Comparative efficacy of autologous versus cadaveric saphenous vein grafts in cerebral revascularization surgery

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OBJECTIVE Cerebral bypasses are performed for the purpose of either flow augmentation for ischemic cerebrovascular disease or flow replacement for vessel sacrifice during complex aneurysm or tumor surgery. Saphenous vein grafts (SVGs) are commonly used interposition grafts. The authors of this study sought to compare the efficacy of autologous versus cadaveric SVGs in a large series of cerebral bypasses using interposition vein grafts with long-term angiographic follow-up.

METHODS All intracranial bypass procedures performed between 2001 and 2018 were reviewed. Demographic, clinical, angiographic, and operative data were recorded and then analyzed according to SVG type.

RESULTS A total of 308 consecutive intracranial bypasses were performed during the study period, 53 (17.2%) of which were bypasses with an interposition SVG (38 autologous, 15 cadaveric). At a median follow-up of 2.2 months (IQR 0.2–29.1), 39 (73.6%) bypasses were patent (26 [68.4%] autologous, 13 [86.7%] cadaveric, $p = 0.30$). Comparing autologous and cadaveric SVG recipients, there were no statistically significant differences in age ($p = 0.50$), sex ($p > 0.99$), history of smoking ($p = 0.75$), hypertension ($p > 0.99$), diabetes mellitus ($p = 0.13$), indication for bypass ($p = 0.27$), or SVG diameter ($p = 0.65$). While there were higher intraoperative (autologous, 100.0 ml/min, IQR 84.3–147.5; cadaveric, 80.0 ml/min, IQR 47.3–107.8; $p = 0.11$) and postoperative (autologous, 142.2 ml/min, IQR 76.8–160.8; cadaveric, 92.0 ml/min, IQR 69.2–132.2; $p = 0.42$) volumetric flow rates in the autologous SVGs compared to those in the cadaveric SVGs, the difference between the two groups did not reach statistical significance. In addition, the blood flow index, or ratio of postoperative to intraoperative blood flow, for each bypass was similar between the groups (autologous, 1.3, IQR 0.9–1.6; cadaveric, 1.5, IQR 1.0–2.3; $p = 0.37$). Kaplan-Meier estimates showed no difference in bypass patency rates over time between autologous and cadaveric SVGs ($p = 0.58$).

CONCLUSIONS Cadaveric SVGs are a reasonable interposition graft option in cerebral revascularization surgery when autologous grafts are not available.

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KEYWORDS cerebral blood flow; cerebral ischemia; extracranial-intracranial bypass; intracranial aneurysm; saphenous vein graft; vascular disorders

CEREBRAL revascularization remains an important aspect of neurovascular surgery.¹ In flow augmentation and flow replacement surgery, the use of interposition grafts is sometimes necessary when native donor vessels, such as the superficial temporal artery, are inadequate for either flow or length purposes.^{2,3} The saphenous vein and radial artery are commonly used autologous interposition grafts.^{4–6} Cadaveric, cryopreserved saphenous vein grafts (SVGs) have been used extensively in

peripheral vascular^{7–13} and cardiac surgery.^{14–18} We previously reported our preliminary experience using cadaveric SVGs in 10 cerebral revascularization cases and noted a short-term patency rate of 100%.¹⁹ However, long-term patency rates and efficacy compared to those for autologous SVGs remain unknown. In the present report, we sought to compare demographic, clinical, angiographic, and hemodynamic data from cerebral bypasses with autologous or cadaveric SVGs.

ABBREVIATIONS QMRA = quantitative phase-contrast MRA; SVG = saphenous vein graft; WSS = wall shear stress.

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Methods

Clinical Cohort

After receiving approval from the University of Illinois at Chicago Institutional Review Board, we performed a retrospective review of all intracranial bypass operations performed at the University of Illinois at Chicago between January 2001 and December 2018. Demographic, clinical, angiographic, and operative data were collected from the electronic medical record.

Patients with atherosclerotic disease were considered suitable candidates for revascularization if the following criteria were met: 1) symptomatic steno-occlusive disease affecting the anterior or posterior circulation with stroke or transient ischemic attack despite maximal medical therapy; 2) lack of medical comorbidities precluding surgery; and 3) evidence of impaired cerebrovascular hemodynamics.

Materials

ABO/Rh blood group-compatible cadaveric, cryopreserved SVGs were obtained from CryoLife Inc. Veins were harvested from single cadavers using a “no-touch” technique, kept moist with Dulbecco’s modified Eagle medium (10% bovine serum, 0.12 mg/ml papaverine), then cryopreserved and stored at -196°C in a solution of dimethyl sulfoxide.²⁰ At surgery, the graft was then thawed and diluted over 30–45 minutes prior to preparation and implantation; all patients were given 1 g of methylprednisolone intraoperatively.

