The Effect of Extracranial-to-Intracranial Bypass on Cerebral Vasoreactivity: A 4D Flow MRI Pilot Study

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ABSTRACT

BACKGROUND AND PURPOSE: **Extracranial-to-intracranial (EC-IC) surgical bypass improves cerebral blood flow (CBF) and cerebrovascular vasoreactivity (CVR) for patients with carotid occlusion. Bypass graft patency and contribution of the graft to the postoperative increase in CVR are challenging to assess.**
To assess the effectiveness of 4D flow magnetic resonance imaging (MRI) to evaluate bypass graft patency and flow augmentation through the superficial temporal artery (STA) before and after EC-IC bypass.

METHODS: **Three consecutive patients undergoing EC-IC bypass for carotid occlusion were evaluated pre- and postoperatively using CVR testing with pre- and poststimulus 4D flow-MRI for assessment of the bypass graft and intracranial vasculature.**

RESULTS: **Preoperatively, 2 patients (patients 1 and 3) did not augment flow through either native STA. The third, who had evidence of extensive native EC-IC collateralization on digital subtraction angiography (DSA), did augment flow through the STA preoperatively (CVR = 1). Postoperatively, all patients demonstrated CVR > 1 on the side of bypass. The patient who had CVR > 1 preoperatively demonstrated the greatest increase in resting postoperative graft flow (from 40 to 130 mL/minute), but the smallest CVR, with a poststimulus graft flow of 160 mL/minute (CVR = 1.2). The 2 patients who did not demonstrate augmentation of graft flow preoperatively augmented postoperatively from 10 to 20 mL/minute (CVR = 2.0) and 10-80 mL/minute (CVR = 8.0), respectively. Intracranial flow was simultaneously interrogated. Two patients demonstrated mild reductions in resting flow velocities in all interrogated vessels immediately following bypass. The patient who underwent CVR testing on postoperative day 48 demonstrated a stable or increased flow rate in most intracranial vessels.**

CONCLUSION: **Four-dimensional flow MRI allows for noninvasive, simultaneous interrogation of the intra- and extracranial arterial vasculature during CVR testing, and reveals unique paradigms in cerebrovascular physiology. Observing these flow patterns may aid in improved patient selection and more detailed postoperative evaluation for patients undergoing EC-IC bypass.**

Keywords: 4D flow MRI, cerebrovascular vasoreactivity, extracranial to intracranial bypass.

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Introduction

Extracranial-to-intracranial (EC-IC) surgical bypass for carotid occlusion is indicated for carefully selected patients with decreased cerebrovascular reserve and refractory symptoms despite maximal medical therapy.[1] By improving cerebral blood flow (CBF) both at rest and providing additional cerebrovascular reserve in states of tissue demand, bypass has been shown to reduce further ischemic events, reverse vascular "steal" phenomenon, and improve long-term neurocognitive function in this patient population.[2-5]

Cerebrovascular vasoreactivity (CVR) testing estimates the compensatory capacity of the arterial system by observing changes in CBF in response to a vasoactive stimulus. CVR is impaired in patients with obliterative arteriopathy.[6] It has been previously demonstrated that surgical bypass leads to improved CVR in both the affected and unaffected hemispheres.[7,8]

After bypass surgery, patency of the graft and its contribution to CBF are typically evaluated with digital subtraction angiography (DSA). While noninvasive imaging techniques such as computed tomography angiography (CTA) and time of flight MR angiography (TOF-MRA) can suggest graft patency, CTA is dependent on bolus timing, and TOF-MRA is prone to artifact and signal loss, which can lead to an overestimation of stenosis, particularly in small caliber vessels. In addition, neither CTA nor TOF-MRA provides quantitative data regarding blood flow.[9]

Two-dimensional phase contrast magnetic resonance imaging (2D PC-MRI) is an alternate method for noninvasive measurement of intracranial blood flow. Two-dimensional PC-MRI

is an imaging technique whereby a bipolar magnetic gradient is established, and flowing blood moving in the same direction as the gradient develops a phase shift proportional to the flow velocity, allowing for quantification of blood velocity and flow. Two-dimensional PC-MRI provides accurate and reproducible blood flow measurements, but is limited by velocity encoding in a single flow direction and 2D anatomic coverage, restricting the assessment of vasculature to parallel vessels in a single plane.[10] In the case of an often tortuous bypass graft, restricting flow quantification to a single direction can result in quantification errors. In addition, 2D PC MRI remains limited to one plane per acquisition, such that the assessment of multiple vessels during CVR testing yields impractically long imaging sessions.

