 2) Reliable aBF quantification was achieved by the proposed method, average estimation error was 1.74% across five SNR levels. Sensitivity analysis demonstrated that the proposed method is robust to over-estimated τ_d . A relatively high threshold ($3 \times SD_{\text{noise}}$) was used to minimize the influence of signal fluctuations on τ_d estimation, and under-estimation of τ_d was effectively eliminated, as demonstrated in Figure 1.

In this study, bSSFP and spoiled GRE readouts were applied in radial and Cartesian NCE-dMRA, respectively, both of which have been employed in NCE-dMRA. Compared to spoiled GRE, bSSFP offers higher SNR efficiency without significantly attenuating ASL blood signal (25). A comprehensive delineation of vascular structure including distal arteries can be achieved with bSSFP readout. However, arterial pulsation induced dephasing and motion artifacts along phase direction are occasionally observed in bSSFP with Cartesian trajectory, which may affect the aBF quantification in larger arterial segments that is susceptible to arterial pulsation effects. Therefore, spoiled GRE readout with flow compensation instead of bSSFP was applied with Cartesian acquisition in the present study at the cost of compromised visualization of distal arterial segments due to the saturation effects on slow flowing spins during GRE readout (24). On the other hand, bSSFP in conjunction with radial trajectory can effectively mitigate the pulsatile motion artifacts due to the resilience of radial acquisition to motion. bSSFP was employed in radial acquisition which improved the delineation of blood vessels with different sizes while reducing pulsatile motion artifacts. A significant linear correlation ($P < 0.0001$) was found between average aBF

in large vascular branches acquired with Cartesian and radial trajectories, suggesting that the proposed method provides a robust aBF measurement with different image readouts or acquisition trajectories. It was noted that distal arterial segments became invisible with GRE based Cartesian acquisition, which was likely to be caused by the saturation effect of spoiled GRE readout (24). Compared to Cartesian acquisition, radial NCE-dMRA offers advantage of better delineation of all-size vessels with fast acquisition and less sensitivity to motion, which should benefit clinical applications.

PC-MRI can be used for volumetric blood flow measurement by multiplying blood flow velocity with the cross-sectional area of an individual vessel. Different from PC-MRI, our method provides voxel-wise aBF map, which is expected to be directly associated with blood flow velocity. Significant positive correlation between aBF and blood flow velocity was found in this study, further supporting the validity of our method. 2D PC-MRI requires manually positioning of the acquisition slice and only a single velocity encoding direction (orthogonal to slice) is acquired. Moreover, it's challenging to define optimal VENC. As an alternative, 4D flow MRI techniques extends blood flow quantification to three dimensions, however, at the cost of acquisition time, resolution and sensitivity to motion (3,26). In contrast, the setup of NCE-dMRA is straightforward, and quantitative mapping can be accomplished using a simple algorithm. Another advantage of NCE-dMRA is the 3D hemodynamic parametric maps in terms of aBF, aBV, ATT and TTP can be simultaneously quantified in a few minutes, which could benefit clinical diagnosis with more comprehensive hemodynamic information. It was worth noting that the spatial coverage of the NCE-dMRA method could be limited as compared to the 4D flow MRI techniques. Multi-slab NCE-dMRA may be a solution to increase coverage and/or cover the whole brain. In addition, our method could be expanded to perfusion measurements using DSC MRI and/or CT perfusion.

The standard 4D NCE-dMRA mainly focuses on the depiction of flow passage through the lesion. However, complementary information could be derived from the quantitative maps when diagnosis is made. Our preliminary results on the AVM patient suggested altered hemodynamics at the lesion from the quantitative hemodynamic maps compared to the contralateral side. Several angiographic high-risk criteria have been defined for un-ruptured AVMs that herald a higher risk of future rupture (27). These are anatomic variants or clinic presentations that do not directly address the quantitative hemodynamics of the AVM itself. A quantitative analysis has the potential to further elucidate how these structural variations affect the hemodynamics (28–30). Many ruptured AVMs lack clear high-risk features. Refining our understanding of the hemodynamics that predispose to rupture will help us understand which lesions are more likely to rupture despite lacking high-risk features.

