

Perioperative covert stroke in patients undergoing coronary artery bypass graft surgery



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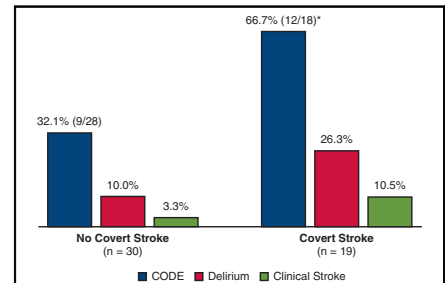
ABSTRACT

Objectives: Covert stroke is a complication of coronary artery bypass graft surgery that is increasingly recognized as a serious problem. In noncardiac surgery settings, covert stroke is associated with the development of delirium, long-term cognitive decline, and future clinical stroke. Therefore, we sought to determine the feasibility of conducting a large, prospective cohort study of the influence of covert stroke on neurocognitive outcomes in patients undergoing coronary artery bypass graft surgery.

Methods: NeuroVISION Cardiac pilot was a prospective cohort study enrolling patients aged ≥ 21 years undergoing isolated coronary artery bypass graft surgery to receive diffusion-weighted magnetic resonance imaging of the brain after surgery to identify patients with covert stroke. Patients were screened for postoperative delirium in-hospital and were administered questionnaires of cognitive and global function (once before and twice after surgery). Regional cerebral oxygen saturation was recorded during surgery using near-infrared spectroscopy.

Results: Between March 27, 2017, and February 11, 2018, 50 of 66 patients enrolled (76%) completed the brain magnetic resonance imaging (1 patient per week). Among the 49 patients included in the analysis, 19 (39%; 95% confidence interval, 26%-53%) experienced perioperative covert stroke and 3 (6%) had a clinical stroke within 30 days of surgery. Postoperative delirium occurred in 5 (26%) patients with covert stroke and in 3 (10%) patients who did not experience covert stroke.

Conclusions: The NeuroVISION Cardiac pilot study established the feasibility of conducting a large, prospective cohort study of the determinants and consequences of covert stroke in patients undergoing coronary artery bypass graft surgery. (JTCVS Open 2020;4:1-11)



Incidence of neurologic complications in patients who experienced or did not experience covert stroke.

CENTRAL MESSAGE

This pilot study established the feasibility of conducting a large, prospective cohort study of the determinants and consequences of covert stroke in patients undergoing cardiac surgery.

PERSPECTIVE

In cardiac surgery settings, we know little about the determinants and consequences of perioperative covert stroke. The NeuroVISION Cardiac pilot study demonstrates the feasibility of conducting a large, prospective cohort study of the influence of covert stroke on delirium, long-term cognitive decline, and future clinical stroke in patients undergoing cardiac surgery.

See Commentaries on pages 12 and 14.

▶ Video clip is available online.

Coronary-artery bypass grafting (CABG) is a commonly performed surgical procedure that improves clinical outcomes in patients with severe coronary artery disease.¹ A key

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
DSST	= Digit Symbol Substitution Test
DW-MRI	= diffusion-weighted magnetic resonance imaging
MoCA	= Montreal Cognitive Assessment
SAGE	= Standard Assessment of Global Activities in the Elderly

limitation of CABG surgery is neurological complications such as clinical strokes, covert strokes, short-term delirium, and long-term cognitive decline.²⁻⁶ Despite efforts to reduce neurologic complications (eg, precannulation assessment of aortic atherosclerosis, off-pump CABG, anaortic off-pump CABG, clampless proximal aortic devices, cerebral perfusion techniques, and cerebral oxygen saturation monitoring) clinical strokes, covert strokes, delirium, and cognitive decline are still among the most frequent and feared complications.

Covert strokes are recent small brain infarcts detected on brain imaging that are not associated with symptoms of clinical (overt) stroke. Diffusion-weighted magnetic resonance imaging (DW-MRI) allows for the detection of acute brain infarcts occurring up to 10 days before imaging; thus, it is not necessary to obtain a preoperative MRI scan to diagnose perioperative covert stroke. Although patients with covert strokes may present with no obvious symptoms, their presence is associated with the development of delirium,⁷ cognitive decline,^{7,8} dementia,^{5,8} and a 2- to 3-fold higher risk of future clinical stroke.^{7,9-12}

Cardiac surgery patients are at elevated risk for developing cerebral injury due to their baseline comorbidities and the procedural risks of cardiac surgery.¹³ Like clinical stroke, atherosclerotic emboli liberated by surgical manipulation of the aorta most likely represents a key modifiable determinant of covert stroke.¹⁴ The prevalence of covert stroke in CABG surgery is estimated to be 25% (95% confidence interval [CI], 15%-35%),¹⁵ more than 3-fold higher than patients undergoing noncardiac surgery (7%; 95% CI, 6%-9%).⁷ A 2019 international study (Detection and Neurological Impact of Cerebrovascular Events in Noncardiac Surgery Patients: A Cohort Evaluation [NeuroVISION]) of 1114 noncardiac surgery patients using DW-MRI demonstrated that perioperative covert stroke is associated with an increased risk of delirium within 3 days and cognitive decline 1 year after surgery.⁷ In addition, a 2019 systematic review has outlined an important trend—the prevalence of covert strokes is increased in cardiac procedures with increasing levels of aortic manipulation¹⁵—suggesting that aortic manipulation is a contributing mechanism for perioperative

covert stroke. However, no large study has established associations between perioperative covert stroke and delirium, long-term cognitive decline, or the degree of aortic manipulation in patients undergoing cardiac surgery.