More recently, time-resolved PC-MRI with velocity encoding along all three flow directions and three-dimensional anatomic coverage has been developed (termed four-dimensional [4D] flow-MRI), allowing for the quantitative evaluation of complex blood flow patterns through multiple vessels simultaneously: a measure not easily obtained with 2D PC-MRI. Four-dimensional flow-MRI has been used to accurately measure intracranial arterial flow, even in the case of hemodynamically significant stenosis.[11] Whether this technique can be extended to interrogate EC-IC bypass graft flow and vasoreactivity is unknown.

The imaging assessment after bypass requires both the assessment of flow through the graft (patency) as well the graft's functional significance toward downstream brain and vasoregulatory capacity. The purpose of this pilot study was to evaluate the feasibility of assessing EC-IC bypass graft patency and vasoreactivity with 4D flow-MRI. Simultaneously, CVR throughout the major intracranial vasculature was quantified.

Methods

This retrospective pilot study was approved by the Institutional Review Board of our institution. Three consecutive patients who underwent EC-IC bypass for symptomatic multifocal obliterative arteriopathy (moyamoya disease) were included. All patients underwent pre- and postoperative multimodal MRI with CVR testing, including pre- and poststimulus 4D flow-MRI for assessment of the bypass graft. Two patients received their postoperative imaging exam 3 days following surgery, and another patient did not receive their exam until postoperative day 48.

Surgical Approach

All patients underwent direct superficial temporal artery (STA) to middle cerebral artery (MCA) bypass, anastomosing the parietal branch of the STA to an M4 division of the MCA. Intraoperatively, the STA course was mapped using a Doppler flow probe and dissected under the microscope. The STA was left in continuity, while a frontotemporal craniotomy was performed and a recipient MCA vessel was identified. The STA and M4 vessels were then temporarily clipped and anastomosed using a microsurgical technique. Graft patency was confirmed intraoperatively with indocyanine green angiography and Doppler ultrasound. Somatosensory and motor-evoked potential monitoring was performed throughout the procedure. Electroencephalography (EEG) was performed and burst suppression of the EEG signal was obtained during the anastomosis. Systolic blood pressure was elevated approximately 10 to 20 mm Hg above the patient's baseline during the anastomosis.

Cerebrovascular Reactivity Testing

To measure CVR, 4D PC sequences were performed before and after administration of intravenous acetazolamide. Through its inhibition of carbonic anhydrase, acetazolamide lowers blood pH, leading to a predictable increase in CBF in normal healthy adults.[6] Acetazolamide of 15 mg/kg was administered intravenously over 5 minutes, and flow imaging sequences were repeated.

Imaging Protocol

All imaging was performed on a 3T MR machine from a single vendor (Discovery 750, GE Healthcare, Waukesha, WI, USA). Four-dimensional flow imaging was acquired using a field centered on the circle of Willis to include the surgical anastomosis (or projected site of anastomosis, in the case of preoperative imaging). The contralateral STA was included in the field of view. Acquisition parameters included repetition time: 4.9-5.1 milliseconds, echo time: 2 milliseconds, slice thickness 1 mm, velocity encoding (VENC): 100 cm/second, number of averages = 4, flip angle = 12 degrees, spatial resolution = 1 mm. The sequence uses kat-ARC-acceleration with an undersampling factor of 8. While *k-t* acceleration methods have the potential to induce quantitative errors in velocity due to blurring in the temporal and spatial domains, prior work has shown that modern sequences with even higher undersampling factors can accurately capture the hemodynamics of the principal intracranial vasculature.[12] Additional imaging parameters, including spatial resolution, were chosen to accurately capture hemodynamics while avoiding partial volume effects, and were based on prior work in 4D flow intracranial imaging.[13,14] Postprocessing and flow analysis was performed using Arterys (Arterys Inc. [CardioAI Software], 2019). Regions of interest were selected by a neuroradiologist (AC). Preoperative STA measurements were performed at the proximal portion of the parietal branch of the STA.

