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Original Research

Motor Impairment and Disuse Are Independent Predictors of Vascular Outcomes Poststroke

Tiev Miller, PhD[1], Huixi Ouyang, PT, PhD[1,2], Charlotte S.L. Tsang, PT, PhD[1], Martín Calderón-Juárez, MD, PhD[3], Michael T.C. Ying, PhD[4], Marco Y.C. Pang, PT, PhD[1,*]

[1]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong, SAR, China
[2]School of Biomedical Engineering, Guangzhou Medical University, Guangzhou 510180, China
[3]Faculty of Science, Universidad Nacional Autónoma de México, Ciudad de México, México
[4]Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Hong Kong, SAR, China

*Corresponding author: Marco Y.C. Pang, PT, PhD, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong, SAR, China (marco.pang@polyu.edu.hk).

ABSTRACT

Importance. Cardiorespiratory fitness is reduced after stroke due to inactivity which may cause structural and functional changes to blood vessels in the extremities. Identifying clinical factors contributing to vascular function may be important for tailoring rehabilitation programs that reduce secondary disease risk and adverse events.
Objective. The study objective was to compare measures of arterial and intramuscular blood flow between the paretic and nonparetic upper limbs of individuals with stroke and healthy comparators. Associations between these parameters and stroke-related impairment were also examined.
Design. This was a cross-sectional study.
Setting. The setting was a university laboratory.
Participants. Participants were individuals with stroke ($n = 64$; mean age = 60.8 [SD = 7.7] years) and matched controls ($n = 64$; mean age = 59.4 [SD = 7.8] years).
Main Outcomes/Measures. Brachial artery blood flow volume (Vflow) and arterial diameter (AD) were measured using Doppler ultrasound. Intramuscular blood perfusion of the biceps brachii was estimated using the vascularity index (VI). Motor recovery and perceived use of paretic upper limbs were assessed with the Fugl–Meyer Assessment (FMA) and Motor Activity Log (MAL), respectively.
Results. Side × group interactions were observed for AD ($F = 22.6$) and VI ($F = 4.00$). Post hoc analyses showed lower AD and VI for paretic sides (stroke group), greater Vflow for dominant sides (comparators), and greater percent side-to-side differences (%SSDs) in AD and VI for the stroke group than for comparators. %SSDs in Vflow, AD, and VI demonstrated weak correlations with impairment (MAL, FMA; $\rho = 0.253$ to 0.347). MAL was an independent predictor of %SSD in Vflow ($\beta = -0.286$), and FMA was an independent predictor of %SSDs in AD ($\beta = -0.307$) and VI ($\beta = 0.371$).
Conclusions/Relevance. Relative to the nonparetic and bilateral limbs of comparators, arterial size and intramuscular blood flow in the paretic upper limbs of individuals with stroke were significantly reduced. Motor impairment and disuse emerged as independent predictors of all vascular outcomes and may be potential intervention targets for reducing cardiovascular disease risk after stroke.

Key words: Doppler Ultrasound; Motor Impairment; Stroke; Upper Limb; Vascular.

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INTRODUCTION

Lower cardiorespiratory fitness[1,2] and changes to peripheral vasculature in paretic limbs[3,4] are known consequences resulting from inactivity after stroke. According to a recent meta-analysis, people with stroke are estimated to spend ≥78% of their time being sedentary or inactive, irrespective of the elapsed duration since onset.[5] As people with stroke are often unable to meet routine physical activity guidelines recommended for older adults (ie, ≥150 minutes of moderate-intensity aerobic activity per week),[6] their risk for developing other cardiometabolic diseases (eg, heart failure, diabetes)[7] and subsequent cardiovascular events (eg, myocardial infarction, secondary stroke) may increase.[8] While rehabilitation has traditionally focused on enhancing neuroplasticity after stroke,[9] concomitant declines in cardiovascular function and adverse musculoskeletal morphology (eg, stroke-related sarcopenia)[10] are often evident but underemphasized in treatment.[11] Identifying clinically relevant factors that contribute to cardiovascular outcomes may be important for tailoring rehabilitation programs which improve function and reduce the risk of secondary diseases and adverse events.

Evidence suggests that reduced arterial blood flow, compliance, and unilateral vascular remodeling occur after stroke.[3,12–15] To date, relatively few studies have examined the effects of stroke on vascular function in the paretic upper extremities relative to healthy comparators without prior history of stroke.[14,16,17] These factors may also influence microcirculatory networks in peripheral musculature. Bilateral disparities in resting intramuscular blood perfusion are evident during the chronic stages of stroke recovery, with greater perfusion observed for less-affected extremities.[18] Additional evidence suggests interlimb differences in lower extremity microvascularity and intramuscular blood perfusion are also likely to influence functional recovery.[19,20] However, comparisons between possible unilateral changes in intramuscular blood perfusion in upper extremity muscles affected by stroke relative to those in individuals who are healthy and have no history of stroke have not been examined.

The extent to which motor recovery can predict vascular outcomes in people with stroke is also relatively understudied. Previous research indicates a possible relationship between vascular function and stroke-related impairment.[15,21] In people with acute stroke, baseline concentrations of vascular endothelial growth factor, a signaling neuroprotective glycoprotein mediating angiogenesis,[22] have been shown to be predictive of greater neurological recovery.[21] In people with chronic stroke, an association between bilateral limb disparities in radial artery blood flow volume and paretic hand motor function has also been reported.[15] Additionally, the contribution of psycho-physiological components which further exacerbate stroke-related motor impairment may be substantial. During the early stages of stroke recovery (ie, acute and subacute), unsuccessful attempts at routine paretic arm usage during daily activities have been shown to reinforce or perpetuate psychological patterns of disuse, often referred to as "learned non-use."[23] The degree to which perceived usage is predictive of vascular function in the paretic upper extremity is largely unknown.

This cross-sectional study aimed to (1) compare measures of arterial and intramuscular blood flow between the paretic and nonparetic upper limbs of individuals with stroke and those of age- and sex-matched comparators without history of stroke and (2) examine the relationship between these parameters and clinical assessments of stroke-related impairment.