Brain oximetry is increasingly used during cardiac surgery to noninvasively monitor regional cerebral oxygen saturation to ensure adequate cerebral perfusion.¹⁶ Few studies have combined brain oximetry recordings with DW-MRI screening and therefore we aimed to clarify whether covert stroke is associated with acute declines in regional cerebral oxygen saturation during CABG surgery.

We conducted the NeuroVISION Cardiac pilot study to determine the feasibility of undertaking a large multicenter cohort study to clearly established an association between covert stroke and long-term cognitive decline and to determine whether surgical techniques that aim to reduce or avoid aortic manipulation can reduce rates of covert stroke.

MATERIALS AND METHODS

Study Design and Participants

The NeuroVISION Cardiac pilot study was a prospective cohort study of 66 patients undergoing cardiac surgery conducted at the Hamilton General Hospital from March 2017 to February 2018. Patients were eligible to participate if they were aged ≥ 21 years, scheduled to undergo isolated CABG surgery through a median sternotomy and had at least 1 of the following risk factors: peripheral vascular disease, cerebrovascular disease, renal insufficiency, diabetes mellitus, urgent CABG surgery, recent smoker, or left ventricular ejection fraction $< 35\%$. Patients were not eligible if they had a previous or emergency CABG surgery, planned circulatory arrest during surgery, dementia of any kind, or contraindication for DW-MRI.

The study was approved by the Hamilton Integrated Research Ethics Board before patient recruitment and registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier NCT04241289). The funding agencies had no role in data interpretation and all participants provided written informed consent before completing any study-specific tasks.

Data Collection

Before surgery, trained research staff collected demographic and clinical information, assessed baseline cognitive function using the standardized Montreal Cognitive Assessment (MoCA)¹⁷ and Digit Symbol Substitution Test (DSST)^{18,19} questionnaires, and assessed global function using the Standard Assessment of Global Activities in the Elderly (SAGE). A description of each test is provided ([Appendix 1](#)). On the day of surgery, bilateral oximetry probes were positioned on the forehead before induction of supplemental oxygen and operative brain oxygenation was continuously recorded using the INVOS 5100C monitoring device (Covidien/Medtronic, Mansfield, Mass). A list of participating surgeons ([Appendix Table 1](#)) and study personnel ([Appendix Table 2](#)) are provided. Patients were screened for delirium twice daily in-hospital using the standardized Confusion Assessment Method²⁰ starting the second day after surgery and ending after 3 days of negative tests. Cognitive assessments were administered in-person at discharge and 30 days after surgery. The SAGE was administered in-person at 30 days and by telephone at 90 days. The incidence of adverse clinical events (ie, death, stroke, myocardial infarction, and new renal failure requiring dialysis) were assessed at 30 and 90 days. Clinical outcomes were adjudicated by an expert clinician independent of study design and conduct.

Brain MRI

Brain MRI were scheduled between 3 and 9 days after surgery. The MRI sequences included fluid-attenuated inversion-recovery, gradient-recalled echocardiogram, T2, and DW-MRI with apparent diffusion coefficient mapping. A Siemens 1.5 Tesla machine (Siemens Healthineers AG, Erlanger, Germany) was used and resulting images of cerebral infarcts were subclassified into acute (<24 hours) and subacute (24 hours to 5 days) periods. Covert strokes were defined based on DW-MRI evidence of acute or subacute brain infarcts and the absence of a clinical stroke diagnosis following the brain MRI. The patients, outcome assessors, and clinical team were blinded to the results of the brain MRI to minimize potential evaluation bias. An expert in neuroradiology interpreted each brain MRI for acute infarction, chronic infarction, and incidental clinical findings (eg, tumors).

Brain Oximetry

In the operating room, a trained research coordinator applied 2 adhesive oximeter pads bilaterally over the frontotemporal area before induction of anesthesia. The sensors recorded regional cerebral oxygen saturation values for the duration of surgery with the output monitor covered to ensure that all members of the operative and research teams were blinded to the oximetry transcript to minimize potential treatment bias. During analysis of oximetry transcripts, baseline regional cerebral oxygen saturation measurements were determined for each patient, taken to be the mean of 20 recorded values between 25 and 15 minutes before cardiopulmonary bypass (ie, after the administration of supplemental oxygen by nasal cannula). We defined cerebral oxygen desaturation events as any regional cerebral oxygen saturation values $\geq 20\%$ below baseline in either left or right or both hemispheres during surgery.

Outcomes

The primary outcome of the single-center NeuroVISION Cardiac pilot study was to determine the feasibility of conducting a larger multicenter study of covert stroke in patients undergoing CABG surgery. Feasibility was assessed by determining the overall recruitment rate at our center, the rate of brain MRI completion, and the proportion of patients lost to follow-up. Secondary outcomes included the incidence of covert stroke, delirium, intraoperative cerebral oxygen desaturation events based on oximetry transcripts, cognitive decline at discharge and 30-day follow-up based on MoCA and DSST, global function at 30- and 90-day follow-up based on SAGE, and major adverse cardiovascular events (composite of death, myocardial infarction, clinical stroke, and new renal failure requiring dialysis).