Blood Flow, Vessel Diameter, and Wall Shear Stress Measurements

Intraoperative blood flow measurements were made using an ultrasonic flow probe (Charbel Micro-Flow Probe, Transonic Systems Inc.) that provides flow quantification using the principle of ultrasonic transit time to sense flow in vessels independent of the flow velocity profile, turbulence, or hematocrit.²¹ The probe is manufactured in a variety of sizes to accommodate vessel width. Postoperative vessel diameter calculations and blood flow measurements were made using quantitative phase-contrast MRA (QMRA). This technique was implemented using the commercially available noninvasive optimal vessel analysis software (NOVA, VasSol Inc.) and has been described and validated previously.^{22,23} Wall shear stress (WSS; dynes/cm²) was calculated using the Hagen-Poiseuille equation ($\text{WSS} = 32\mu Q/\pi D^3$), where μ is blood viscosity (assumed to be constant at 0.035 poise), Q is volumetric flow rate (ml/min), and D is vessel diameter (cm).²⁴

Statistical Analysis

Descriptive statistics were calculated for the demographic, clinical, angiographic, and operative factors, using the median (interquartile range) as a measure of central tendency. Comparisons of continuous variables with nonnormal distributions were made using the nonparametric Kruskal-Wallis H-test, and categorical variables were compared using the Fisher exact test or chi-square test. Kaplan-Meier estimates of bypass patency were per-

formed using the log-rank (Mantel-Cox) test. Statistical analyses were performed using JMP (version 14, SAS Institute Inc.) and Prism (version 8.0.1, GraphPad Software). Values of $p < 0.05$ were considered significant.

Results

A total of 308 consecutive intracranial bypasses were performed during the study period, 53 (17.2%) of which were bypasses with an interposition SVG (38 autologous, 15 cadaveric). Preliminary outcome data from 3 (20.0%) of the 15 cadaveric cases have been previously reported.¹⁹ Bypass procedures were performed for the purpose of either flow augmentation for steno-occlusive atherosclerotic disease (14 cases) or flow replacement during complex aneurysm (38 cases) or tumor (1 case) surgery. Between autologous and cadaveric SVG recipients, there were no statistically significant differences in age ($p = 0.50$), sex ($p > 0.99$), history of smoking ($p = 0.75$), hypertension ($p > 0.99$), diabetes mellitus ($p = 0.13$), or indication for bypass ($p = 0.27$; Table 1). There were no reported complications associated with autologous SVG harvest. There were higher intraoperative blood flow rates in autologous (32 cases, 100.0 ml/min, IQR 84.3–147.5) versus cadaveric (14 cases, 80.0 ml/min, IQR 47.3–107.8) SVGs; however, the difference between the two did not rise to the level of statistical significance ($p = 0.11$). Overall bypass patency was not associated with raw intraoperative or postoperative bypass flow rates.

Twenty-nine (55.8%) patients underwent postoperative QMRA with NOVA within 1 week of bypass (18 autologous SVGs, 11 cadaveric SVGs). As with intraoperative flow rates, there were higher postoperative flow rates in autologous (142.2 ml/min, IQR 76.8–160.8) versus cadaveric (92.0 ml/min, IQR 69.2–132.2) SVGs, but again the difference between the two groups was not significant ($p = 0.42$). The blood flow index, or ratio of postoperative to intraoperative blood flow, for each patient did not differ significantly between the groups (autologous, 1.3, IQR 0.9–1.6; cadaveric, 1.5, IQR 1.0–2.3; $p = 0.37$; Fig. 1). As calculated on postoperative QMRA with NOVA, the median diameter of autologous SVGs was 4.4 mm (IQR 3.7–4.9) compared with 4.6 mm (IQR 4.0–5.1) for cadaveric SVGs ($p = 0.65$; Fig. 2). The median WSS for autologous SVGs was 8.1 dynes/cm² (IQR 5.4–11.7) compared with 6.1 dynes/cm² (IQR 5.1–8.9) for cadaveric SVGs ($p = 0.28$; Fig. 3). The aforementioned data are summarized in Table 1.

At a median follow-up of 2.2 months (IQR 0.2–29.1), 39 (73.6%) bypasses were patent (26 [68.4%] autologous, 13 [86.7%] cadaveric, $p = 0.30$). Kaplan-Meier estimates showed no difference in bypass patency rates over time between autologous and cadaveric SVGs ($p = 0.58$; Fig. 4). Two (5.3%) patients with autologous SVGs required endovascular balloon angioplasty to maintain graft patency.

Over the course of the entire study period, relative to our institution’s overall cerebral revascularization volume, bypasses with interposition grafts were used with declining frequency: 2001–2006, 30.1%; 2007–2012, 15.6%; and 2013–2018, 5.7% (Fig. 5).