METHODS

Participants

A total of 64 individuals with chronic stroke and 64 age- and sex-matched comparators without prior history of stroke were recruited through convenience sampling between April and December of 2018. Screening, recruitment, and assessment procedures were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Suppl. Table 1).[24] Participants were screened via phone interviews for potential inclusion. Community-dwelling individuals with a history of chronic stroke (onset >6 months), ≥18 years of age, passive range of motion required to be positioned in 60 degrees of elbow flexion during assessments, and who were able to provide consent and follow instructions (indicated by an Abbreviated Mental Test score of ≥6)[25] were included in the study. Individuals with other neurological conditions, severe contractures prohibiting passive elbow flexion within the desired testing range, or other serious contraindications for participation were excluded. With the exception of prior stroke history, the same set of inclusion/exclusion criteria applied to participants in the comparator group. A flow diagram outlining participant identification and inclusion is provided in Figure 1. Written informed consent was obtained prior to data collection. Study approval was granted by the Human Subjects Ethics Subcommittee of the University (HSEARS20171212003) and all procedures were conducted in accordance with the Helsinki Declaration for human experiments.

Stroke-Related Impairment

The Fugl–Meyer Assessment (FMA) was used to determine the degree of paretic upper limb motor impairment with scores ranging from 0 to 66 (higher scores indicate greater motor impairment).[26] Paretic elbow flexor muscle spasticity was graded according to the multicomponent composite spasticity index (CSI) with ordinal scores ranging from 0 to 16. The composite score is comprised of 3 components: biceps tendon jerk (score range of 0–4, 5-point scale), resistance to full range of passive joint displacement for elbow flexion (score range of 0–8, 5-point scale doubly weighted), and the duration and amount of wrist clonus elicited (score range of 1–4, 4-point scale). Scores of 0 to 9, 10 to 12, and 13 to 16 reflect mild, moderate, and severe spasticity, respectively.[27–29] Perceived paretic arm usage quality and frequency for 30 functional activities of daily living was determined with the motor activity log (MAL; lower scores being indicative of greater perceived paretic upper limb impairment among participants when performing daily activities).[23] Average scores from the quality-of-movement and amount-of-use subscales of the MAL (MAL-QOM and MAL-AOU, respectively) were used for further analysis. Other bilateral limb assessments and procedures (ie, isometric strength, sensory function, physical activity level, body composition) are described in the Supplementary Material.

Ultrasound Measures

An AixPlorer ultrasound unit (Supersonic Imagine, Aix en-Provence, France) coupled with a linear-array transducer (4–15 MHz; 15-4; SuperLinear, Vermon, France) was used

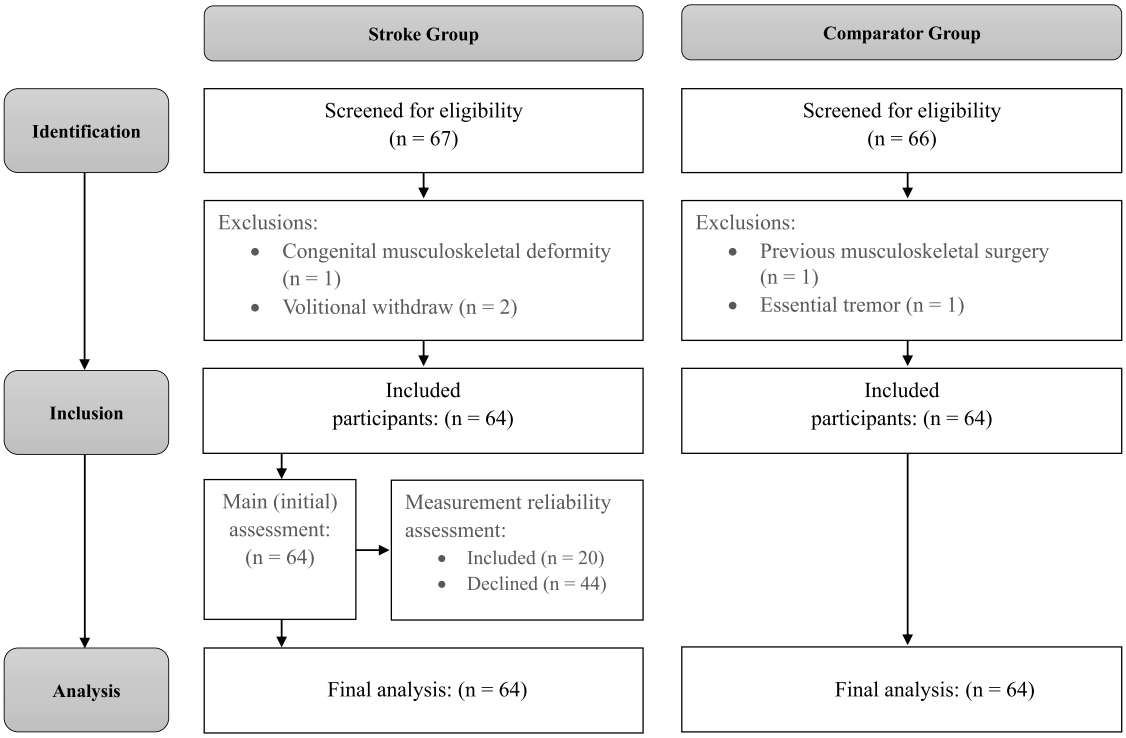

Figure 1. Flow Diagram Depicting the Identification, Inclusion, and Analysis of Study Participants in Accordance With Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Reporting Guidelines.[24]

to measure intramuscular blood perfusion of the bilateral biceps brachii muscles and arterial diameter, and blood flow volume. To optimize visualization of anatomical structures, super-compound and high penetration modes were set at a medium frame rate. A 2-mm-thick transmission gel layer was applied between the skin and probe surface to reduce tissue compression during measures. Participants were instructed to remain relaxed while lying in a supine position with the elbow joint fixed in 60 degrees of flexion and 45 degrees of shoulder abduction using a custom immobilization device. Measures of intramuscular blood perfusion for the bilateral biceps brachii muscles were collected at the distal third (ie, ~66%) of the total humeral length between the coracoid process of the scapula and the crease of cubital fossa on the radial side.[30] Brachial artery diameter and blood flow were taken on the medial aspect of the upper arm in alignment with the biceps brachii measurement site. The average of 3 measurement trials for each parameter was used for further analysis. Test-retest reliability of vascular ultrasound measures was assessed for a cohort of 20 participants from the stroke group approximately 7 to 14 days following the initial assessment using a 2-way random-effects Intraclass Correlation Coefficient (ICC; 2,3) model for absolute agreement between measures performed by a single rater. ICC values of <0.5, 0.51 to 0.75, 0.76 to 0.90, and >0.90 represented poor, moderate, good, and excellent reliability, respectively.[31] The remaining 44 individuals from the stroke group declined to participate in the retest assessment due to limited availability (Figure 1).