Statistical Analysis

Enrollment of a small series of patients at our center was a convenient sampling method to demonstrate feasibility. The primary analysis was per protocol and included only patients who completed the brain MRI. Patients who did not complete the MRI, completed the MRI but had results that could not be interpreted, or who were diagnosed with clinical stroke between the time of surgery and their MRI were excluded. The secondary analyses compared outcomes of the patients who had (covert stroke group) and who did not have (no covert stroke) a perioperative covert stroke at preoperative baseline, hospital discharge, 30 days, and 90 days after surgery. Analyses of cognitive and global function outcomes included only patients who completed the baseline assessment. Patients not completing assessments at subsequent time points were omitted from comparisons between time points. Changes in cognitive function from baseline were assessed using differences in test scores and clinical thresholds (ie, decrease of ≥ 2 points on the MoCA and decrease of ≥ 5 points on the DSST) used in recent studies.^{7,21} Analyses of oximetry data included only patients with complete intraoperative data who underwent surgery with the use of cardiopulmonary bypass. We report

continuous variables using mean \pm standard deviation (SD) or median (interquartile range [IQR]) after testing for normality and binary or categorical variables as counts and proportions. Overall recruitment and feasibility characteristics are reported for all study participants. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Feasibility Outcomes

A total of 375 participants were screened for eligibility and 66 participants were enrolled over a 48-week period for an overall recruitment rate of 1.4 patients per week (Figure 1). Fifty (76%) of these patients completed the brain DW-MRI resulting in a pragmatic recruitment rate of 1 patient per week. The 16 patients without MRI results were excluded from analyses. The most common reasons for not completing the brain DW-MRI were patient refusal (8 [12%] patients) or contraindication for MRI (5 [8%] patients). A single patient with uninterpretable MRI results was excluded from the analyses. No participants were lost to follow-up at the final 90-day visit.

Baseline and Operative Data

Following the brain MRI study, 19 patients (39%; 95% CI, 26%-53%) had DW-MRI evidence of perioperative covert stroke in comparison to 30 patients (61%; 95% CI, 47%-73%) who did not experience a perioperative covert stroke (Table 1). Baseline characteristics were similar between patients with or without covert stroke. The mean \pm SD age of study participants was 67 ± 9.3 years; 42 (86%) were men; mean European System for Cardiac Operative Risk Evaluation was 4.8 ± 2.3 points; 43 (88%) had hypertension; 20 (41%) had diabetes; and 2 (4%) had a history of stroke.

Operative characteristics were also similar between patients with or without covert stroke. Overall, the mean \pm SD duration of cardiopulmonary bypass and crossclamping were 105.9 ± 26.8 and 79.9 ± 29.0 , respectively; patients received 3.8 ± 0.7 grafts each; and 48 (98%) patients underwent on-pump CABG surgery.

Cognitive and Global Function Assessments

Among all patients, mean \pm SD or median (IQR) preoperative baseline testing scores were 24.2 ± 3.1 on the MoCA; 42.9 ± 13.2 on the DSST; and 2.0 (IQR, 0.0-3.5) on the SAGE (Table 2). No differences in mean baseline scores between groups were found in either MoCA or DSST. However, baseline global function, as measured by SAGE, was superior (ie, lower scores) in patients who had a covert stroke compared with patients who did not have a covert stroke (0.5; IQR, 0.0-2.0 vs 2.0; IQR, 0.0-5.0; $P = .02$). No differences in MoCA or SAGE assessment completion rates were found between groups (Table 3). However, fewer patients completed the