Our study has limitations. First, correction for dispersion of AIF was not successfully addressed. When dispersion exists, de-convoluted signal equals to the convolution of the true residual function and a dispersion function, which causes under-estimation of aBF and prolonged mean transit time of the bolus. The correction of dispersion needs to be addressed in the future by integrating a vasculature model into our analysis or using local AIFs. Second, our method was only evaluated on a limited number of patients. The sample size of the study was relatively small. Future studies with a larger sample size are required to replicate the reported association between aBF and PC MRI assessment as well as to

investigate the relationship between hemodynamic parameters and clinical outcomes. Third, low SNR still causes a relatively large standard deviation of aBF generated by the proposed method. Improving the SNR, such as combining golden-angle stack-of-stars trajectory and compressed sensing with magnitude subtraction is desired. To further improve the precision of aBF quantification, future studies on improving accuracy of τ_d estimation are desired. Under situations when SNR becomes even lower, t-SVD would be a robust alternative where under-estimation should be expected. Lastly, the practical applicability of this technique to critically ill patients with acute cerebrovascular disorders has yet to be validated.

CONCLUSION

We proposed a robust analytical solution for quantifying quantitative hemodynamic information (aBF, aBV, ATT and TTP) based on NCE-dMRA. This model-free method is robust to noise, and its clinical value in the diagnosis of cerebrovascular disorders awaits further evaluation.

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REFERENCES

1. Gupta V, Chugh M, Walia BS, Vaishya S, Jha AN. Use of CT angiography for anatomic localization of arteriovenous malformation Nidal components. *AJNR Am J Neuroradiol* 2008;29(10):1837–1840. [PubMed: 18768733]
2. Brisman JL, Pile-Spellman J, Konstant AA. Clinical utility of quantitative magnetic resonance angiography in the assessment of the underlying pathophysiology in a variety of cerebrovascular disorders. *Eur J Radiol* 2012;81(2):298–302. [PubMed: 21316169]
3. Wetzel S, Meckel S, Frydrychowicz A, Bonati L, Radue EW, Scheffler K, Hennig J, Markl M. In vivo assessment and visualization of intracranial arterial hemodynamics with flow-sensitized 4D MR imaging at 3T. *AJNR Am J Neuroradiol* 2007;28(3):433–438. [PubMed: 17353308]
4. Yan L, Wang S, Zhuo Y, Wolf RL, Stiefel MF, An J, Ye Y, Zhang Q, Melhem ER, Wang DJ. Unenhanced dynamic MR angiography: high spatial and temporal resolution by using true FISP-based spin tagging with alternating radiofrequency. *Radiology* 2010;256(1):270–279. [PubMed: 20574100]
5. Bi X, Weale P, Schmitt P, Zuehlsdorff S, Jerecic R. Non-contrast-enhanced four-dimensional (4D) intracranial MR angiography: a feasibility study. *Magn Reson Med* 2010;63(3):835–841. [PubMed: 20187191]
6. Song HK, Yan L, Smith RX, Xue Y, Rapacchi S, Srinivasan S, Ennis DB, Hu P, Pouratian N, Wang DJ. Noncontrast enhanced four-dimensional dynamic MRA with golden angle radial acquisition and K-space weighted image contrast (KWIC) reconstruction. *Magn Reson Med* 2014;72(6):1541–1551. [PubMed: 24338944]
7. Zhou Z, Han F, Yu S, Yu D, Rapacchi S, Song HK, Wang DJJ, Hu P, Yan L. Accelerated noncontrast-enhanced 4-dimensional intracranial MR angiography using golden-angle stack-of-stars trajectory and compressed sensing with magnitude subtraction. *Magn Reson Med* 2017.
8. Knutsson L, Stahlberg F, Wirestam R. Absolute quantification of perfusion using dynamic susceptibility contrast MRI: pitfalls and possibilities. *MAGMA* 2010;23(1):1–21. [PubMed: 19960361]
9. Meier P, Zierler KL. On the theory of the indicator-dilution method for measurement of blood flow and volume. *J Appl Physiol* 1954;6(12):731–744. [PubMed: 13174454]