Arterial Blood Flow Volume and Diameter

Brachial artery blood flow volume (Vflow; mL/min) was measured using pulse wave Doppler ultrasound at the anatomical site previously specified. The probe was placed transversely along the medial aspect of the upper arm. Following visual confirmation of laminar flow using color Doppler ultrasound, the probe was then rotated sagittally and tilted to visualize the artery longitudinally. An electronic caliper was positioned in the lumen center and the sample volume standardized at 0.5 mm. Doppler steering and fine angle correction were adjusted to optimize angle to flow at an insonation of ≤ 60 degrees. Pulse repetition frequency were adjusted until spectral waveforms were clearly visualized. The autotrace function was applied in estimating the full range of positive and negative flow for 5 consistent waveform cycles. Test-retest reliability for Vflow was good for the nonparetic biceps brachii (ICC = 0.83; 95% CI = 0.56–0.93) and moderate for the paretic biceps brachii (ICC = 0.76; 95% CI = 0.40–0.91). Within the same image, arterial diameter (AD; centimeters) was measured by placing the calipers at each end of the superior and inferior borders of the endothelial wall. Vflow was then calculated using the system tools (Supersonic Imagine). Test-retest reliability for AD was excellent for the nonparetic biceps brachii (ICC = 0.91; 95% CI = 0.79–0.96) and good for the paretic biceps brachii (ICC = 0.89; 95% CI = 0.72–0.95).

Intramuscular Blood Perfusion

The vascularity index (VI) was used to estimate intramuscular blood perfusion of the bilateral biceps brachii. The VI is a quantitative postprocessing technique that has been used to estimate site-specific intramuscular blood perfusion following exercise interventions among healthy young adults[32] as well as clinical populations with plantar fasciitis[33] and unilateral limb impairment (ie, hemiparesis).[18,19] The measurement was first proposed as a qualitative grading scale for measuring exercise-induced changes in muscle blood flow using power

Doppler ultrasound by Newman et al[34] and was later adapted and refined as a semiquantitative approach for estimating thyroid vascularity using high-sensitivity power Doppler ultrasound by Ying et al.[35] The later method, involves calculation of the VI as a ratio of color pixels to the number of total pixels within a given region of interest. The semiquantitative approach has demonstrated strong correlation with the previous qualitative grading method when measuring the same construct in plantar fascia ($r = 0.70$; $P = .001$).[33] The method used in the current study was adapted from Huang et al.[19] The probe was placed in a transverse orientation on the muscle belly of the biceps brachii at the measurement site described previously. In color flow Doppler imaging mode, a rectangular region of interest was placed within the fascial borders of the biceps brachii and standardized according to a frame rate of 11 Hz, pulse repetition frequency of 6 cm/s, 50% gray scale gain, and color gain range of 70% to 85%. For each participant, color gain was slowly reduced from 85% (ie, upper gain limit) until color noise was absent or reached the lower gain limit (70%). The color gain setting was kept the same for the opposing upper limb. Image processing of exported Doppler recordings and estimation of VI (ie, ratio of color to total pixels within the region of interest)[35] were performed using custom scripts in MATLAB (version R2023a; The MathWorks, Inc, Natick, MA, USA). The highest VI from 3 trials were used to calculate the mean for further analysis.[19] Test-retest reliability for VI was moderate for the nonparetic (ICC = 0.73; 95% CI = 0.31–0.89) and paretic biceps brachii (ICC = 0.74; 95% CI = 0.35–0.90).

Data Analysis

Sample size estimation was conducted with GPower software (version 3.1; Heinrich Heine University, Dusseldorf, Germany)[36] at a power of 0.8 and an α of .05. Sample size calculations for between-group differences in vascular outcomes were based on a study by Omisore et al, who assessed brachial artery endothelial function using flow-mediated dilation; they showed lower dilation rates for the acute stroke group (4.37% [SD = 1.50%]) than for controls (10.33% [SD = 1.96%]).[14] The between-group difference yielded a very large effect size (ie, Cohen $d = 3.4$). Assuming an equivalent effect for 3 vascular outcomes (Vflow, AD, VI) measured bilaterally and an attrition rate of 5%, a minimum of 50 participants would be required. Sample size calculations for correlations between vascular measures and impairment in the stroke group were based on a study by Tiftik et al involving participants with chronic stroke; that study demonstrated a weak, negative correlation ($r = -0.314$; $P = .020$) between the side-to-side difference (ie, paretic-nonparetic) in radial artery blood flow volume using pulse wave Doppler ultrasound and paretic hand motor function assessed with Brunnstrom motor recovery stages.[15] Assuming a similar correlation ($r = 0.35$) and a possible attrition rate of 5%, it was estimated that a minimum of 64 participants with chronic stroke would be required. In considering the aforementioned estimations, a minimum sample of 64 participants for each group was required.

Other analyses were performed using SPSS software (version 28.0; IBM Inc, Armonk, NY, USA). Data normality and homogeneity of variance were assessed with Shapiro–Wilk and Levene tests, respectively. Associations between vascular measures and all other assessments (ie, MAL, CSI, FMA, bioelectrical impedance analysis, demographics) were determined using Pearson correlations ($P \leq .05$) with values of 0.0 to 0.2, 0.2 to 0.4, 0.4 to 0.6, 0.6 to 0.8, and 0.8 to 1.0 representing very weak, weak, moderate, strong, and very strong associations, respectively.[37] A nonparametric equivalent was used (ie, Spearman ρ) in the event assumptions of data normality and variance were not met.

