

Intracranial Blood Flow Quantification by Accelerated Dual-venic 4D Flow MRI: Comparison With Transcranial Doppler Ultrasound

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Background: Dual-venic 4D flow MRI, recently introduced for the assessment of intracranial hemodynamics, may provide a promising complementary approach to well-established tools such as transcranial Doppler ultrasound (TCD) and overcome some of their disadvantages. However, data comparing intracranial flow measures from dual-venic 4D flow MRI and TCD are lacking.

Purpose: To compare cerebral blood flow velocity measures derived from dual-venic 4D flow MRI and TCD.

Study Type: Prospective cohort.

Subjects: A total of 25 healthy participants (56 ± 4 years old, 44% female).

Field Strength/Sequence: A 3 T/dual-venic 4D flow MRI using a time-resolved three-dimensional phase-contrast sequence with three-dimensional velocity encoding.

Assessment: Peak velocity measurements in bilateral middle cerebral arteries (MCA) were quantified from dual-venic 4D flow MRI and TCD. The MRI data were quantified by two independent observers (S.M. and Y.M.) and TCD was performed by a trained technician (A.L.M.). We assessed the agreement between 4D flow MRI and TCD measures, and the interobserver agreement of 4D flow MRI measurements.

Statistical Tests: Peak velocity from MRI and TCD was compared using Bland–Altman analysis and coefficient of variance. Intraclass correlation coefficient (ICC) was used to assess MRI interobserver agreement. A *P* value < 0.05 was considered statistically significant.

Results: There was excellent interobserver agreement in dual-venic 4D flow MRI-based measurements of peak velocity in bilateral MCA (ICC = 0.97 and 0.96 for the left and right MCA, respectively). Dual-venic 4D flow MRI significantly underestimated peak velocity in the left and right MCA compared to TCD (bias = 0.13 [0.59, −0.33] m/sec and 0.15 [0.47, −0.17] m/sec, respectively). The coefficient of variance between dual-venic 4D flow MRI and TCD measurements was 26% for the left MCA and 22% for the right MCA.

Data Conclusion: There was excellent interobserver agreement for the assessment of MCA peak velocity using dual-venic 4D flow MRI, and ≤20% under-estimation compared with TCD.

Evidence Level: 3

Technical Efficacy: Stage 2

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Transcranial Doppler ultrasound (TCD) is an established method for noninvasive, real-time assessment of blood flow within the intracranial vessels with very low operational cost and high temporal resolution.¹ Over the past few decades, TCD has been routinely utilized in the clinical evaluation of cerebrovascular pathologies² as well as quantitative assessment of hemodynamic alterations associated with these pathologies.^{3–6} However, despite its advantages—low cost, high temporal resolution, and ease of use—TCD has drawbacks, notably, operator dependency, susceptibility to changes in vessel diameter, and low spatial resolution.^{7–10}

Four-dimensional (4D) flow MRI has been recently introduced for assessment of cerebrovascular hemodynamics.¹¹ Using electrocardiogram-synchronized three-dimensional phase-contrast MRI with advanced postprocessing strategies, 4D flow MRI provides a comprehensive and quantitative view of cerebrovascular hemodynamics.^{11–13} It has been successfully applied for *in vivo* measurement of cerebrovascular hemodynamics in healthy intracranial vessels^{14–18} as well as in the context of cerebrovascular pathologies, such as stroke, intracranial aneurysm, cerebral vascular malformations, and intracranial atherosclerosis.^{11,19–24}

Current 4D flow MRI protocols are mainly based on measuring blood flow using a single predefined velocity encoding (venc). This results in velocity aliasing for unexpected high velocities or high noise for slow flow velocities and limits the ability of 4D flow MRI to fully capture the dynamic range of velocities within the measured vessels.¹¹ To address this limitation, the recently developed dual-venc technique relies on a shared reference scan for the acquisition of low- and high-venc data. In this approach, high-venc data are used to correct for velocity aliasing in the low-venc data, generating a single dual-venc dataset with a high velocity-to-noise ratio.²⁵