To validate and corroborate 4D flow measurements, 2D PC imaging was also performed, comparing flow through the vertebral artery as an internal control. The PC scan was acquired

Table 1. Patient Characteristics

Subject	Age	Sex	Postoperative Exam Occurred # of Days after Bypass	Side of Bypass	Diagnosis	Angiographic Finding
1	50	F	48	Right	Moyamoya	MCA occlusion
2	45	F	3	Right	Moyamoya	ICA, MCA occlusion, extensive EC-IC collateralization
3	47	F	3	Left	Moyamoya	MCA occlusion

F = female; MCA = middle cerebral artery; ICA = internal carotid artery; EC-IC = external carotid artery to internal carotid artery.

with the following acquisition parameters: repetition time: 15 milliseconds, pixel size: .8 × .8 mm^2, VENC: 100 cm/second, echo time 4.276 seconds, slice thickness 4 mm, number of averages = 1, scan time = 5 minutes 56 seconds.

Results

Patient characteristics are summarized in Table 1. All 3 patients were female. Patient age ranged from 45 to 50. All patients underwent surgical anastomosis of the parietal branch of the STA to an M4 branch of the MCA. In 1 patient (Subject 1), the postoperative exam was performed 48 days following bypass. In the other 2 patients, the postoperative exam was performed 3 days following bypass. Two-dimensional PC imaging through the vertebral arteries demonstrated flow velocities concordant to 4D imaging.

STA flow measurements during CVR testing at pre- and postoperative time points are summarized in Figure 1. Preoperatively, 2 patients (patients 1 and 3) did not augment flow through either native STA, with flow remaining at 10 and 20 mL/minute on the eventually bypassed side (CVR = 1.0) and 20 and 30 mL/minute on the nonbypassed side, respectively (CVR = 1.0). One patient (patient 2) augmented flow in both STA preoperatively, from 40 to 70 mL/minute (CVR = 1.8) on the eventually bypassed side and 40 to 50 mL/minute (CVR 1.3) on the nonbypassed side.

Postoperatively, all patients demonstrated CVR > 1 on the side of bypass. The patient who had CVR > 1 preoperatively demonstrated the greatest increase in resting postoperative graft flow (from 40 to 130 mL/minute), but the smallest CVR, with a poststimulus flow of 160 mL/minute (CVR = 1.2). The 2 patients who did not demonstrate augmentation of graft flow preoperatively augmented postoperatively from 10 to 20 mL/minute (CVR = 2.0) and 10 to 80 mL/minute (CVR = 8.0), respectively. In addition, the nonbypassed STA demonstrated CVR < 1 in 2 patients, and flow <5 mL/minute in 1 patient.

Intracranial flow results are summarized in Table 2. Negative values are indicative of retrograde flow. Two patients demonstrated mild reductions in resting flow velocities in all interrogated vessels immediately following bypass. The patient who underwent CVR testing on postoperative day 48 demonstrated a stable or increased flow rate in most intracranial vessels (Table 2).

Discussion

Four-dimensional flow MRI allows for noninvasive detection of patency and quantification of flow through a bypass graft as well as simultaneous interrogation of the global flow profile within the intracranial vasculature (Figures 2 & 3). The assessment of graft patency and flow traditionally has relied on conventional angiography and intraoperative Doppler ultrasound, respectively.

We have presented 3 patients who underwent STA-MCA bypass for whom 4D flow PC imaging was able to detect a contribution to CBF from the bypass graft both at rest and in response to acetazolamide, a vasoactive stimulus. Our preliminary results indicate that 4D flow MRI is a feasible, noninvasive alternative for evaluating EC-IC bypass grafts in the early postoperative period.

It is notable that for 2 of our patients, prior to bypass, the STA did not augment flow in response to acetazolamide.