For within- and between-group comparisons, a mixed-design 2-way repeated-measures analysis of variance (within-subject factor: side [paretic or nonparetic stroke], comparator [nondominant or dominant]; between-subject factor: group [stroke vs comparator]) was performed for each variable that was measured bilaterally. The effect sizes were expressed as partial eta-squared (η_p^2) values, with $\leq$0.01, 0.06, and 0.14 denoting small, medium, and large effects, respectively.[38] Significant side × group interaction effects represent a group-dependent side-to-side difference for a given variable. Post hoc paired t tests were used to compare between the 2 sides, and post hoc independent t tests were used to compare the percent side-to-side difference (%SSD), calculated as 100 × [(nonparetic side − paretic side)/nonparetic side], between the stroke and comparator groups, with a correction for multiple comparisons (Bonferroni correction: $P \leq .05/3 = .017$). For the stroke group, hierarchical multiple regression analyses were used to identify determinants of the %SSDs in vascular parameters (dependent variables) which demonstrated significant bivariate correlations with motor impairment measures (ie, FMA, MAL, CSI; $P \leq .05$). These variables, along with sex, age, body mass index, Physical Activity Scale for the Elderly, total comorbidities and medications, stroke type, and duration after stroke, were forced into each regression model using the enter method.

Prior to the regression analysis, separate bivariate correlation analyses were performed to assess the degree of association among the independent predictor variables (eg, FMA, MAL, CSI, bioelectrical impedance analysis, touch and pain pressure thresholds). Predictor variables with a correlation of >0.6 were used in separate regression models using the stepwise method to avoid multicollinearity.[39] As limb dominance may also modulate peripheral blood flow,[40] subgroup analyses were conducted to examine the influence of this factor on all bilaterally assessed outcomes for participants with stroke (ie, dominant side affected vs nondominant side affected) using paired and independent t tests to compare between sides (ie, paretic vs nonparetic) and groups (ie, %SSD), respectively ($P \leq .05$). Effects for within- and between-group differences were expressed as Cohen's d, with values of 0.00 to 0.20, 0.20 to 0.50, 0.50 to 0.80, and > 0.80 denoting very small, small, medium, and large effect magnitudes, respectively.[41] Between-group comparisons for motor impairment measures were performed using Mann–Whitney U tests ($P \leq .05$), and effects were expressed as correlation coefficients (r), with values of 0.1 to 0.3, 0.3 to 0.5, and > 0.5 denoting small, medium, and large effect magnitudes, respectively.[42] To adjust for limb dominance in subsequent hierarchical multiple regression analyses, the side affected by stroke (ie, dominant affected side vs nondominant affected side) was added as a base model covariate using the enter method.

Role of the Funding Source

The funder played no role in the design, conduct, and reporting of this study.

RESULTS

Participant Characteristics

A summary of participant characteristics for stroke and comparator groups is provided in Table 1. Significant between-group differences were observed for the Abbreviated Mental Test, total number of medications and comorbidities ($P \leq .05$). Participants with stroke had an average duration of 5.7 (SD = 3.9) years since onset, with most having a history of ischemic stroke (n = 41). Participants with stroke had moderate motor impairment (FMA = 35.9 [SD = 18.8])[43] and mild spasticity (CSI = 8.5 [SD = 2.4])[44] in paretic arms. Mean scores for MAL subscales indicated that perceived usage frequency of the paretic arm was minimal (MAL-AOU = 1.3 [SD = 1.3]) and that movement quality was perceived as low overall (MAL-QOM = 1.4 [SD = 1.3]). For subgroups based on limb dominance (ie, dominant side affected [subgroup 1; n = 28] vs nondominant side affected [subgroup 2; n = 36]), no significant between-group differences were observed for stroke-related impairment scores (Suppl. Table 2).

Within- and Between-Group Comparisons

Vascular Ultrasound Measures

A summary of within- and between-group comparisons for all variables assessed bilaterally is provided in Table 1 and Supplementary Table 3. Significant side × group interaction effects were observed for AD ($\eta_p^2 = 0.152$; $F = 22.6$; $P \leq .001$) and VI ($\eta_p^2 = 0.031$; $F = 4.00$; $P = .048$). Post hoc paired t tests showed significantly lower AD and VI for paretic than for nonparetic sides in the stroke group. Vflow was greater for the dominant sides of comparators ($P \leq .017$) but did not differ between sides for the stroke group. Post hoc independent t tests showed greater %SSDs in AD and VI for the stroke group than for comparators ($P \leq .017$; Figure 2). Subgroup analyses according to limb dominance showed significantly lower AD for paretic than for nonparetic sides in both subgroup 1 (dominant affected side) and subgroup 2 (nondominant affected side) and significantly lower VI for paretic than for nonparetic sides in subgroup 1. Vflow was significantly lower for paretic than for nonparetic sides in subgroup 2. The %SSD in Vflow was significantly greater for subgroup 1 than for subgroup 2, while the %SSD in AD was greater for subgroup 2 than for subgroup 1 (Suppl. Table 2).

Other Bilateral Measures

Significant side × group interaction effects were also observed for isometric peak torque ($\eta_p^2 = 0.356$; $F = 69.7$; $P \leq .001$), touch pressure threshold ($\eta_p^2 = 0.187$; $F = 29.0$; $P \leq .001$), upper limb impedance ($\eta_p^2 = 0.162$; $F = 24.4$; $P \leq .001$) and fat percentage ($\eta_p^2 = 0.032$; $F = 4.18$; $P = .043$). Post hoc paired t tests showed significantly lower isometric peak torque and lean mass for the paretic side and significantly higher touch pressure threshold, impedance and fat percentage for the paretic side ($P \leq .017$). For the comparator group, impedance and fat percentage were also significantly lower on the nondominant side, while touch pressure threshold, lean and predicted muscle mass were significantly higher on the dominant side ($P \leq .017$). Post hoc independent t tests showed greater %SSDs in isometric peak torque, touch pressure threshold, pain pressure threshold, and upper limb impedance for the stroke group than for the comparator group ($P \leq .017$; Table 1; Suppl. Table 3; Suppl. Figure 1; Suppl. Figure 2). Subgroup analyses for limb dominance showed significantly lower isometric peak torque and lean mass for the paretic side and significantly higher touch pressure threshold and impedance in subgroups 1 and 2. In subgroup 2, fat percentage was significantly higher for the paretic side with significantly lower paretic side lean mass and predicted muscle mass. The %SSDs in touch pressure threshold, fat percentage, lean mass, and predicted muscle mass were significantly greater for subgroup 2 than for subgroup 1 (Suppl. Table 2).