With these advancements, 4D flow MRI may be a strong candidate to assess cerebrovascular hemodynamics without some of the limitations associated with TCD. However, it has its own limitations—notably, temporal averaging of flow data, requiring segmentation that can be time-consuming, and relatively slow scan time.¹¹ The complementary advantages—and limitations—of TCD and 4D flow MRI noted above highlight the important role of multimodal approaches necessary to provide a comprehensive understanding of the physiology and pathophysiology of cerebrovascular hemodynamics. To that end, there is a need to assess alignment between 4D flow MRI and TCD-based measures. Previous work has shown that single-venc 4D flow MRI maybe a valid complementary measure to TCD for intracranial hemodynamic measurements,^{18,26,27} but these studies did not assess dual-venc 4D flow MRI with its higher velocity-to-noise ratio advantage. Thus, the aim of this study was to compare measures of intracranial blood flow velocity from dual-venc 4D flow MRI and TCD among healthy middle-

aged adults. Given temporal averaging of flow data by MRI, we hypothesize that dual-venc 4D flow MRI would underestimate measurement of intracranial flow velocity compared to TCD.

Materials and Methods

Study Population

The institutional review board approved the study, and all participants provided written informed consent for both TCD and MRI assessments.

Participants consisted of 25 middle age volunteers (56 ± 4 years old, 44% female) from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort.²⁸ Around 1–3 years after the 30th year of CARDIA follow-up examination, a total of 202 CARDIA participants were recruited in the Cerebral Small Vessel in Motor and Cognitive Decline (CSVD) ancillary study and underwent TCD to assess resting middle cerebral artery (MCA) blood flow velocity. Out of these 202 participants, 25 underwent brain MRI with full three-dimensional coverage of the Circle of Willis (CoW) within a mean period of 1.5 ± 0.6 years (range 0.5–2.5 years) from TCD examination. Accordingly, we included 25 participants with both TCD and MRI measurements in our analysis. One of the participants had missing left MCA measurement by TCD, and another had missing right MCA measurement by TCD (due to lack of an acoustic window). Participants were asked to refrain from eating a large meal or consuming caffeine prior to TCD and MRI scanning.

Brain MRI Data Acquisition

All brain MRI scans were performed on a 3 T PET/MR scanner (Siemens Biograph mMR, Erlangen, Germany) and included three-dimensional time of flight MR angiography (TOF MRA, to determine the position of the field of view), followed by dual-venc 4D flow MRI. Both TOF and dual-venc 4D flow MRI scan volumes covered the CoW with the major intracranial arteries including bilateral internal carotid arteries, MCA, anterior cerebral arteries, posterior cerebral arteries, and basilar artery. Accelerated dual-venc 4D flow MRI was based on a prospectively electrocardiogram gated time-resolved three-dimensional phase-contrast technique with three-directional velocity encoding as previously described.²⁵ Acceleration of dual-venc 4D flow MRI was achieved using PEAK-GRAPPA acceleration (a k-t method).²⁵ The acquisition time was 10–12 minutes. MRI sequence parameters are summarized in Table 1.

4D Flow MRI Data Postprocessing and Flow Quantification

The 4D flow MRI data analysis workflow is presented in Fig. 1 (top panels). Data were first corrected for eddy currents, noise, and velocity aliasing using an in-house tool (MATLAB, MathWorks, Natick, MA) as previously described.²⁹ The same tool was used to calculate a three-dimensional phase-contrast MRA, which was the basis for the segmentation of the CoW arteries (MIMICS, Materialise, Belgium). Color-coded three-dimensional velocities were used to visualize time-resolved arterial blood flow patterns in the CoW (ParaView, Los Alamos National Laboratory).

TABLE 1. Average MRI Scan Parameters (range in parenthesis)

Parameters	3D TOF MRA	Dual-venc 4D flow MRI
TR, msec	22	5.6 (5.5–5.6)
TE	3.75	3.29 (3.17–3.29)
Flip angle, °	18	15
Temporal resolution, msec	N/A	78.3 (77–78.4)
Spatial resolution, mm ³	[0.5 × 0.26 × 0.26]	[1 × 1.04 × 1.04]
Low Venc, m/sec	N/A	0.5 (0.5–0.6)
High Venc, m/sec	N/A	1.0 (1.0–1.2)

TR = repetition time; TE = echo time.