10. Gobbel GT, Fike JR. A deconvolution method for evaluating indicator-dilution curves. *Phys Med Biol* 1994;39(11):1833–1854. [PubMed: 15559994]
11. Rempp KA, Brix G, Wenz F, Becker CR, Guckel F, Lorenz WJ. Quantification of regional cerebral blood flow and volume with dynamic susceptibility contrast-enhanced MR imaging. *Radiology* 1994;193(3):637–641. [PubMed: 7972800]
12. Ostergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: Mathematical approach and statistical analysis. *Magn Reson Med* 1996;36(5):715–725. [PubMed: 8916022]
13. Murase K, Shinohara M, Yamazaki Y. Accuracy of deconvolution analysis based on singular value decomposition for quantification of cerebral blood flow using dynamic susceptibility contrast-enhanced magnetic resonance imaging. *Phys Med Biol* 2001;46(12):3147–3159. [PubMed: 11768497]
14. Knutsson L, Stahlberg F, Wirestam R. Aspects on the accuracy of cerebral perfusion parameters obtained by dynamic susceptibility contrast MRI: a simulation study. *Magn Reson Imaging* 2004;22(6):789–798. [PubMed: 15234447]
15. Larson KB, Perman WH, Perlmutter JS, Gado MH, Ollinger JM, Zierler K. Tracer-kinetic analysis for measuring regional cerebral blood flow by dynamic nuclear magnetic resonance imaging. *J Theor Biol* 1994;170(1):1–14. [PubMed: 7967632]
16. Calamante F, Gadian DG, Connelly A. Quantification of bolus-tracking MRI: Improved characterization of the tissue residue function using Tikhonov regularization. *Magn Reson Med* 2003;50(6):1237–1247. [PubMed: 14648572]
17. Mouridsen K, Friston K, Hjort N, Gyldensted L, Ostergaard L, Kiebel S. Bayesian estimation of cerebral perfusion using a physiological model of microvasculature. *Neuroimage* 2006;33(2):570–579. [PubMed: 16971140]
18. Andersen IK, Szymkowiak A, Rasmussen CE, Hanson LG, Marstrand JR, Larsson HB, Hansen LK. Perfusion quantification using Gaussian process deconvolution. *Magn Reson Med* 2002;48(2):351–361. [PubMed: 12210944]
19. Willats L, Connelly A, Calamante F. Minimising the effects of bolus dispersion in bolus-tracking MRI. *NMR Biomed* 2008;21(10):1126–1137. [PubMed: 18727165]
20. Petersen ET, Lim T, Golay X. Model-free arterial spin labeling quantification approach for perfusion MRI. *Magn Reson Med* 2006;55(2):219–232. [PubMed: 16416430]
21. Wu O, Ostergaard L, Weisskoff RM, Benner T, Rosen BR, Sorensen AG. Tracer arrival timing-insensitive technique for estimating flow in MR perfusion-weighted imaging using singular value decomposition with a block-circulant deconvolution matrix. *Magn Reson Med* 2003;50(1):164–174. [PubMed: 12815691]
22. Calamante F, Gadian DG, Connelly A. Delay and dispersion effects in dynamic susceptibility contrast MRI: simulations using singular value decomposition. *Magn Reson Med* 2000;44(3):466–473. [PubMed: 10975900]
23. Gunther M, Bock M, Schad LR. Arterial spin labeling in combination with a look-locker sampling strategy: inflow turbo-sampling EPI-FAIR (ITS-FAIR). *Magn Reson Med* 2001;46(5):974–984. [PubMed: 11675650]
24. Okell TW, Schmitt P, Bi X, Chappell MA, Tijssen RH, Sheerin F, Miller KL, Jezzard P. Optimization of 4D vessel-selective arterial spin labeling angiography using balanced steady-state free precession and vessel-encoding. *NMR in Biomedicine* 2016;29(6):776–786. [PubMed: 27074149]
25. Yan L, Li C, Kilroy E, Wehrli FW, Wang DJ. Quantification of arterial cerebral blood volume using multiphase-balanced SSFP-based ASL. *Magn Reson Med* 2012;68(1):130–139. [PubMed: 22127983]
26. Shen X, Schnell S, Barker AJ, Suwa K, Tashakkor L, Jarvis K, Carr JC, Collins JD, Prabhakaran S, Markl M. Voxel-by-voxel 4D flow MRI-based assessment of regional reverse flow in the aorta. *J Magn Reson Imaging* 2017.
27. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg* 1986;65(4):476–483. [PubMed: 3760956]