Correlations

The %SSDs in vascular measures (Vflow, AD, VI) demonstrated weak correlations with stroke-related impairments (MAL, FMA; $\rho = 0.253$ to 0.347; $P \leq .05$). Correlations between the %SSDs in vascular measures and segmental limb analyses ranged from weak to moderate ($\rho = -0.292$ to 0.415; $P \leq .05$). A summary of correlations between ultrasound and all other variables is provided in Supplementary Table 4. Intercorrelations among ultrasound measures were also weak to moderate in magnitude ($r = 0.436$–0.476 [$P \leq .05$]; $\rho = -0.288$ to 0.566 [$P \leq .05$]; Suppl. Table 5).

Regression

Predictor variables were significantly correlated (ie, >0.6; Suppl. Table 6) and were entered in separate models using the stepwise method to avoid multicolinearity.[39] The first regression analysis was performed to determine the factors associated with %SSD in Vflow. After adjustment for other factors (ie, age, sex, body mass index, Physical Activity Scale for the Elderly, medications, comorbidities, duration after stroke, and stroke type), the MAL-AOU ($\beta = -0.286$; $P = .046$) was found to be an independent predictor of the %SSD in Vflow, accounting for 6.5% of the variance (Table 2, model 2). However, this variable was eliminated as a predictor after adjustment for limb dominance (Suppl. Table 7, model 1).

A second regression analysis was conducted to identify the determinants of the %SSD in AD. It was found that the FMA ($\beta = -0.307$; $P = .018$) was an independent predictor of the %SSD in AD, accounting for 8% of the variance (Table 3, model 2). FMA remained an independent predictor following the inclusion of limb dominance as a base model covariate ($\beta = -0.266$; $P = .033$; Suppl. Table 8, model 2).

A final regression model was constructed to identify the determinants of the %SSD in VI. The FMA ($\beta = 0.302$; $P = .025$) and %SSD in pain pressure threshold ($\beta = 0.315$; $P = .021$) were both significant predictors of the %SSD in VI, accounting for an additional 11.7% and 8.0% of the variance, respectively (Table 4, model 3). The FMA ($\beta = 0.281$; $P = .038$) and %SSD in pain pressure threshold ($\beta = 0.311$; $P = .022$) also remained significant predictors with the inclusion of limb dominance in the base model (Suppl. Table 9, model 3).

DISCUSSION

This study assessed differences in upper extremity vascular function among individuals with stroke and their healthy age and sex-matched counterparts. Associations between vascular parameters and stroke-related impairment were also examined. Brachial artery size and intramuscular blood perfusion of the biceps brachii were reduced on the paretic side relative to the nonparetic side in individuals with stroke as well as the bilateral limbs of comparators. Bilateral differences in arterial blood flow volume were only observed among comparators.

Table 1. Characteristics of Participant Groups[a]

Characteristic	Stroke Group ($n = 64$)				Comparator Group ($n = 64$)			
	Value	Paretic	Nonparetic	%SSD	Value	Non-dominant	Dominant	%SSD
Demographic								
Sex, men/women, no.	38/26				39/25			
Age, y	60.8 (7.7)				59.4 (7.8)			
Hand dominance, left/right/equivalent, no. of participants	1/62/1				2/62/0			
Paretic side, left/right, no. of participants	36/28							
Duration after stroke, y	5.7 (3.9)							
Type of stroke, ischemic/hemorrhagic, no. of participants	41/23							
Abbreviated mental test, scored from 0 to 10	9.3 (1.1)				9.9 (0.4)[b]			
Physical activity scale for the elderly, scored from 0 to 400	114.7 (87.4)				142.2 (79.4)			
Total no. of comorbidities/person	1.3 (1.3)[b]				0.6 (0.9)			
Total no. of medications/person	4.0 (2.7)[b]				0.8 (1.2)			
BIA for total body								
Body mass index, kg/m^2	24.3 (3.0)				23.4 (2.8)			
Basil metabolic rate, kcal	1275.11 (202.5)				1297.5 (221.1)			
Body fat, %	27.7 (8.3)				26.2 (6.5)			
Fat mass, kg	17.3 (6.2)				16.5 (4.7)			
Lean mass, kg	52.8 (60.13)				46.6 (8.6)			
Total body water, kg	32.5 (5.6)				32.7 (5.9)			
Visceral fat rating	10.5 (3.1)				10.4 (3.6)			
Impedance, Ω	621.2 (83.5)				645.9 (90.7)			
BIA for segmental limb analysis								
Impedance, Ω		353 (52.3)[c]	328 (43.4)	−7.59 (9.47)[b]		350 (53.6)[c]	346 (55.0)	−1.23 (3.17)
Body fat, %		23.8 (9.46)[c]	22.6 (9.60)	−7.45 (13.6)		21.2 (7.45)[c]	20.5 (7.26)	−3.97 (5.00)
Fat mass, kg		0.68 (0.30)	0.69 (0.32)	−0.45 (12.3)		0.60 (0.22)	0.61 (0.22)	−1.02 (14.2)
Lean mass, kg		2.21 (0.52)	2.37 (0.54)[c]	6.55 (7.73)		2.28 (0.55)	2.41 (0.57)[c]	5.34 (3.55)
Predicted muscle mass, kg		2.08 (0.49)	2.21 (0.50)	5.91 (7.15)		2.16 (0.55)	2.26 (0.54)[c]	4.53 (5.61)
Vascular measures								
Blood flow volume, mL/min		42.5 (23.2)	49.7 (23.3)	−2.78 (88.5)		30.6 (19.8)	41.8 (22.6)[c]	11.6 (61.7)
Arterial diameter, cm		0.33 (0.06)	0.38 (0.06)[c]	11.7 (10.4)[b]		0.34 (0.06)	0.36 (0.06)[c]	3.80 (7.88)
Vascularity Index		0.56 (0.48)	0.67 (0.36)[c]	18.1 (42.1)[b]		0.57 (0.53)	0.59 (0.62)	−9.49 (47.6)
Other measures								
Isometric peak torque, N·m		18.4 (9.3)	29.6 (11.2)[c]	31.6 (49.7)[b]		26.5 (10.3)	27.0 (11.1)	−0.14 (11.6)
Touch pressure threshold, monofilament size		3.9 (1.5)[c]	2.9 (0.5)	−37.4 (58.0)[b]		2.7 (0.2)	2.8 (0.3)[c]	1.5 (6.1)
Pain pressure threshold, kg		3.20 (1.81)	3.36 (1.59)	−15.9 (148.4)[b]		2.19 (1.05)	2.38 (1.25)	1.19 (31.6)
Motor impairment								
Composite spasticity index, total, scored from 1 to 16		8.5 (2.4)						
Fugl–Meyer assessment, scored from 0 to 66		35.9 (18.8)						
Motor activity log amount-of-use subscale, scored from 0 to 5		1.3 (1.3)						
Motor activity log quality-of-movement subscale, scored from 0 to 5		1.4 (1.3)						