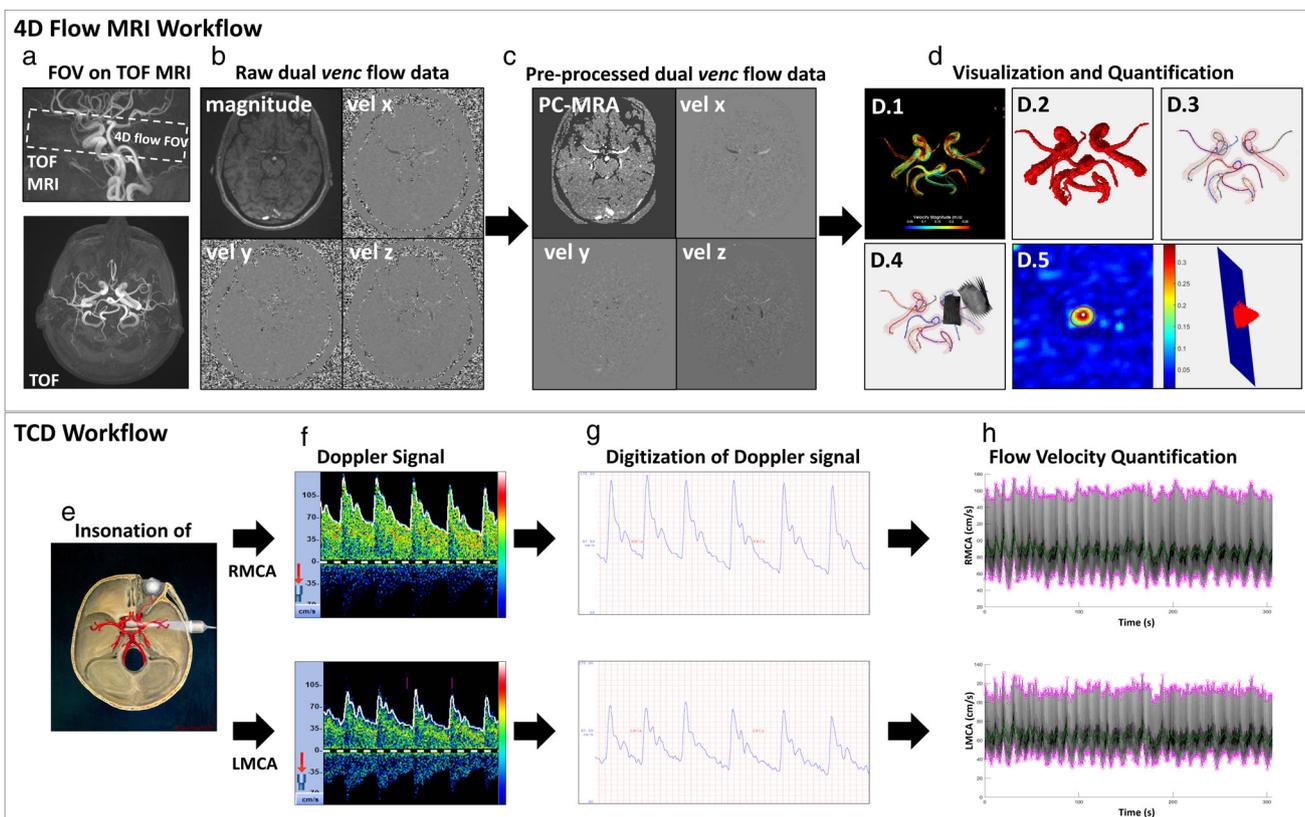


FIGURE 1: Dual-venc 4D flow MRI and transcranial Doppler ultrasound workflow. 4D flow MRI workflow example shows: (a) the volume coverage of the dual-venc 4D flow MRI data based on TOF MRI; (b) the dual-venc flow raw data including magnitude images and velocity encoded phase images in x, y, and z directions; (c) preprocessed data after eddy current correction, noise filtering, and velocity anti-aliasing; (d) visualization and quantification of data by (d1) visualization of streamlines; (d2) PC-MRA vessel segmentation; (d3) extraction of centerlines; (d4) placement of 2D analysis planes and (d5) lumen segmentation and velocity profile on a 2D plane. Transcranial Doppler workflow example shows (e) insonation of the middle cerebral artery via the transtemporal window; (f) the Doppler signal of the middle cerebral artery with the color bar representing signal intensity; (g) the digitization of the Doppler signal by Fast Fourier transform displayed by Windaq software; and (h) the middle cerebral artery flow velocities over time. FOV = field of view; TOF = time-of-flight; TCD = transcranial Doppler; MCA = middle cerebral artery; RMCA = right middle cerebral artery; LMCA = left middle cerebral artery.