Discussion

In the present report, we demonstrated that cadaveric

TABLE 1. Demographic, clinical, angiographic, and operative characteristics

	Autologous SVG	Cadaveric SVG	p Value*
No. of cases	38	15	
Median age in yrs (IQR)	58.0 (50.0–66.3)	56.0 (48.0–62.0)	0.50
Male sex	12	5	>0.99
Smoking	13	4	0.75
Hypertension	24	10	>0.99
Diabetes mellitus	2	3	0.13
Indication			0.27
Aneurysm	28	10	
Atherosclerosis	10	4	
Tumor	0	1	
Median blood flow in ml/min (IQR), no. of cases			
Intraop	100.0 (84.3–147.5), 32	80.0 (47.3–107.8), 14	0.11
1st postop	142.2 (76.8–160.8), 18	92.0 (69.2–132.2), 11	0.42
Last postop†	94.0 (61.4–139), 17	64.0 (32.0–90.0), 3	0.17
Median blood flow index (IQR), no. of cases‡	1.3 (0.9–1.6), 15	1.5 (1.0–2.3), 10	0.37
Median SVG diameter in mm (IQR), no. of cases	4.4 (3.7–4.9), 18	4.6 (4.0–5.1), 11	0.65
Median WSS in dynes/cm ² (IQR), no. of cases	8.1 (5.4–11.7), 18	6.1 (5.1–8.9), 11	0.28
Blood flow < 40 ml/min§	6	2	0.68
Patent	26	13	0.30

* Kruskal-Wallis H-test, Fisher exact test, or chi-square test.

† If patent, the last recorded blood flow. If nonpatent, the last recorded blood flow prior to the angiographic study diagnostic of nonpatency.

‡ Ratio of first postoperative blood flow to intraoperative blood flow.

§ On intraoperative, first postoperative, or last postoperative blood flow evaluation.

SVGs perform similarly to autologous SVGs in cerebral bypasses conducted for either flow augmentation or flow replacement purposes. In our analysis of numerous clinical, angiographic, hemodynamic, and outcome parameters, we identified no significant differences between autologous and cadaveric SVGs. While there were higher intraoperative and postoperative volumetric flow rates in autologous SVGs and higher patency rates in cadaveric SVGs, these differences did not rise to the level of statistical significance.

The central concern with regard to the use of cadaveric interposition grafts for revascularization procedures is the observation of reduced long-term (i.e., beyond 1 year) patency rates compared to those with autologous grafts in cardiac and peripheral vascular procedures.^{7–18} For instance, Sellke et al. compared patency rates following coronary artery bypass surgery with cadaveric SVGs in 10 patients and with autologous internal mammary artery (IMA) grafts in 7 patients.¹⁶ While 7 (100%) of the IMA grafts were patent at a follow-up range of 2–18 months after surgery, only 6 (60.0%) of the cadaveric SVGs were patent at 1–8 weeks' follow-up and none were patent at 6–30 months' follow-up, even though all had been patent at the time of surgery. Similarly, following 80 procedures for lower-extremity ischemia in 76 patients, Harris et al. found that 36.8% of cadaveric SVGs were patent at 1 year, whereas only 23.6% were patent at 3 years.¹² Our preliminary report on the use of cadaveric SVGs in cerebral revascularization surgery noted a 100% short-term graft patency rate.¹⁹ In the present analysis, at a median follow-

up of 2.2 months (IQR 0.2–29.1), 13 (86.7%) of 15 cadaveric SVGs were patent compared with 26 (68.4%) of 38 autologous SVGs ($p = 0.30$), and Kaplan-Meier estimates showed no difference in the bypass patency rate over time between SVG types ($p = 0.58$). In addition, of the 13 cadaveric SVGs patent beyond the 1st postoperative day, 13 (100%) were patent at the last follow-up.

Commonly used interposition graft options for cerebral bypasses include SVGs and radial artery grafts, although use of the cephalic vein,²⁵ internal maxillary artery,^{26,27}

FIG. 1. Individual blood flow index values for 15 autologous (median 1.3, IQR 0.9–1.6) and 10 cadaveric (median 1.5, IQR 1.0–2.3) SVGs ($p = 0.37$).