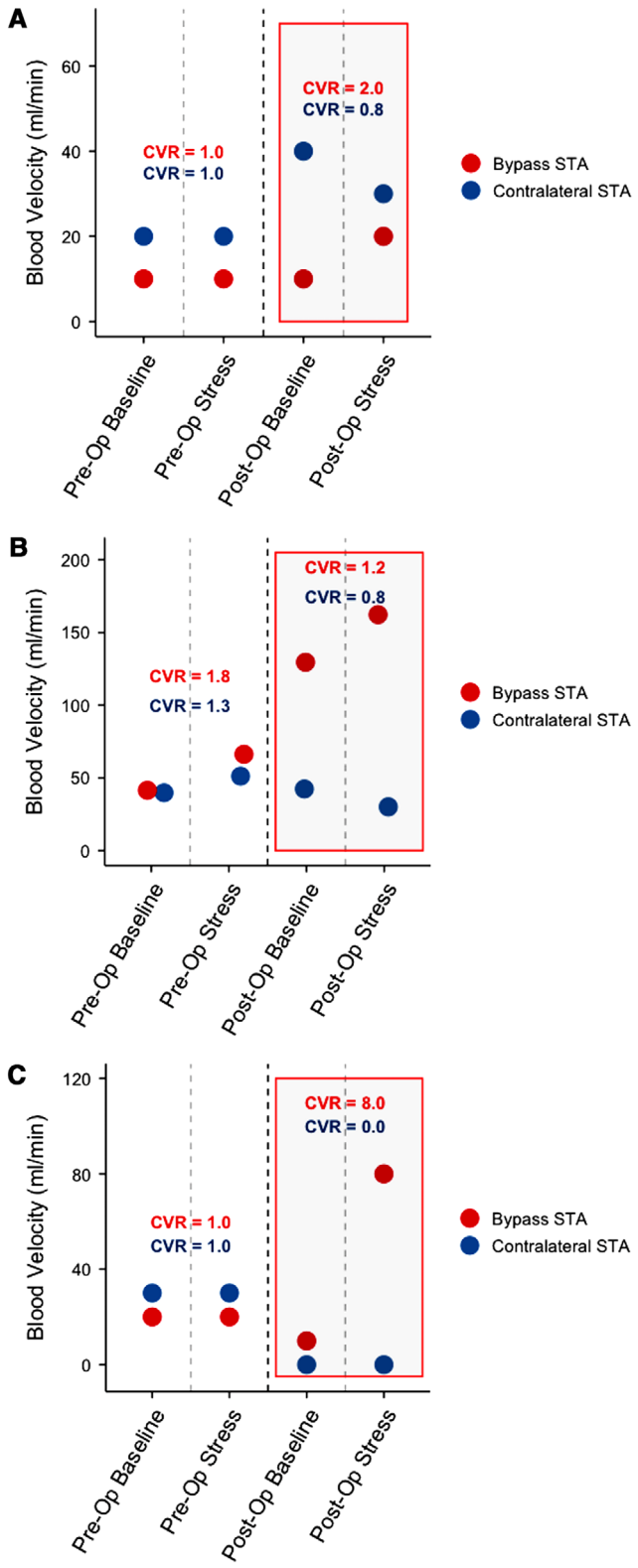

Fig 1. 4D velocity measurements of the left and right superficial temporal artery pre- and postbypass in patients 1-3 (A-C). In two-third patients, the velocity in the nonbypassed superficial temporal artery decreased after acetazolamide challenge, whereas the bypass graft showed augmented flow in all 3 patients. The fractional increase in velocity (cerebral vasoreactivity) was 2.0, 1.2, and 8.0 for patients 1-3, respectively. STA = superficial temporal artery; Op = Operative.

Table 2. Intracranial Flow: Flow Measurements for Intracranial Vasculature Pre- and Postbypass

	1				2				3			
	Preop Pre (mL/minute)	Preop Post (mL/minute)	Postop Pre (mL/minute)	Postop Post (mL/minute)	Preop Pre (mL/minute)	Preop Post (mL/minute)	Postop Pre (mL/minute)	Postop Post (mL/minute)	Preop Pre (mL/minute)	Preop Post (mL/minute)	Postop Pre (mL/minute)	Postop Post (mL/minute)
L Cav ICA	160	230	150	190	220	170	150	150	240	380	260	490
L M1	90	130	80	180	140	130	90	120	140	380	-30	260
L M2	-	-	-	-	40	50	30	70	-	-	-	-
L A1	.	30	10	40	90	70	40	80	30	90	0	30
L A2	-	-	-	-	40	40	20	60	-	-	-	-
L Pcomm	10	50	40	10	40	30	20	10	30	80	-10	60
L P2	110	200	130	330	50	70	30	50	50	90	10	90
L OA	10	40	40	60	-90	-130	-90	-60	-	-	-	30
L MMA	20	10	20	30	70	90	60	70	-	-	-	-
Basilar	240	370	250	410	130	90	50	130	80	140	80	160
R Cav ICA	170	320	130	250	180	170	90	130	150	290	150	310
R M1	90	150	70	110	-	-	-	-	90	170	40	70
R M2	-	-	-	-	-	-	-	-	40	60	10	50
R A1	20	50	30	60	90	100	40	50	30	70	10	50
R A2	-	-	-	-	-	-	-	-	-	-	-	-
R Pcomm	50	80	50	130	60	60	30	50	40	160	10	80
R P2	90	190	90	210	30	30	10	40	50	120	40	50
R OA	10	10	40	20	-100	-110	-50	-90	-	-	10	20
R MMA	20	30	10	10	80	120	30	50	-	-	-	-