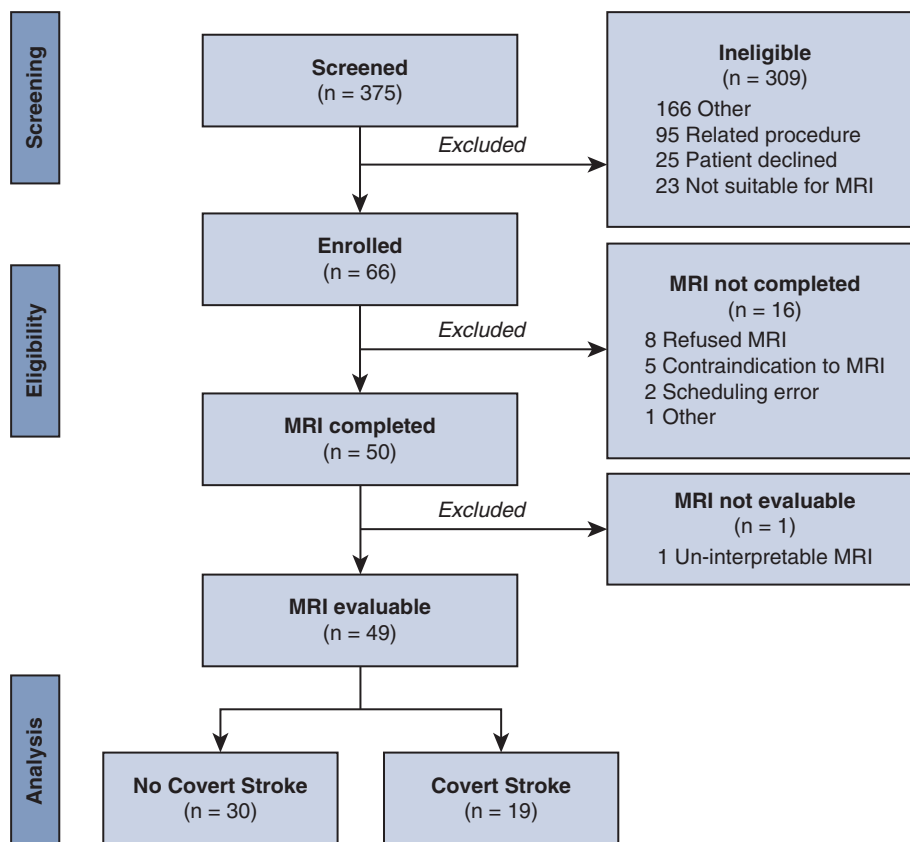


FIGURE 1. Distribution of patients in the pilot study with breakdown of reasons for exclusion. The most common reason for not completing the magnetic resonance imaging (MRI) was patient refusal. Forty-nine patients with evaluable MRI results were included in the final analysis, of whom 19 experienced a covert stroke. Covert strokes were defined based on diffusion-weighted MRI evidence of acute or subacute brain infarcts and the absence of a clinical stroke diagnosis following the brain MRI.

DSST at both baseline and discharge visits in patients who had a covert stroke compared with those who did not have a covert stroke (13 [68%] vs 29 [97%]; $P = .006$).

Changes in mean MoCA and DSST scores from preoperative baseline to discharge after surgery were similar between groups (Table 2). There was a small decline in cognitive function, as measured by the DSST, in patients who had a covert stroke (-0.2 ± 7.2 [1% decline]) that was not observed in patients who did not have a covert stroke (3.6 ± 11.4 [15% increase]) at the time of discharge, but this was followed by improvements in cognitive function in both groups at 30 days after surgery. Increases in cognitive test scores from baseline to 30 days were greater in patients with covert stroke compared with without covert stroke on the MoCA (1.8 ± 2.9 [7% increase] vs 1.2 ± 2.5 [5% increase]; $P = .003$) and DSST (13.4 ± 10.5 [56% increase] vs 11.8 ± 11.8 [27% increase]; $P < .001$). Lastly, there was a lack of improvement in global function, as measured by SAGE (ie, negative changes correspond to improved global function), in patients who had a covert stroke that were not seen in patients who did not have a covert stroke at 30 days (0.0; IQR, -1.0 to 1.0 [0%

improvement] vs -2.0 ; IQR, -3.0 to 0.0 [100% improvement]; $P = .20$) and 90 days after surgery (0.0 ; IQR, -2.0 to 0.0 [0% improvement] vs -0.5 [-3.5 to 0.0] [25% improvement]; $P = .73$).

In addition to changes in mean test scores of the cohort, we also identified patients with clinically relevant declines in cognition function (ie, cognitive decline) from baseline to 30 days after surgery. Cognitive decline, defined as a decrease of ≥ 2 points on the MoCA, occurred in 1 (8%) of 13 patients who had a covert stroke and in 2 (8%) of 24 patients who did not have a covert stroke. Cognitive decline, defined as a decrease of ≥ 5 points on the DSST, occurred in a single patient who did not experience covert stroke.

Clinical Outcomes and Adverse Events

Postoperative delirium occurred in 8 of 49 patients (16%; 95% CI, 8%-29%). Among patients with delirium, 5 (26%) had a covert stroke compared to 3 (10%) who did not have a covert stroke (Figure 2 and Table 4).

Twenty-one of 46 patients (46%; 95% CI, 32%-60%) had cerebral oxygen desaturation events during surgery.

TABLE 1. Baseline and operative characteristics

Characteristic	Overall (N = 49)	No covert stroke (n = 30)	Covert stroke (n = 19)	P value
Age (y)	67.1 ± 9.3	65.5 ± 9.1	69.6 ± 9.4	.14
Male sex	42 (85.7)	26 (86.7)	16 (84.2)	.81
EuroSCORE	4.8 ± 2.3	4.7 ± 2.7	5.0 ± 1.6	.59
History of				
Hypertension	43 (87.8)	26 (86.7)	17 (89.5)	.77
Myocardial infarction	29 (59.2)	19 (63.3)	10 (52.6)	.56
Diabetes	20 (40.8)	10 (33.3)	10 (52.6)	.24
Sleep apnea	11 (22.4)	7 (23.3)	4 (21.1)	.85
Current tobacco use	9 (18.4)	6 (20.0)	3 (15.8)	.71
COPD	5 (10.2)	5 (16.7)	0 (0.0)	.14
Atrial fibrillation	3 (6.1)	2 (6.7)	1 (5.3)	.84
Stroke	2 (4.1)	2 (6.7)	0 (0.0)	.51
Transient ischemic attack	1 (2.0)	0 (0.0)	1 (5.3)	.39
Family history of dementia	0 (0.0)	0 (0.0)	0 (0.0)	—
Intraoperative data				
CPB time (min)	105.9 ± 26.8	103.4 ± 27.2	110.0 ± 26.5	.41
Crossclamp time (min)	79.9 ± 29.0	78.8 ± 28.6	81.9 ± 30.3	.73
No. of grafts per patient	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (3.0-4.0)	.96
On-pump CABG*	48 (98.0)	30 (100)	18 (94.7)	.39
Urgent surgery	46 (93.9)	29 (96.7)	17 (89.5)	.55
Aortic calcification†	4 (8.2)	3 (10.0)	1 (5.3)	.56

Values are presented as mean ± standard deviation, n (%), or median (quartile 1-quartile 3) unless otherwise indicated. *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *COPD*, chronic obstructive pulmonary disease; *CPB*, cardiopulmonary bypass; *CABG*, coronary artery bypass surgery. *A single patient in the covert stroke group underwent off-pump CABG surgery. †Moderate or severe aortic calcification.