A semi-automated analysis tool³⁰ was used for the quantification of cerebral blood flow velocities. First, centerlines of the bilateral MCAs were extracted to then automatically create equidistant

2D planes perpendicular to the centerline at every 1 mm along the vessels. Since the TCD measurements were limited to the M1 segment of MCA, 2D planes placed over the M1 segment of MCA

were chosen for comparison between dual-venic 4D flow MRI and TCD values. The M1 segment was determined from the carotid bifurcation up to where the vessel turned superiorly to the temporal lobe. The lumen boundary was then outlined automatically at each 2D plane and was adjusted manually if needed to delineate the vessel wall from noise voxels or adjacent vessels. Finally, the peak velocity (m/s) values representing the maximum velocity over the cardiac cycle was extracted for each analysis plane.³⁰ Because velocity values were resampled and interpolated by a factor of 2 onto each cross-sectional plane from the original image grid, the location of the maximum velocity over time was identified for each plane. The peak velocity of each vessel was computed as the maximum value, across all planes of the vessel, of the resampled velocity at the maximum velocity location. The 4D flow MRI data were quantified by two independent observers (observer 1 SM, 2 years of experience with MRI and observer 2 YM, 5 years of experience with MRI, under the supervision of S.S with over 10 years of experience) to assess inter-observer variability. To compare peak velocities between single-plane and multiplane approaches, the analysis plane positioned in the middle of the M1 segment was selected for comparison.¹⁴

Transcranial Doppler Ultrasound Procedure

The lower panel in Fig. 1 summarizes the TCD workflow. TCD measurements were performed bilaterally with the use of 2 MHz digital TCD transducer probes (Digi-Lite™, Rimed Ltd, New York, USA) to track the blood flow velocity in the M1 segment of MCAs at depths ranging from 38 to 64 mm. Once the MCAs were insonated, transducer probes were held in place with the LMY-3 probe fixation device (Rimed Ltd, New York, USA). A three-lead electrocardiogram was used for continuous heart rate monitoring (Finapres®NOVA, Finapres Medical Systems BV, Enschede, the

Netherlands). The recordings were taken continuously for 10 minutes while participants were seated in an upright position with their eyes open. Doppler waveforms were digitized at 500 Hz, displayed simultaneously with the electrocardiogram signal (Windaq, DataQ Instruments, Ohio, USA), and saved for offline analysis. For each participant, resting cardiac intervals were identified as the interval between two consecutive RR peaks on the time-synchronized electrocardiogram recordings. After visual inspection of the waveforms for artifacts, peak cerebral blood flow velocity within each cardiac interval was calculated as the maximum flow velocity within that interval, separately for each side. Subsequently, resting peak cerebral blood flow velocity for each MCA was calculated as the average of all peak velocities across all cardiac intervals. All TCD data quality control and postprocessing were performed by A.L.M. under the supervision of C.O.T. All calculations were performed using custom functions written in MATLAB (MathWorks, Natick, MA).

Statistical Analysis

Interobserver agreement for MRI measurements was assessed by calculating the intraclass correlation coefficient for absolute agreement, calculating the coefficient of variance between the two observers using the root mean square method as: $CV = 100 \times \sqrt{\frac{(d/m)^2}{2n}}$,³¹ (where CV is the coefficient of variance, d is the difference between measurements, and m is the mean of measurements) and calculating the bias (mean difference between the observers) and limits of agreement (bias \pm 2 standard deviation of bias) using the Bland and Altman approach.³² Peak velocity values derived from TCD and MRI were compared by assessing the mean difference between TCD and 4D flow MRI values using paired sample t -testing, calculating the