[a]Data are reported as mean (SD) unless otherwise indicated. BIA = bioelectrical impedance analysis; %SSD = percent side-to-side difference. [b]Statistically significant between-group difference at $P \leq .05$, as determined by an independent t-test. [c]Statistically significant between-side difference at $P \leq .05$, as determined by a paired t-test.

Table 2. Determinants of %SSD in Blood Flow Volume Among Individuals With Stroke[a]

Predictor	Model Summary					Coefficients						
	R	R^2	ΔR^2	ΔF	*P* (ΔF)	B	SE	β	*t*	*P*	95% CI		VIF
											Lower	Upper	
Model 1 (enter method)	0.305	0.093	0.093	0.708	0.684								
Sex (0 = male, 1 = female)						−5.710	24.690	−0.032	−0.231	0.818	−55.190	43.771	1.161
Age (y)						0.349	1.777	0.031	0.197	0.845	−3.213	3.911	1.464
BMI (kg/m^2)						3.366	3.997	0.116	0.842	0.403	−4.645	11.377	1.152
PASE						−0.145	0.153	−0.143	−0.945	0.349	−0.452	0.162	1.392
Total no. of comorbidities						5.961	11.530	0.087	0.517	0.607	−17.145	29.068	1.701
Total no. of medications						2.191	4.632	0.077	0.473	0.638	−7.092	11.474	1.588
Stroke type (0 = ischemic, 1 = hemorrhagic)						−29.837	29.368	−0.163	−1.016	0.314	−88.693	29.018	1.568
Duration after stroke (y)						−1.384	3.439	−0.062	−0.402	0.689	−8.275	5.508	1.445
Model 2 (stepwise method)	0.398	0.158	0.065	4.157	0.046[b]								
Model 1 covariates													
MAL-AOU						−19.417	9.523	−0.286	−2.039	0.046[b]	−38.510	−0.324	1.262

[a]Eliminated predictors (entered in separate blocks using the stepwise method): percent side-to-side difference (%SSD) in touch pressure threshold, %SSD in fat percentage, %SSD in lean mass, and %SSD in predicted muscle mass. B = unstandardized regression coefficient; β = standardized regression coefficient; BMI = body mass index; ΔF = change in *F* value; MAL-AOU = amount-of-use subscale of the motor activity log; PASE = physical activity scale for the elderly; *R* = correlation; R^2 = total variance; ΔR^2 = additional predictor variance; SE = standard error; *t* = *t* score; VIF = variance inflation factor. [b]Statistically significant at $P \leq .05$.

Figure 2. Between-Group Comparisons for Vascular Outcome Measures. Percent side-to-side difference (%SSD) in arterial diameter and intramuscular blood perfusion (ie, Vascularity Index) were significantly greater for the stroke group than for individuals who were healthy and matched for age and sex (controls). Values are presented as mean %SSD (error bars = 95% CIs). *Statistically significant difference between groups (independent *t*-test; $P \leq .017$).

Additionally, the degree of motor recovery, perceived use of the paretic arm, and the %SSD in sensory function (ie, pain) emerged as significant predictors of the %SSDs in vascular outcomes. These findings are discussed in further detail in the proceeding sections.

Within- and Between-Group Differences in Vascular Function

The side × group interaction effect observed for brachial AD was large ($\eta_p^2 = 0.152$) indicating a substantial reduction in artery size at rest for the paretic side relative to the nonparetic side and bilateral limbs of comparators. This finding is largely consistent with those of previous studies demonstrating diminished unilateral vascular remodeling after stroke,[3,12–15,17] particularly in paretic upper extremities in comparison to healthy individuals without stroke.[14,16,17] Unilateral changes in arterial size are also likely to affect vessel compliance after stroke. A study by Ribeiro et al showed that arterial compliance measured using the Artery Elasticity Index was significantly lower in women with stroke than in matched controls ($P = .02$).[45] Another study assessing brachial artery endothelial function using flow-mediated dilation found significantly lower dilation rates for the stroke group (4.37% [SD = 1.50%]) than for controls (10.33% [SD = 1.96%]; $P < .001$).[14]