Covert stroke was associated with higher rates of cerebral oxygen desaturation events during surgery (12 [67%] patients with covert stroke vs 9 [32%] without covert stroke; *P* = .02) (Figure 2 and Table 4).

Between MRI and 30-day follow-up, 3 (6%) patients had clinical stroke; 2 (11%) with covert stroke, and 1 (3%) without covert stroke (Figure 2 and Table 4). One death occurred within 90 days of surgery in a patient

TABLE 2. Cognitive and global function assessments

Assessment	Overall (N = 49)	No covert stroke (n = 30)	Covert stroke (n = 19)	P value
MoCA*				
Baseline	24.2 ± 3.1	24.2 ± 3.0	24.1 ± 3.3	.95
Change from baseline				
To discharge	0.5 ± 2.4 (2)	0.6 ± 2.1 (3)	0.4 ± 3.0 (2)	.19
To 30 d	1.4 ± 2.6 (6)	1.2 ± 2.5 (5)	1.8 ± 2.9 (7)	.003
Cognitive decline	3/37 (8.1)	2/24 (8.3)	1/13 (7.7)	.95
DSST*				
Baseline	42.9 ± 13.2	44.0 ± 12.8	41.1 ± 14.1	.48
Change from baseline				
To discharge	2.4 ± 10.3 (6)	3.6 ± 11.4 (15)	-0.2 ± 7.2 (-1)	.14
To 30 d	12.4 ± 11.3 (29)	11.8 ± 11.8 (27)	13.4 ± 10.5 (56)	<.001
Cognitive decline	1/38 (2.6)	1/25 (4.0)	0/13 (0.0)	.46
SAGE†				
Baseline	2.0 (0.0, 3.5)	2.0 (0.0, 5.0)	0.5 (0.0, 2.0)	.02
Change from baseline				
To 30 d	0.0 (-3.0, 0.0) (0)	-2.0 (-3.0, 0.0) (-100)	0.0 (-1.0, 1.0) (0)	.20
To 90 d	0.0 (-3.0, 0.0) (0)	-0.5 (-3.5, 0.0) (-25)	0.0 (-2.0, 0.0) (0)	.15

Values are presented as mean ± standard deviation, mean ± standard deviation (% change from baseline), median (quartile 1, quartile 3) (% change from baseline), or n/N (%). Total numbers are included when they differ from those in the overall study group. *MoCA*, Montreal Cognitive Assessment; *DSST*, Digit Symbol Substitution Test; *SAGE*, Standard Assessment of Global Activities in the Elderly. *For both *MoCA* and *DSST*, a positive change from baseline represents an improvement in test score (cognitive improvement), whereas negative change represents a decline in test score (cognitive decline). †For *SAGE*, a negative change from baseline represents an improvement in test score (functional improvement), whereas positive change represents a decline in test score (functional decline).

TABLE 3. Assessment completion rates

Assessment	Overall (N = 49)	No covert stroke (n = 30)	Covert stroke (n = 19)	P value
MoCA				
Baseline	46 (94)	29 (97)	17 (89)	.31
Change from baseline				
To discharge	40 (82)	27 (90)	13 (68)	.06
To 30 d	37 (76)	24 (80)	13 (68)	.36
DSST				
Baseline	47 (96)	30 (100)	17 (89)	.07
Change from baseline				
To discharge	42 (86)	29 (97)	13 (68)	.006
To 30 d	38 (78)	25 (83)	13 (68)	.22
SAGE				
Baseline	48 (98)	30 (100)	18 (95)	.20
Change from baseline				
To 30 d	46 (94)	28 (93)	18 (95)	.84
To 90 d	45 (92)	28 (93)	17 (89)	.63

Values are presented as n (%). *MoCA*, Montreal Cognitive Assessment; *DSST*, Digit Symbol Substitution Test; *SAGE*, Standard Assessment of Global Activities in the Elderly.

who had covert stroke followed by a clinical stroke 10 days later.

Patients with covert stroke may have an increased demand of health care resources. Median length of in-hospital stay was 2.5 days longer in patients who had a covert stroke (10.0 days; IQR, 6.0-14.0 days) compared with patients who did not have a covert stroke (7.5 days; IQR, 6.0-10.0 days). In addition, 17 (90%) patients with covert stroke were discharged home from the hospital compared to 29 (97%) patients without covert stroke.

DISCUSSION

This study demonstrates the feasibility of conducting a large cohort study to clearly establish the potential association between covert stroke and cognitive decline in patients 1 year after cardiac surgery and to determine whether surgical techniques that aim to reduce or avoid aortic manipulation can reduce rates of covert stroke. The primary outcome of NeuroVISION Cardiac pilot was feasibility. We demonstrated feasibility of DW-MRI scanning 3 to 9 days after CABG surgery at a rate of 1 patient per week. At our center, we were limited to 1 brain MRI series for the purpose of research per week due to limited availability of the MRI scanner. In the main study, we will recruit from multiple collaborating centers to overcome the limited MRI availability at our center. In addition, no patients were lost to follow-up at the final 90-day visit. Together, these results demonstrate good feasibility of the study protocol that will be used to inform the main study (Video 1).