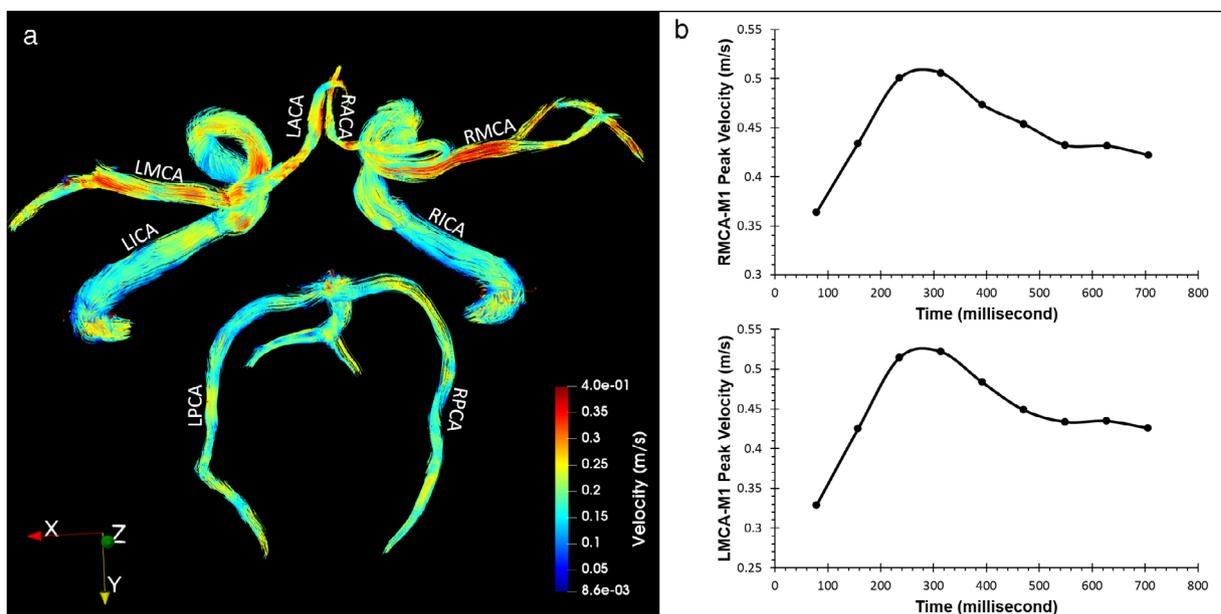


FIGURE 2: Example of intracranial flow analysis from dual-venic 4D flow MRI in a representative participant. (a) 3D visualization of time-resolved arterial blood flow during early systole ($t = 39.2$ msec) in the circle of Willis (color coded by velocity magnitude from red to blue). (b) Peak velocity values over one cardiac cycle for the M1 segment of middle cerebral arteries. Peak velocity values represent the median over the M1 segment of the middle cerebral artery for several analysis planes with 1 mm distance for this representative participant. MCA = middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery; ICA = internal carotid artery.

coefficient of variance, and plotting results in a Bland–Altman graph. A P value < 0.05 was defined as statistically significant. All analyses were performed using the SPSS statistical package (IBM SPSS Statistics, version 25).

Results

Dual-Venc 4D Flow MRI Interobserver Agreement

A representative intracranial flow quantification from dual-venc 4D flow MRI is shown in Fig. 2, demonstrating typical flow velocity-time curves and the damping effect of flow curves over the cardiac cycle in one participant. Results of the interobserver agreement for assessment of peak velocity in the M1 segment of MCA from dual-venc 4D flow MRI are presented in Table 2. The intraclass correlation coefficient for the left and right MCA was 0.97 and 0.96, respectively. The coefficient of variance between observers was 6% for the left MCA and 5% for the right MCA, indicating excellent

agreement between the two observers. Bland–Altman analyses showed a bias of 0.02 m/sec (limits of agreement = 0.11, –0.06 m/sec) and –0.02 m/sec (limits of agreement = 0.07, –0.10 m/sec) for the left and right MCA, respectively (Fig. 3).

Dual-Venc 4D Flow MRI vs. TCD in Assessing Intracranial Flow Velocity

Results of analyses comparing peak velocity quantification in the M1 segment of MCA from TCD and dual-venc 4D flow MRI are presented in Table 3. The peak velocity values obtained from TCD in the left and right MCAs were significantly higher than those obtained from dual-venc 4D flow MRI (Table 3). Dual-venc 4D flow MRI underestimated MCA peak velocity compared to TCD by 17% in the left MCA and 20% in the right MCA. Bland–Altman analysis of dual-venc 4D flow MRI compared with TCD for the left

TABLE 2. Interobserver Agreement of MCA Peak Velocity as Measured by Dual-venc 4D Flow MRI

	LMCA	RMCA
Observer 1 mean (±SD), m/sec	0.65 (0.16)	0.62 (0.12)
Observer 2 mean (±SD), m/sec	0.62 (0.15)	0.64 (0.13)
Mean difference (±SD), m/sec	0.02 (0.05)	–0.02 (0.05)
ICC, P -value	0.973	0.962
Coefficient of variance, %	6%	5%

ICC = intraclass correlation coefficient; LMCA = left middle cerebral artery; RMCA = right middle cerebral artery.