28. Shakur SF, Liesse K, Amin-Hanjani S, Carlson AP, Aletich VA, Charbel FT, Alaraj A. Relationship of Cerebral Arteriovenous Malformation Hemodynamics to Clinical Presentation, Angioarchitectural Features, and Hemorrhage. *Neurosurgery* 2016;63 Suppl 1:136–140. [PubMed: 27399378]
29. Burkhardt JK, Chen X, Winkler EA, Cooke DL, Kim H, Lawton MT. Delayed Venous Drainage in Ruptured Arteriovenous Malformations Based on Quantitative Color-Coded Digital Subtraction Angiography. *World Neurosurg* 2017;104:619–627. [PubMed: 28457930]
30. Wu C, Ansari SA, Honarmand AR, Vakil P, Hurley MC, Bendok BR, Carr J, Carroll TJ, Markl M. Evaluation of 4D vascular flow and tissue perfusion in cerebral arteriovenous malformations: influence of Spetzler-Martin grade, clinical presentation, and AVM risk factors. *AJNR Am J Neuroradiol* 2015;36(6):1142–1149. [PubMed: 25721076]

Figure 1.

(a) Simulated time series signal with gamma-variate shaped AIF and exponential decaying residual function. Black arrow indicates the τ_d . Ten simulated time series signals with noise were shown in (b–f) for SNR = 5, 10, 15, 20 and 25, respectively. Black dashed lines indicate the threshold equals to three times of standard deviation of background noise, which eliminates the background noise fluctuations for τ_d estimation.

Figure 2.

Simulated aBF values with the proposed and t-SVD methods (threshold=1.0%, 2.5%, 5.0%, 7.5% and 10.0%) at five SNR levels. Error bar indicates standard deviation from 1000 Monte-Carlo simulations. Reference aBF is 100 ml/ml/min (indicated by the red dashed line) and average aBF values calculated by the proposed method were 96.1, 106.5, 104.6, 101.9 and 99.6 ml/ml/min when SNR=5,10,15, 20 and 25, respectively.

Figure 3.

Simulated aBF values with the proposed method when τ_d was accurate (400 ms), underestimated (200, 300 ms) and over-estimated (500, 600 ms) at five SNR levels, respectively. Error bar indicates standard deviation from 1000 Monte-Carlo simulations. Reference aBF is 100 ml/ml/min (indicated by the red dashed line).

Figure 4.

Axial, sagittal and coronal views of aBF maps from one representative subject reconstructed with the proposed (a) and t-SVD methods (threshold 20%, 10%, 1% in b-d). Plot of normalized singular values of t-SVD method was shown in (e). Three thresholds and corresponding number of components for reconstruction were listed next to black arrows.

Figure 5.

Comparison of the proposed quantification method with radial and Cartesian acquisitions. Three-plane views of three time frames of the NCE-dMRA signals acquired with radial and Cartesian trajectory were shown in (a) and (c), respectively. Corresponding aBF maps were shown in (b) and (d), respectively. White arrows indicate the distal vasculature, which was invisible with GRE based Cartesian acquisition due to the its dephasing effects for slow blood flow.

Figure 6.

Scatter plot between aBF (ml/ml/min) (X-axis) measured by the proposed method and blood flow (ml/min) (Y-axis) measured by PC-MRI in both sides of MCA and PCA from seven healthy subjects. Subjects are identified in different colors. Correlation coefficient β , R^2 and P value of linear fitting (dashed line) are listed at the bottom of the figure.

Figure 7.

(a) Four time frames of NCE-dMRA images with GA-SOS radial acquisition and hemodynamic maps from the AVM patient (white arrows indicate the lesion). Corresponding aBF, aBV, ATT and TTP maps were shown in (b-e) respectively.

Table 1.

aBF (ml/ml/min) values of six subjects measured with radial and Cartesian acquisitions in major vascular branches.

		Subject ID						
		1	2	3	4	5	6	Average
aBF (ml/ml/min)	Radial	226.4	260.4	250.5	185.0	192.2	172.3	214.4±36.6
	Cartesian	250.0	234.3	215.4	217.7	188.1	181.6	214.5±26.2