To our knowledge, this is the first study to compare unilateral changes in intramuscular blood perfusion in upper extremity muscles affected by stroke with those in individuals who are healthy. Although the side × group interaction effect observed for VI was small in magnitude ($\eta_p^2 = 0.031$), these findings suggest that microcirculatory network density and localized blood perfusion in paretic biceps brachii muscles were significantly diminished relative to the nonparetic muscles of individuals with stroke and bilateral muscles of comparators. Previous studies have also demonstrated significant bilateral differences in upper[18] and lower extremity[18–20] intramuscular blood perfusion in people with stroke. A study by Whyte et al found lower intramuscular blood perfusion in paretic relative to nonparetic muscles at rest before exercise but not after exercise, with no observable correlation between these measures and walking ability (ie, 6-m walk test distance; paretic: $r = -0.06$ [$P = .85$]; nonparetic: $r = 0.25$ [$P = .46$]).[20] Conversely, a study by Huang et al reported a significantly

Table 3. Determinants of %SSD in Arterial Diameter Among Individuals With Stroke[a]

Predictor	Model Summary					Coefficients							
	R	R^2	ΔR^2	ΔF	*P* (ΔF)	B	SE	β	*t*	*P*	95% CI		VIF
											Lower	Upper	
Model 1 (enter method)	0.447	0.200	0.200	1.717	0.115								
Sex (0 = male, 1 = female)						6.886	2.729	0.328	2.524	0.015[b]	1.418	12.355	1.161
Age (y)						−0.572	0.196	−0.425	−2.913	0.005[b]	−0.966	−0.179	1.464
BMI (kg/m^2)						−0.281	0.442	−0.082	−0.636	0.528	−1.166	0.604	1.152
PASE						−0.027	0.017	−0.228	−1.605	0.114	−0.061	0.007	1.392
Total no. of comorbidities						1.095	1.274	0.135	0.859	0.394	−1.459	3.648	1.701
Total no. of medications						−0.590	0.512	−0.175	−1.153	0.254	−1.616	0.436	1.588
Stroke type (0 = ischemic, 1 = hemorrhagic)						−7.098	3.246	−0.330	−2.187	0.033[b]	−13.603	−0.594	1.568
Duration after stroke (y)						−0.084	0.380	−0.032	−0.221	0.826	−0.846	0.678	1.445
Model 2 (stepwise method)	0.529	0.280	0.080	6.004	0.018[b]								
Model 1 covariates													
FMA-UE						−0.169	0.069	−0.307	−2.450	0.018[b]	−0.307	−0.031	1.175

[a]Eliminated predictors (entered in separate blocks using the stepwise method): amount-of-use subscale of the Motor Activity Log, quality-of-movement subscale of the motor activity log, percent side-to-side difference (%SSD) in lean mass, and %SSD in predicted muscle mass. B = unstandardized regression coefficient; β = standardized regression coefficient; BMI = body mass index; ΔF = change in *F* value; FMA-UE = Fugl–Meyer assessment for the upper extremity; PASE = physical activity scale for the elderly; *R* = correlation; R^2 = total variance; ΔR^2 = additional predictor variance; SE = standard error; *t* = *t* score; VIF = variance inflation factor. [b]Statistically significant at $P \leq .05$.

Table 4. Determinants of %SSD in Vascularity Index Among Individuals With Stroke[a]

Predictor	Model Summary					Coefficients							
	R	R^2	ΔR^2	ΔF	*P* (ΔF)	B	SE	β	*t*	*P*	95% CI		VIF
											Lower	Upper	
Model 1 (enter method)	0.250	0.063	0.063	0.459	0.879								
Sex (0 = male, 1 = female)						9.885	12.034	0.116	0.821	0.415	−14.231	34.002	1.161
Age (y)						0.205	0.866	0.037	0.236	0.814	−1.531	1.941	1.464
BMI (kg/m^2)						0.589	1.948	0.042	0.302	0.764	−3.316	4.493	1.152
PASE						−0.019	0.075	−0.040	−0.258	0.797	−0.169	0.130	1.392
Total no. of comorbidities						−2.698	5.620	−0.082	−0.480	0.633	−13.960	8.564	1.701
Total no. of medications						3.300	2.258	0.241	1.462	0.149	−1.224	7.825	1.588
Stroke type (0 = ischemic, 1 = hemorrhagic)						9.473	14.314	0.108	0.662	0.511	−19.213	38.158	1.568
Duration after stroke (y)						−0.230	1.676	−0.022	−0.137	0.891	−3.589	3.129	1.445
Model 2 (stepwise method)	0.424	0.180	0.117	7.714	0.008[b]								
Model 1 covariates													
FMA-UE						0.833	0.300	0.371	2.777	0.008[b]	0.232	1.434	1.175
Model 3 (stepwise method)	0.509	0.259	0.080	5.688	0.021[b]								
Model 1 covariates													
FMA-UE						0.678	0.295	0.302	2.301	0.025[b]	0.087	1.269	1.235
PPT (%SSD)						0.090	0.038	0.315	2.385	0.021[b]	0.014	0.165	1.248

[a]B = unstandardized regression coefficient; β = standardized regression coefficient; BMI = body mass index; ΔF = change in *F* value; FMA-UE = Fugl–Meyer assessment for the upper extremity; PASE = physical activity scale for the elderly; PPT = pain pressure threshold; *R* = correlation; R^2 = total variance; ΔR^2 = additional predictor variance; %SSD = percent side-to-side differences; *t* = *t* score; VIF = variance inflation factor. [b]Statistically significant at $P \leq .05$.

greater intramuscular blood perfusion in the nonparetic limb after exercise relative to the paretic limb but no significant bilateral differences at rest.[19]

No interaction was observed for Vflow. The %SSD in Vflow was also slightly greater among comparators than among individuals with stroke. Though conjecture, these findings suggest that stroke-related impairment may influence changes in peripheral vascular factors (ie, brachial artery diameter and compliance, endothelial function, microvascular changes in paretic musculature) to a greater extent than arterial Vflow, which is modulated in large part by central cardiovascular components (ie, stroke volume, cardiac output).