TABLE 3. Comparison Between TCD and Dual-venc 4D Flow MRI in Measurement of MCA Peak Velocity

	LMCA	RMCA
TCD mean (±SD), m/sec	0.76 (0.16)	0.77 (0.13)
4D flow MRI mean (±SD), m/sec	0.64 (0.15)	0.61 (0.12)
Mean difference TCD – MRI (±SD), m/sec	0.13 (0.24)	0.15 (0.16)
Coefficient of variance, %	26%	22%

4D flow MRI results are from the observer 1. LMCA = left middle cerebral artery; RMCA = right middle cerebral artery.

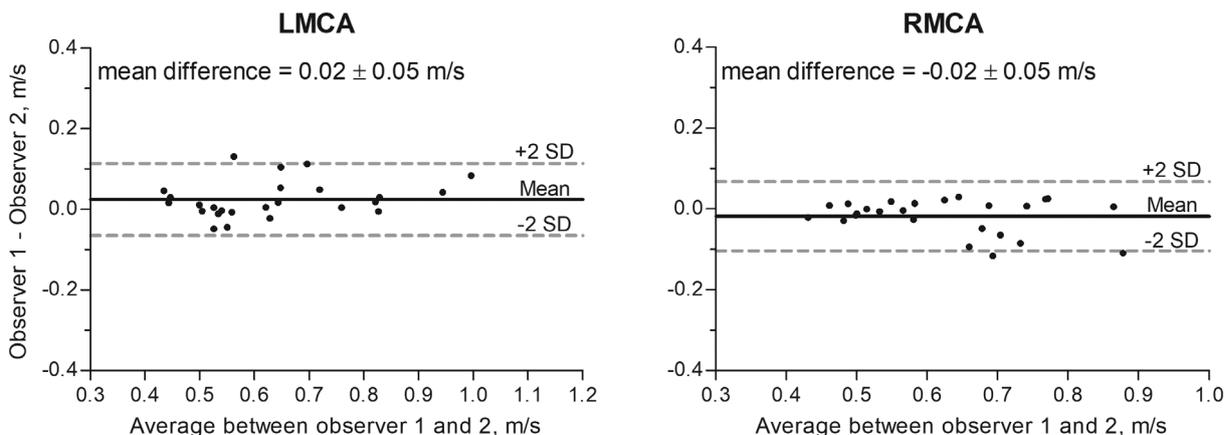


FIGURE 3: Bland–Altman plots for inter-observer agreement of MCA-M1 peak velocity by dual-venc 4D flow MRI. LMCA = left middle cerebral artery; RMCA = right middle cerebral artery.