We found a high incidence of perioperative covert stroke (39%), which was more than 6-fold higher than the

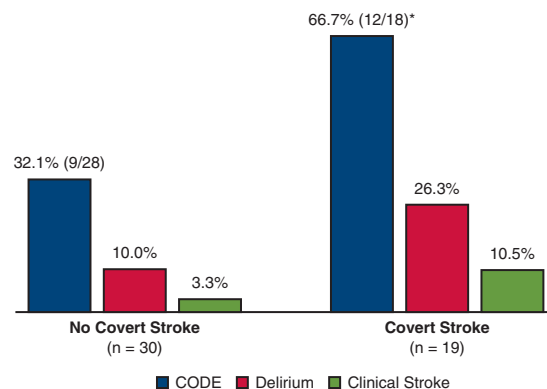


FIGURE 2. Shown left to right is the incidence of intraoperative cerebral oxygen desaturation events (blue bars), postoperative delirium (red bars), and clinical stroke within 30 days of coronary artery bypass grafting (CABG) surgery (green bars) in patients not experiencing (left) or experiencing (right) a perioperative covert stroke. Cerebral oxygen desaturation events (CODEs) occurred when regional cerebral oxygen saturation (ie, oximetry) values declined $\geq 20\%$ below baseline in either left, right, or both hemispheres during surgery. Three patients were excluded from the oximetry analysis: 2 patients with incomplete transcripts and 1 patient undergoing off-pump CABG surgery. *Covert stroke was associated with higher rates of CODEs during surgery (12 [67%] patients experiencing covert stroke vs 9 [32%] without covert stroke [$P = .02$]).

incidence of clinical stroke (6%) in patients undergoing CABG surgery. Similar differences between covert stroke and clinical stroke rates have been reported in other small studies (covert stroke vs clinical stroke [fold change]): 16% versus 2% [8-fold] in a study of 50 patients²²; 28% versus 3% [9-fold] in a study of 127 patients²³; and 20% versus 2% [10-fold] in a study of 104 patients.²⁴ The relatively high incidence of covert stroke and clinical stroke in our study may, in part, be explained by the relatively high mean age (67 years vs 61 years²³ or 69 years²⁴) of our cohort, as age is well-known risk factor for covert stroke.⁵ Our cohort also had at least 1 risk factor necessary for inclusion and thus would be expected to have an elevated risk of covert stroke compared with the other studies.

We also found high rates of clinical stroke in patients who had a covert stroke compared with patients who did not have a covert stroke (11% vs 3%). Large population-based studies⁹⁻¹² and the large NeuroVISION⁷ study of noncardiac surgery patients suggest there is an association between covert stroke and future clinical stroke. These results are consistent with our findings and suggest that covert stroke increases the risk of future clinical stroke. If so covert stroke may serve as a valuable marker for predicting/preventing clinical stroke. The main NeuroVISION Cardiac study will definitively establish whether or not this association exists in the cardiac surgery setting.

The NeuroVISION Cardiac pilot study is the first study to examine the relationship between covert stroke and postoperative delirium in patients undergoing isolated

TABLE 4. Clinical outcomes and adverse events

Outcome	Overall (N = 49)	No covert stroke (n = 30)	Covert stroke (n = 19)	P value
Perioperative				
Delirium	8 (16.3)	3 (10.0)	5 (26.3)	.13
Delirium burden	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	.26
Cerebral oxygen desaturation event*	21/46 (45.7)	9/28 (32.1)	12/18 (66.7)	.02
Adverse events at 30 d				
Composite of death, MI, clinical stroke, and new renal failure requiring dialysis	3 (6.1)	1 (3.3)	2 (10.5)	–
Death (all-causes)	0 (0.0)	0 (0.0)	0 (0.0)	–
MI	0 (0.0)	0 (0.0)	0 (0.0)	–
Clinical stroke	3 (6.1)	1 (3.3)	2 (10.5)	–
New renal failure requiring dialysis	0 (0.0)	0 (0.0)	0 (0.0)	–
Adverse events at 90 d				
Composite of death, MI, clinical stroke, and new renal failure requiring dialysis	3 (6.1)	1 (3.3)	2 (10.5)	–
Death (all causes)	1 (2.0)	0 (0.0)	1 (5.3)	–
MI	0 (0.0)	0 (0.0)	0 (0.0)	–
Clinical stroke	3 (6.1)	1 (3.3)	2 (10.5)	–
New renal failure requiring dialysis	0 (0.0)	0 (0.0)	0 (0.0)	–
Use of health care resources				
ICU length of stay (d)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	.85
Hospital length of stay (d)	9.0 (6.0-11.0)	7.5 (6.0-10.0)	10.0 (6.0-14.0)	.12
Patients discharged to home	46 (93.9)	29 (96.7)	17 (89.5)	.31

Values are presented as mean \pm standard deviation, n (%), n/N (%), or median (quartile 1-quartile 3). Total numbers are included when they differ from those in the overall study group. *MI*, Myocardial infarction; *ICU*, intensive care unit. *Three patients were excluded from the cerebral oxygen desaturation analysis: 2 patients with incomplete transcripts and 1 patient undergoing off-pump coronary artery bypass graft surgery.