Association Between Vascular Function and Motor Impairment

The degree of motor recovery in the paretic upper limb (ie, FMA scores) was an independent predictor of the %SSD in AD ($\beta = -0.307$; Table 3, model 2) and the %SSD in VI ($\beta = 0.371$; Table 4, model 3). Previous studies have also demonstrated a possible link between arterial blood flow, endothelial function, and stroke-related impairment.[15,21] Among patients with acute stroke, baseline concentrations of vascular endothelial growth factor have been shown to be predictive of greater neurological recovery (ie, Modified Rankin Score of ≤ 2 vs ≤ 3) within the first 6 months following stroke onset.[21] Additionally, an association between the %SSD in radial artery blood flow volume and paretic hand motor function measured using Brunnstrom motor recovery stages was also observed in people with chronic stroke ($r = -0.314$; $P = .020$).[15]

The association between perceived paretic upper limb use and vascular function is another novel aspect of this study. Initially, the MAL-AOU (ie, usage frequency) emerged as an independent predictor of the %SSD in Vflow ($\beta = -0.286$) but was subsequently eliminated as a predictor after adjustment for other relevant factors (eg, dominance of the affected limb). Although commonly used to overcome nonuse,[23] the effect of conventional therapies (eg, constraint-induced movement) for improving vascular function in the upper extremities after stroke has not been explored. As paretic upper limb usage frequency is a largely modifiable factor, further studies are warranted.

Associations Between Vascular Function and Other Outcomes

Changes in sensory function after stroke may also be reflective of underlying vascular changes. Previous evidence shows an association between diminished sympathetic skin response and reductions in cutaneous blood flow after stroke,[46] but not with pain.[47] In the current study, a large side × group interaction effect was observed for touch pressure threshold ($\eta_p^2 = 0.187$), with post hoc analyses demonstrating significantly larger %SSDs in touch and pain pressure thresholds for the stroke group than for comparators. In subsequent regression analyses, although the %SSD in touch pressure threshold was eliminated as a predictor of the %SSD in Vflow, the %SSD in pain pressure threshold emerged as a significant predictor of the %SSD in VI ($\beta = 0.315$). Additional studies involving a more comprehensive battery of vascular and sensory assessments are needed to examine the association between stroke-related sensory dysfunction and alterations in site-specific blood flow.

Diminished arterial blood flow and unilateral vascular remodeling after stroke are thought to be resultant adaptations of lower metabolic demand in paretic muscles of the upper[14–16,48] and lower extremities.[3,13,49,50] Previous studies showing bilateral differences in femoral artery blood flow after stroke have also reported significantly lower lean tissue mass for paretic sides using dual energy x-ray absorptiometry.[4,13] As in previous studies, bioelectrical impedance analysis was conducted to test the assumption that with a general decline in cardiovascular fitness following stroke, relatively lower metabolic demand from paretic muscles (ie, loss of metabolically active lean tissue) would result in unilateral vascular remodeling and reduced arterial blood flow.[3,12] In the current study, the side × group interaction effects observed for upper limb fat percentage ($\eta_p^2 = 0.032$) and impedance ($\eta_p^2 = 0.162$) were small and large in magnitude, respectively. Although the %SSD values in fat percentage, lean mass, and predicted muscle mass were significantly associated with vascular outcomes in the bivariate correlation analysis, these variables were ultimately eliminated as predictors in subsequent regressions.

Study Limitations

In addition to characterizing upper extremity vascular changes, this study also attempted to assess their association with stroke-related sarcopenia (ie, bioelectrical impedance analysis). The increasing prevalence of cardiometabolic multimorbidity (ie, having a diagnosis of ≥ 2 cardiometabolic conditions, such as stroke, heart disease, and diabetes)[7] adds to the difficulty of recruiting and assessing a large cohort of participants with stroke but without additional comorbidity. Thus, it remains challenging to delineate which vascular adaptations are specific to stroke. Although our findings indicate a stroke-related reduction in arterial size and intramuscular blood perfusion, bilateral differences in arterial blood flow were only observed for comparators. This discrepancy may be due to differences in limb dominance among participants with stroke. The magnitude of bilateral difference in arterial blood flow was relatively larger for participants with a nondominant affected side ($d = -0.78$) than for those with a dominant affected side ($d = -0.24$), suggesting greater bilateral disparity among the former. Future studies investigating peripheral vascular changes in people with stroke should consider controlling for potential inconsistencies arising from interlimb differences between participants.

Additionally, due to the cross-sectional nature of the study, no causal link between bilateral differences in vascular outcomes and motor impairment or disuse after stroke could be established. Whether or not vascular changes precede or result from these impairments and compensatory strategies also remains inconclusive. Further research is needed to investigate whether peripheral vascular adaptations occur independently or in tandem with motor impairment and/or disuse at different stages of stroke recovery (ie, acute, subacute).

Conclusions

Relative to the nonparetic and bilateral limbs of comparators, brachial artery size and intramuscular blood flow in the paretic upper limbs of individuals with stroke were reduced. Measures of stroke-related motor and sensory impairment also emerged as independent predictors of these vascular outcomes. Further research is needed to determine whether

changes in these vascular parameters occur independently or in tandem with functional motor recovery after stroke.

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CRediT—CONTRIBUTOR ROLES

Tiev Miller (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Project administration [equal], Validation [equal], Visualization [equal], Writing—original draft [lead], Writing—review & editing [equal]), Huixi Ouyang (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Project administration [equal], Validation [equal], Visualization [equal], Writing—review & editing [equal]), Charlotte S.L. Tsang (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Project administration [equal], Validation [equal], Visualization [equal], Writing—review & editing [equal]), Martín Calderón-Juárez (Conceptualization [supporting], Data curation [supporting], Formal analysis [supporting], Investigation [supporting], Methodology [supporting], Project administration [supporting], Validation [supporting], Visualization [supporting], Writing—review & editing [equal]), Michael T.C. Ying (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Software [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—review & editing [equal]), and Marco Y.C. Pang (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [lead], Software [lead], Supervision [lead], Validation [equal], Visualization [equal], Writing—review & editing [equal]).

SUPPLEMENTARY MATERIAL

Supplementary material is available online.

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ETHICS APPROVAL

Ethical approval was granted by the Human Subjects Ethics Subcommittee of the University (HSEARS20171212003) and all procedures were conducted in accordance with the Helsinki Declaration for human experiments. Written informed consent was obtained from all study participants.

DISCLOSURES

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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