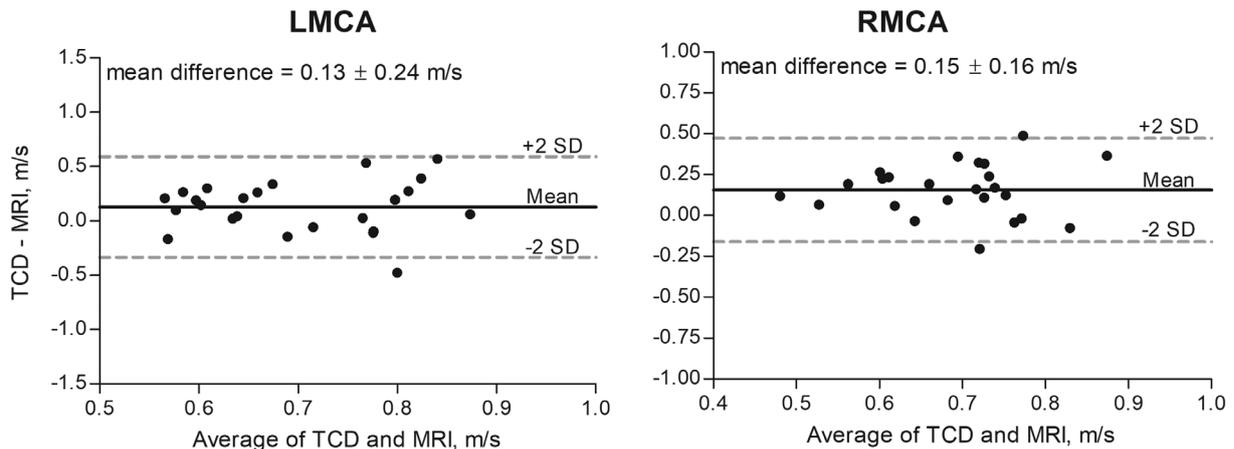


FIGURE 4: Bland–Altman plots of dual-venic 4D flow MRI compared with TCD for MCA-M1 peak velocity measurement. TCD = transcranial Doppler ultrasound; LMCA = left middle cerebral artery; RMCA = right middle cerebral artery.

MCA showed a bias of 0.13 m/sec and limits of agreement of 0.50 and -0.33 m/sec. Similarly, Bland–Altman analysis of 4D flow MRI compared with TCD for the right MCA showed a bias of 0.15 m/sec and limits of agreement of 0.47, -0.17 m/sec (Fig. 4). The underestimation of dual-venic 4D flow MRI measurements compared with TCD was observed in 18 individuals for the left MCA (75% of participants) and 19 individuals for the right MCA (79% of participants) in Bland–Altman plots. The coefficient of variance between dual-venic 4D flow MRI and TCD values were 26% for the left MCA and 22% for the right MCA (Table 3).

When using only a single analysis plane to quantify MCA peak velocity from dual-venic 4D flow MRI, we observed an underestimation of 28% in the left MCA and 29% in the right MCA compared to TCD measures (Table S1 in the Supplementary material). The coefficient of variance between dual-venic 4D flow MRI using a single-plane approach and TCD were 32% for the left MCA and 29% for the right MCA (Table S1 in the Supplementary material). Bland–Altman analysis showed a bias of 0.21 m/sec (limits of agreement = 0.66 and -0.25 m/sec), and 0.15 m/sec (limits of agreement = 0.47 and -0.17 m/sec) for the left and right MCA, respectively (Fig. S1 in the Supplementary material).

Discussion

Our results showed excellent interobserver agreement for measurement of intracranial flow velocity using dual-venic 4D flow MRI and demonstrated the feasibility of dual-venic 4D flow MRI for quantitative assessment of intracranial hemodynamics. Our results also showed a moderate agreement between MCA peak velocity measurements obtained via dual-venic 4D flow MRI and TCD, where the former significantly underestimated peak velocity compared to the latter by $\leq 20\%$.

4D flow MRI has previously been used to quantify three-dimensional blood flow properties within the cerebral

vessels of healthy volunteers and patients.^{14–24} In this work, we extended previous results and showed the strengths of accelerated dual-venic 4D flow MRI for quantification of flow velocity within the major arteries of CoW. In particular, our results not only demonstrate the feasibility and excellent interobserver agreement of intracranial dual-venic 4D flow MRI but also its moderate agreement with TCD ($\leq 20\%$ underestimation) flow velocities, a well-established tool to assess cerebral hemodynamics. This is important to note because assessments via 4D flow MRI go beyond those made by TCD. 4D flow MRI provides a three-dimensional view, with high reproducibility, and a unique ability in visualization of spatio-temporal evolution of blood flow within the CoW¹¹ as well as quantification of numerous additional parameters beyond flow velocity.^{11,25,33} While TCD has been a standard clinical tool owing to its simplicity and low cost, it is not without its limitations.³⁴ However, the moderate agreement between measurements obtained by TCD and 4D flow MRI re-affirms the utility of TCD for assessment of cerebral blood flow patterns in the major arteries of CoW. Given the complementary value of TCD and 4D flow MRI for assessment of cerebrovascular hemodynamics, future work should expand on our findings to assess the value of these two approaches in multimodal imaging applications that can be used in both clinical and research settings.