Preop = preoperative; Postop = postoperative; Cav ICA = cavernous internal carotid artery; M1 = M1 segment of the middle cerebral artery; M2 = M2 segment of the middle cerebral artery; A1 = A1 segment of the anterior cerebral artery; A2 = A2 segment of the anterior cerebral artery; Pcomm = posterior communicating artery; P2 = P2 segment of the posterior cerebral artery; OA = ophthalmic artery; MMA = middle meningeal artery; L = Left; R = Right.

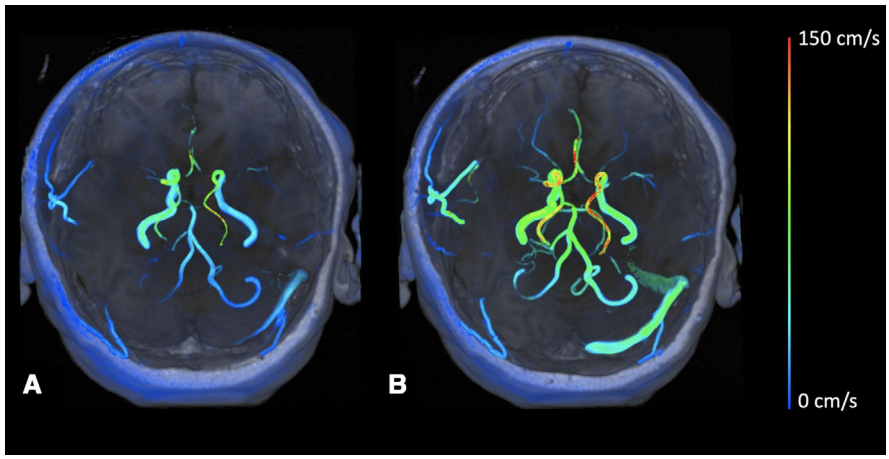

Fig 2. Maximum intensity 3D projection of whole brain 4D flow velocity data before (A) and after (B) acetazolamide administration demonstrating simultaneous augmentation of flow velocities through the bypass graft and intracranial vasculature.

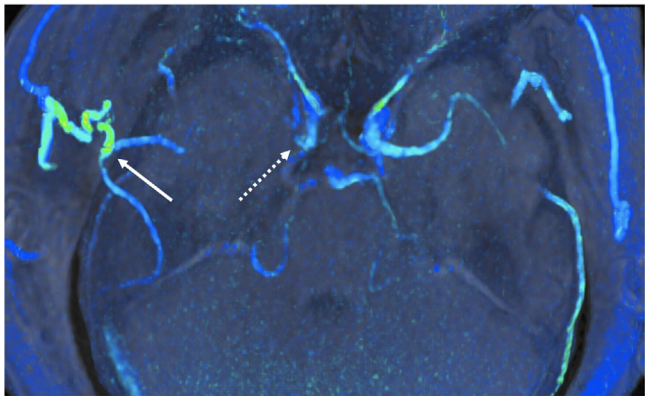

Fig 3. Axial slice through 4D flow acquisition postsuperficial temporal artery to middle cerebral artery bypass (arrow). This patient had predominantly right-sided arteriopathy, with critical occlusion of the right supraclinoid internal carotid artery (dashed arrow).