CABG surgery. The overall incidence of delirium was 16%, with high rates of delirium in patients who had a covert stroke compared with patients who did not have a covert stroke (26% vs 10%).⁷ A similar result was found in a secondary analysis of a randomized trial with brain DW-MRI, where evidence of new ischemic lesions was found in 18 out of 28 (64%) patients who had postoperative delirium and in 26 out of 51 (51%) patients who did not have delirium.²⁵ Our results are also consistent with recent findings from the NeuroVISION study, which demonstrated that perioperative covert stroke was associated with an increased risk of perioperative delirium in patients undergoing noncardiac surgery (hazard ratio, 2.24; 95% CI, 1.06-4.73; absolute

risk increase 6%; $P = .03$). Together, these results support the hypothesis that covert stroke is associated with delirium after cardiac surgery. Future work should evaluate surgical techniques that aim to minimize aortic manipulation, such as the anaortic off-pump coronary artery bypass technique because this technique shows promise for decreasing the incidence of postoperative delirium (odds ratio, 0.26; 95% CI, 0.09-0.68; $P = .002$) and early cognitive decline (odds ratio, 0.20; 95% CI, 0.06-0.58; $P < .001$) compared with the traditional off-pump technique.²⁶

We showed that covert stroke is associated with higher rates of cerebral oxygen desaturation events during CABG surgery (67% vs 32%). A recent study of brain oximetry and DW-MRI in cardiac surgery patients found no difference in cerebral oxygen desaturation events between patients who had evidence of a DW-MRI lesion (44 [54%]) and patients who did not have evidence of a DW-MRI lesion (30 [43%]).²⁷ In a separate analysis of the oximetry data we examined outcomes by intraoperative decline in oxygen saturation. Among 19 patients with covert stroke, 10 (44%) patients had a cerebral oxygen desaturation event and 9 (35%) did not have a cerebral oxygen desaturation event.²⁸ Together, these results suggest that covert strokes (ie, cerebral ischemia) may be associated with acute declines in brain oxygenation (ie, cerebral hypoxemia).

Our study has several strengths. NeuroVISION Cardiac pilot has provided data to inform sample size calculations,



VIDEO 1. A video summary of the main results, relevance, and insights gained from the study. Video available at: [https://www.jtcvs.org/article/S2666-2736\(20\)30081-4/fulltext](https://www.jtcvs.org/article/S2666-2736(20)30081-4/fulltext).

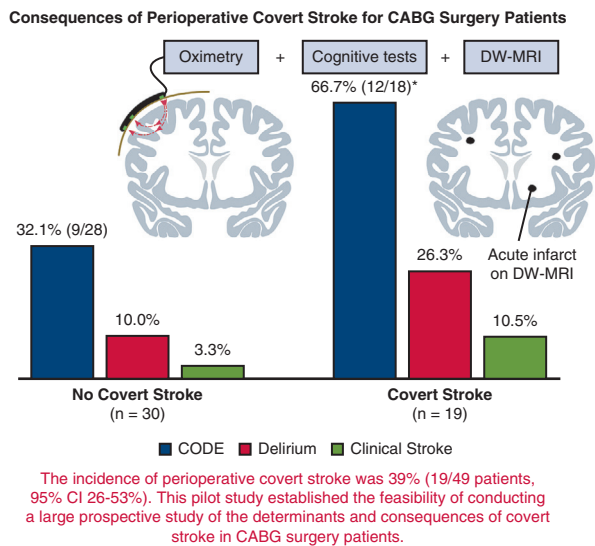


FIGURE 3. Shown left to right is the incidence of intraoperative cerebral oxygen desaturation events (blue bars), postoperative delirium (red bars) and clinical stroke within 30 days of coronary artery bypass grafting (CABG) surgery (green bars) in patients not experiencing (left) or experiencing (right) a perioperative covert stroke. Cerebral oxygen desaturation events (CODEs) occurred when regional cerebral oxygen saturation (ie, oximetry) values declined $\geq 20\%$ below baseline in either left, right, or both hemispheres during surgery. Cognitive tests were administered before surgery, at hospital discharge and again 30 days after surgery. Acute infarcts (visible on diffusion-weighted magnetic resonance imaging [DW-MRI] sequences) were present only in the brain (schematic diagrams in grey) of patients who experienced a perioperative covert stroke (black dots within the right brain diagram). Brain diagrams (frontal sections only) are not drawn to scale. Three patients were excluded from the oximetry analysis: 2 patients with incomplete transcripts and 1 patient undergoing off-pump CABG surgery. CI, Confidence interval; *Covert stroke was associated with higher rates of CODEs during surgery (12 [67%] patients experiencing covert stroke vs 9 [32%] without covert stroke [$P = .02$]).

number of sites required, and expected costs for a larger cohort study of the association between covert stroke and cognitive decline. This study is among the first to examine the relationship between covert stroke and postoperative delirium in patients undergoing isolated CABG surgery to report an association between covert stroke and acute declines in regional cerebral oxygen saturation (Figure 3).

Limitations

Our study also has several limitations. The single-center pilot study design has limited generalizability and was not powered to inform the clinical or cognitive influence of covert stroke. In this regard, the P values provided should be interpreted with caution. For logistical reasons, follow-up was limited to 30 days. Cognitive assessment scores often improve moderately (Cohen's d , 0.36-1.19) with repeat testing over short intervals (within 90 days) in adults due to the practice effect.^{28,29} In the full-scale study, we intend

to extend the follow-up to 1 year after surgery to minimize practice effects and to evaluate the long-term consequences of covert stroke because several studies suggest that deficits in cognitive function can persist up to 1 year after cardiac surgery.^{2,6} Twelve (24%) patients did not complete both the baseline and 30-day MoCA limiting the analysis of changes in cognitive function. To minimize systematic bias from incomplete MoCA assessments we will collect the reasons for missing data and will use a method of evidence-informed data imputation in the larger study.