FIG. 2. Individual graft diameter values for 18 autologous (median 4.4, IQR 3.7–4.9) and 11 cadaveric (median 4.6, IQR 4.0–5.1) SVGs ($p = 0.65$).

and descending branch of the lateral circumflex femoral artery²⁸ has been reported as well. While complications and morbidity associated with saphenous vein²⁹ or radial artery³⁰ harvest are generally low, these autologous options are sometimes unavailable because of prior harvest or are unsuitable for bypass because of poor quality due to a small size, inherent atherosclerotic disease, or trauma from line insertion. The use of cadaveric SVGs allows selection of a graft of a desired length and diameter and avoids the need for a potentially long extremity incision. The disadvantages of using cadaveric, cryopreserved grafts include lack of immediate availability and concern due to peripheral vascular and cardiac surgical precedents of reduced long-term patency rates, possibly from the use of nonnative tissue and immune-related graft rejection. The mechanism of interposition graft occlusion over time, however, is multifactorial. In their analysis of 159 bypasses using the excimer laser-assisted nonocclusive anastomosis (ELANA) technique, Bremmer et al. noted that bypasses with lower

flow (less than 40 ml/min) were significantly more likely to occlude over time than bypasses with medium to high flow.³¹ WSS has also been implicated in the pathophysiology of bypass graft occlusion,³² such that low WSS is believed to promote myointimal hyperplasia and subsequent graft nonpatency.³³ With regard to cadaveric SVGs specifically, chronic rejection has also been postulated as a mechanism of occlusion. While 1 g of methylprednisolone was administered to all patients in this series, the efficacy of steroids or other immunosuppressive agents, such as azathioprine or cyclosporine, with regard to graft patency has not been clearly established.^{34–37}

A recent survey of the National Inpatient Sample (NIS) from 2002 to 2014 showed a nearly two-fold increase in the number of cerebral revascularization procedures between the time periods of 2002–2004 and 2011–2014.¹ However, after the time period from 2008 to 2010, the relative percent of bypass procedures for atherosclerotic disease and aneurysms steadily declined. This trend likely reflects diminished enthusiasm for flow augmentation for atherosclerotic disease following publication of the Carotid Occlusion Surgery Study (COSS)³⁸ and the limited necessity for flow replacement in aneurysm or tumor surgery since the introduction of flow diverters to the endovascular market,³⁹ two bypass scenarios that frequently required the use of interposition grafts. While analysis of the NIS data did not disclose the use of interposition grafts,¹ we noted in our series that bypasses with interposition grafts have been used less frequently over time: 2001–2006, 30.1%; 2007–2012, 15.6%; and 2013–2018, 5.7%. In addition, the reduced use of interposition grafts over time in our practice also reflects the adoption of an algorithmic approach to cerebral revascularization surgery. With the “flow-assisted surgical technique,” intraoperative blood flow measurements guide bypass decisions, and we have often found that a traditional superficial temporal artery–middle cerebral artery bypass is sufficient to meet the flow demands of the territory at risk of ischemia.^{2,3,40–42}

Beyond cerebral bypasses, cadaveric SVGs can also be

FIG. 3. Individual WSS values for 18 autologous (median 8.1, IQR 5.4–11.7) and 11 cadaveric (median 6.1, IQR 5.1–8.9) SVGs ($p = 0.28$).

FIG. 4. Kaplan-Meier curves comparing patency over time for bypasses with autologous versus cadaveric SVGs (p = 0.58).

useful for the creation of temporary bypasses or conduits. Our experience includes the extracranial construction of a carotid to distal vertebral artery bypass^{43,44} to allow endovascular access via the interposition graft to the distal vertebrobasilar system for aneurysm embolization.⁴⁵

This study has the limitations inherent to any single-institution study. While patients were selected for bypass based on institutional protocols, guidelines, and multidis-

ciplinary consensus, there exists the possibility of selection bias. In addition, the period over which this analysis spans includes recruitment for and publication of the COSS and the US Food and Drug Administration approval of the Pipeline embolization device (Medtronic), which have influenced indications for bypass in atherosclerosis and aneurysm cases, respectively. Despite these considerations, the large number of bypass procedures in the study were performed by two experienced cerebrovascular surgeons (S.A.H. and F.T.C.), and bypass protocols remained similar over the study period.

FIG. 5. Utilization of SVGs in cerebral revascularization surgery at one institution from 2001 to 2018.

Conclusions

In our analysis of numerous clinical, angiographic, hemodynamic, and outcome parameters, we identified no significant differences between autologous and cadaveric SVGs utilized in cerebral bypasses performed for either flow augmentation or flow replacement purposes. As volumetric flow rates and long-term patency rates of autologous and cadaveric SVGs were statistically similar, cadaveric SVGs remain a reasonable interposition graft option when autologous grafts are not available.

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Disclosures

Dr. Charbel is a consultant for Transonic Inc.

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Conception and design: Stapleton, Alaraj, Amin-Hanjani, Charbel. Acquisition of data: Stapleton, Hussein, Behbahani. Analysis and interpretation of data: Stapleton, Hussein, Behbahani. Drafting

the article: Stapleton. Critically revising the article: Stapleton, Hussein, Behbahani, Amin-Hanjani. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Stapleton. Statistical analysis: Stapleton, Hussein, Behbahani. Administrative/technical/material support: Alaraj, Amin-Hanjani, Charbel. Study supervision: Alaraj, Amin-Hanjani, Charbel.

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