Our results show that dual-venic 4D flow MRI may underestimate peak velocity in the M1 segment of MCA compared to TCD. This difference may be attributed to TCD being restricted by insonation angles and anatomic windows, which, in turn, may hamper estimation of true flow velocity values by TCD.²⁶ The lower temporal resolution of 4D flow MRI (77–78.4 msec compared to 40 msec for TCD) may have also contributed to lower peak velocities compared to TCD. Systolic upstroke in blood pressure (thus, perfusion) and the subsequent rise in cerebral blood flow is fast, and flow reaches maximum rate in about 100–140 msec

followed by a steady decline.^{35,36} Consequently, the lower temporal resolution of 4D flow MRI may result in underestimating the true peak. Our results are consistent with prior studies that compared peak velocity or mean velocity obtained from 4D flow MRI and TCD in intracranial or carotid arteries.^{16,18,26,27} However, these prior studies used only one analysis plane or slab per vessel to analyze 4D flow MRI and hence did not fully cover the entire volume of the vessel. In contrast, our approach relies on multiple planes along each vessel of interest (mean of 20 ± 6 analyses planes over the M1 segment), providing a comprehensive analysis approach and potentially more robust estimates. Furthermore, previous work has shown a 30%–40% underestimation of intracranial velocity by 4D flow MRI compared to TCD,^{16,18,27,37} while we observed an underestimation of approximately 20% by 4D flow MRI compared to TCD. This may be because our multiplane analysis approach better reflects the measurements obtained from TCD as it is usually challenging to determine which analysis plane/slab on MRI best corresponds to TCD measurements. In support of this, our results showed around 30% underestimation of peak velocity from dual-venic 4D flow MRI compared to TCD when using only a single analyses plane. This 30% underestimation is similar to previous work that also used a single-analysis plane, further supporting the premise that a multiplane approach, that takes full advantage of the three-dimensional nature of the 4D flow MRI data, is superior to a single-plane approach in detecting MCA peak velocity from 4D flow MRI. Finally, the use of the dual-venic approach in our study allowed capturing a wide dynamic range of velocities with a more favorable velocity-to-noise ratio, while previous work focused on a single-venic approach.^{16,18,26,27,37} While peak velocity is not expected to be significantly different between dual-venic and single-venic techniques,²⁵ the dual-venic approach is helpful in situations where a wide or unknown velocity range is present (such as intracranial atherosclerosis), or when both fast arterial and slow venous flows are of interest (eg arteriovenous malformations).^{11,25} Given comparison between dual-venic and single-venic approaches was not within the scope of our study, future work should attempt to directly compare intracranial flow measures between these two techniques and also in the context of various pathologies.

Limitations

A major limitation is the fact that we were not able to acquire MRI and TCD recordings simultaneously, and instead, relied on sequential data acquired up to 30 months apart. However, in our population (healthy volunteers) and under similar conditions (supine rest) major hemodynamic variations are not expected. In fact, it has been shown that there are only small, nonsignificant variations in intracranial velocity measurements using TCD for short-term repeated measurements.^{38,39} Other

studies have also noted only a slow age-dependent decline in cerebral peak velocity after the age of 40 using both TCD and 4D flow MRI techniques.^{14,40} Nonetheless, our results should be validated in future studies by simultaneously acquiring TCD and 4D flow measures to minimize the chance of physiological perturbations or random error. Furthermore, given the scope of our study was to compare 4D flow MRI and TCD in a potential clinical setting, a consistent spatiotemporal resolution was applied in the acquisition of 4D flow MRI. Future studies with a controlled pulsatile flow phantom setup could help address the effect of variability in spatiotemporal resolution. Another limitation is the focus on MCA rather than all vessels in the CoW. This is due to the inherent low spatial resolution of TCD; we relied on MCA as it is the largest vascular territory in the brain and easily accessible with TCD. However, this highlights the need for future work to validate the utility of 4D flow MRI for assessing cerebral blood flow in other vascular territories. It should also be noted that identification of vessel centerlines and segmentation of cross-sectional planes by 4D flow MRI is operator-dependent. This was mitigated by careful plane-by-plane review by two independent operators, and we showed excellent interobserver agreement in analyses of 4D flow MRI data. However, implementation of a more automated analysis pipeline for 4D flow MRI data is warranted in future studies. Other limitations of this study to consider include a small sample size, long acquisition time for dual-venic 4D flow MRI, and inclusion of only healthy volunteers.

Conclusion

Our study provides a quantitative assessment of dual-venic 4D flow MRI for measurement of intracranial hemodynamics and shows a moderate agreement between TCD and dual-venic 4D flow MRI peak velocity measurements in the middle cerebral artery of healthy subjects. These results support the utility of dual-venic 4D flow MRI for reproducible comprehensive flow assessment of the cerebral arteries.

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Conflict of interest

COT served as a data science consultant to Lokavant Inc and received consultant fees.

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