CONCLUSIONS

There is growing interest in determining the causes and consequences of covert strokes, especially in cardiac surgery patients who are at high risk for neurological complications. This pilot study established the feasibility of conducting a large prospective cohort study of covert stroke in CABG surgery patients and suggests that more than 1 in 3 patients aged 67 ± 9 years will experience a perioperative covert stroke. A larger study is needed now to clearly establish an association between covert stroke and cognitive decline 1 year after surgery and determine whether surgical techniques that aim to reduce or avoid aortic manipulation can reduce rates and consequences of covert stroke.

Conflict of Interest Statement

Medtronic provided access to a NIRS monitor for the duration of the study. Dr Mukul Sharma declares financial relationships with Bayer and Bristol Myers Squibb. Funding was received from Regional Medical Associates in the form of a Resident Research grant. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: stroke, covert, delirium, cognitive, coronary artery bypass graft surgery, CABG, magnetic resonance imaging, MRI, oximetry

APPENDIX 1. STUDY QUESTIONNAIRES

Assessments of Cognitive Decline

The Montreal Cognitive Assessment (MoCA) is used extensively to measure cognitive decline after stroke and cerebrovascular disease. It has proved superior to the Mini-Mental State Exam, in assessments of language skills, visuo-spatial and executive function, and in the diagnosis of cognitive decline after stroke.^{1,2} The MoCA has shown good sensitivity and specificity for cognitive decline when compared with the full 60-minute National Institute of Neurological Disorders and Stroke battery of neuropsychological assessments 1 year after stroke.³ The MoCA instrument assesses multiple cognitive domains, and we believe this will provide a thorough assessment of the influence of acute perioperative covert stroke. MoCA scores range from 0 to 30 with higher a higher score indicating superior cognitive function. In the CABG Off- or On-Pump Revascularization Study (CORONARY) trial (n = 2081) the average MoCA score was 23.2 ± 4 before coronary artery bypass graft (CABG) surgery.⁴ Average MoCA scores at preoperative baseline were similar (24.2 ± 3) in our NeuroVISION Cardiac pilot study. A decrease of 2 points or more in MoCA score is perceived to be important to patients, and has been used as a cutoff for important cognitive decline.⁵⁻⁸ In addition, patients with covert stroke are reported to have lower standardized mean MoCA scores compared with patients without covert stroke (standard mean difference -3.36 points; 95% confidence interval, -5.90 to -0.82 ; $P = .01$).⁹

The Digit Symbol Substitution Test (DSST) is a common clinical test that is sensitive to cognitive decline and to changes in cognitive decline across a wide range of clinical populations.¹⁰ The DSST evaluates cognitive speed, attention, and executive functions by requiring participants to match symbols to numbers within a 120 second time limit using a key. Scores range from 0 to a maximum of 133 with a higher score indicating superior cognitive ability. In the CORONARY trial (n = 1975) the average DSST score was 32.5 ± 17.9 before CABG surgery.⁴ In our NeuroVISION Cardiac pilot study the average DSST scores was 42.9 ± 13 before CABG surgery. A decrease of 5 or more points on the DSST is considered clinically meaningful cognitive decline on the basis of differences in score observed between patients aged 70 and 75 years in the Cardiovascular Health Study.^{8,11,12} We will use this threshold to identify patients with cognitive decline.

Assessment of Global Function

The Standard Assessment of Global-activities in the Elderly (SAGE) is a simple and brief 15-item assessment

of ability to independently carry out daily activities of independent living (ie, global function) in older adults. Points are awarded when some, moderate, or complete help is required to carry out a task. SAGE scores range from 0 to 45 with lower scores indicating superior physical function. In our NeuroVISION Cardiac pilot study the average SAGE scores was 2.4 ± 2.7 before CABG surgery. The test has recently (ie, 2019) proven useful in cognitive substudies of the large Heart Outcomes Prevention Evaluation-3 (HOPE-3)⁸ and Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS)¹³ trials.

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APPENDIX TABLE 1. List of participating surgeons by enrollment rate

Name	No. of patients enrolled
André Lamy	27
Lloyd Semelhago	17
Adel Dyub	11
Dominic Parry	5
Victor Chu	2
Irene Cybuslky	2
Jee-Yong (John) Lee	2
Total	66

APPENDIX TABLE 2. List of study personnel by role

Name	Role
Peter Koh	Biometrics programmer
Marko Mrkobrada	Co-investigator
PJ Devereaux	Co-investigator
Richard Whitlock	Co-investigator
Yannick LeManach	Co-investigator
Jessica Spence	Co-investigator/project officer
Lisa Trombetta	Data management
Mukul Sharma	Neurologist
Sara Hussain	PhD student
André Lamy	Principal investigator
Jessica Vincent	Project manager
Shirley Pettit (former)	Project manager
Shauna Kennedy	Radiologist
Austin Browne	Research assistant
Patricia Power	Research assistant
Sarah Apolcer	Research assistant
Tracy Boland	Research assistant
Ingrid Copland	Research coordinator
Hyejung Jung (former)	Statistician
Rajibul Mian	Statistician
Amelia Trombetta	Undergraduate student
Stephanie Gagnon	Undergraduate student