However, after bypass surgery, the STA graft showed flow augmentation in all three cases (CVR > 1), the expected pattern in a vessel that supplies cerebral tissue and prior literature has assumed to be responsible for improvements in brain CVR.[8] In contrast, the contralateral (nonbypassed) STA showed a reduction in CVR after surgery in all cases, including paradoxical reactivity ("steal phenomenon," CVR < 1) in 2/3. The patient with CVR > 1 in the STA prebypass (subject 2) had the most severe disease preoperatively, with angiography demonstrating multifocal occlusive arteriopathy and extensive ECA to ICA collateralization. The 2 patients who did not augment flow through the STA preoperatively demonstrated predominantly lenticulostriate and/or posterior circulation collateralization without significant contribution from the ECA. In this respect, the observation of STA flow augmentation preoperatively via 4D flow imaging correlates with the presence of ECA-ICA collateralization seen on catheter angiography.

Intracranial flow data illustrate shifting flow patterns throughout both hemispheres of the brain after bypass. The 2 patients who received imaging in the immediate postoperative period (postoperative day 3) demonstrated mild reductions in resting flow velocities immediately following bypass. The patient who underwent CVR testing on postoperative day 48 demonstrated a stable or increased flow rate in most intracranial vessels (Table 2). This pattern is in keeping with widely reported observations of adverse neurologic events in the immediate postoperative period, owing to the sudden local increase in blood flow to an otherwise chronically ischemic brain, which leads to derangements in regional CBF.[15,16]

CVR has been extensively studied at the level of parenchymal perfusion using CT, MRI, and nuclear medicine-based techniques including CT perfusion, blood oxygenation-level-dependent MRI (BOLD), arterial spin labeling (ASL) MRI, and Xenon-enhanced CT (XeCT); however, there has been a relative paucity of the literature devoted to evaluating the regional changes in blood flow within the intracranial arterial vasculature before and after STA-MCA bypass.

To our knowledge, this is the first time that surgically acquired CVR within an STA-MCA bypass has been demonstrated with 4D flow. Amin-Hanjani et al demonstrated the ability to assess graft patency and quantitate flow using 2D PC MRI.[17] While feasible, 2D PC MRI is limited by the plane of section prescribed at the scanner and flow measurements are limited to vessels orthogonal to that plane. Four-dimensional flow allows for acquisition of an imaging "slab" and therefore captures flow data throughout the entirety of the region of interest. This is of particular value in CVR testing, as having to scan each vessel plane after the administration of acetazolamide may result in nonstandardized temporal stimulation. Other authors have investigated the utility of 4D flow MRI to characterize EC-IC bypass. Sekine et al evaluated postbypass patients using a combination of 4D flow, CTA, and TOF-MRA.[18] Their work importantly characterized the limitations of 4D flow to evaluate small arteries (<2.4 mm in their study) and illustrated the feasibility of the technique in this patient population. In addition, Orita et al continued to expand the scope of 4D flow in EC-IC bypass by characterizing the hemodynamic changes that occurred after bypass, by measuring both preoperative and postoperative flow measurements in bypass patients who also underwent ICA ligation.[19] Using 4D flow, they were able to quantify the degree to which the bypass graft could compensate for the sacrificed ICA in these patients. Our work adds to the existing body of literature regarding the quantification of EC-IC bypass hemodynamics by utilizing CVR testing before and after bypass, to not only demonstrate the changes

in the resting CBF blood flow in this patient population, but to also illustrate the graft's contribution to cerebrovascular reserve.

This cross-sectional, retrospective, pilot study has several limitations, most notably the small sample size and uniform patient characteristics. In addition, the postprocessing software limited the smallest unit of flow measurement to 10 mL/minute, and therefore, flows less than 5 mL/minute were not registered. In addition, our use of a single VENC precluded the detection of very slow flows. Recent work has demonstrated the utility of using dual-VENC 4D flow in intracranial flow quantification.[20] Dual VENC 4D flow increases the velocity-to-noise ratio and the measurable velocity spectrum by allowing for the simultaneous acquisition of both high- and low-velocity flows. This could be of particular utility in studying patients with obliterative arteriopathy, where involved vessels can exhibit unusually slow flows. While our study only utilized single-VENC imaging, it would be of great interest to perform 4D flow-CVR testing on scanners with dual-VENC capability in future studies.

We demonstrate the feasibility of 4D flow MRI as a robust imaging technique to evaluate patency and cerebrovascular reactivity of an STA-MCA graft following EC-IC bypass, as well as interrogate the shifting flow patterns in the intracranial vasculature. We hope that this work animates future investigations into the pattern of how graft and intracranial flow changes are reflected in clinical outcomes.

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