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Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke

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Editor's key points

- Impaired cerebral autoregulation may predispose to ischaemic brain injury.
- The authors found that impaired cerebral autoregulation occurred in 20% of patients during cardiopulmonary bypass.
- An autoregulation index measured with near infrared spectroscopy was able to identify impaired autoregulation.
- Impaired autoregulation was more common in patients developing stroke after surgery than those without a stroke.

Background. Impaired cerebral autoregulation may predispose patients to cerebral hypoperfusion during cardiopulmonary bypass (CPB). The purpose of this study was to identify risk factors for impaired autoregulation during coronary artery bypass graft, valve surgery with CPB, or both and to evaluate whether near-infrared spectroscopy (NIRS) autoregulation monitoring could be used to identify this condition.

Methods. Two hundred and thirty-four patients were monitored with transcranial Doppler and NIRS. A continuous, moving Pearson's correlation coefficient was calculated between mean arterial pressure (MAP) and cerebral blood flow (CBF) velocity, and between MAP and NIRS data, to generate the mean velocity index (Mx) and cerebral oximetry index (COx), respectively. Functional autoregulation is indicated by an Mx and COx that approach zero (no correlation between CBF and MAP); impaired autoregulation is indicated by an Mx and COx approaching 1. Impaired autoregulation was defined as an Mx ≥ 0.40 at all MAPs during CPB.

Results. Twenty per cent of patients demonstrated impaired autoregulation during CPB. Based on multivariate logistic regression analysis, time-averaged COx during CPB, male gender, Pa_{CO_2} , CBF velocity, and preoperative aspirin use were independently associated with impaired CBF autoregulation. Perioperative stroke occurred in six of 47 (12.8%) patients with impaired autoregulation compared with five of 187 (2.7%) patients with preserved autoregulation ($P=0.011$).

Conclusions. Impaired CBF autoregulation occurs in 20% of patients during CPB. Patients with impaired autoregulation are more likely than those with functional autoregulation to have perioperative stroke. Non-invasive monitoring autoregulation may provide an accurate means to predict impaired autoregulation.

Clinical trials registration. www.clinicaltrials.gov (NCT00769691).

Keywords: cardiac surgery; cardiopulmonary bypass; cerebral autoregulation; stroke

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Autoregulation of cerebral blood flow (CBF) ensures delivery of oxygenated blood to the brain commensurate with cerebral O_2 demand. Intact autoregulation protects the brain from ischaemia caused by acute arterial pressure fluctuations. In contrast, disturbed autoregulation has been found to be independently associated with mortality after brain injury.^{1,2} CBF autoregulation can be monitored in real time by measuring the CBF velocity of the middle cerebral arteries with transcranial Doppler (TCD) and calculating its correlation with cerebral perfusion pressure.^{2–4} When arterial pressure is within the autoregulatory range, there is no correlation

between CBF and arterial pressure. In contrast, when arterial pressure is outside the autoregulatory range or when autoregulation is impaired, CBF and arterial pressure are correlated.

Near-infrared spectroscopy (NIRS) is commonly used during cardiac surgery to monitor regional cerebral O_2 saturation ($rSCo_2$).⁵ We have previously demonstrated that slow waves of cerebral oximetry in relation to arterial pressure can serve as a clinically useful monitor of autoregulation.^{6,7} Because the majority of light-absorbing chromophores in the cranium are venous haemoglobin, $rSCo_2$ provides an index of cerebral O_2

supply vs O_2 metabolic demand. Many determinants of rS_{CO_2} , such as Pa_{O_2} and cerebral metabolic rate of O_2 , are relatively stable over short periods of time; therefore, the fluctuations in rS_{CO_2} provide a surrogate of CBF.^{4–8} Monitoring autoregulation with NIRS circumvents deficiencies associated with TCD monitoring (e.g. lack of insonating window in some patients, the need for frequent transducer readjustments, and the susceptibility to electric cautery interference) and enables continuous CBF autoregulation monitoring in diverse clinical settings, including operating theatres and the intensive care unit.

In previous investigations, we have found that autoregulation is impaired in 24% of patients during CPB and more than twice that many during re-warming from hypothermia.⁹ Identifying patients who are susceptible to impaired autoregulation during CPB might allow for focused patient management strategies aimed at reducing cerebral injury. The purpose of this study was to identify risk factors for impaired autoregulation in adult patients undergoing cardiac surgery with CPB. We further sought to evaluate the usefulness of autoregulation monitoring with NIRS for identifying this condition.

Methods

Patients

From December 8, 2008, to October 2, 2010, we enrolled patients into a prospective study to evaluate the accuracy of NIRS autoregulation monitoring. Data from this cohort have been previously reported.^{7–9, 10} All enrolled patients provided written informed consent and were undergoing coronary artery bypass graft (CABG) surgery, valvular surgery, or both that required CPB. The study was approved by The Johns Hopkins Medical Institutions Investigational Review Board. Patients were excluded if the surgery was emergent or when concomitant carotid endarterectomy was planned.

Direct radial artery arterial pressure and nasal temperature were monitored in all patients. Anaesthesia was induced and maintained with midazolam, fentanyl, and isoflurane; pancuronium was given for skeletal muscle relaxation. Non-pulsatile CPB was achieved with a non-occlusive roller pump, a membrane oxygenator, and a 27 μ m arterial line filter. The CPB flow rate was kept between 2.0 and 2.4 litre min^{-2} and α -stat pH management. During CPB, the concentrations of isoflurane were kept between 0.5% and 1.0% with a vaporizer connected to oxygenator inflow and titrated to mean arterial pressure (MAP). Haemoglobin level and arterial blood gases were measured after tracheal intubation, 10 min after initiation of CPB, and then hourly. Gas flow to the oxygenator of CPB was controlled to maintain normocarbica based on arterial Pa_{CO_2} results or continuous inline arterial blood gas monitoring. Clinical management of CPB was based on institutional standards, including transfusion of packed red blood cells, arterial pressure targets, and re-warming rate. Postoperative care included continuous ECG monitoring. A stroke was defined as a new global or focal neurological deficit lasting >24 h. Stroke was diagnosed based on clinical examination that was confirmed by a neurologist and often with brain imaging.

Autoregulation monitoring

NIRS rS_{CO_2} monitoring with an INVOS (Somenetics, Inc., Troy, MI, USA) monitor and bilateral TCD monitoring (Doppler Box, DWL, Compumedics, Charlotte, NC, USA) of the middle cerebral arteries were performed as previously described.^{6–9, 10} Digitized arterial pressure, TCD, and NIRS signals were processed with ICM+ software (University of Cambridge, Cambridge, UK). The signals were time-integrated as non-overlapping 10 s mean values, a method equivalent to applying a moving average filter with a 10 s time window and resampling at 0.1 Hz. High-frequency noise from the respiration and pulse waveforms was eliminated by this process, and oscillations and transients that occur below 0.05 Hz were detected as well. The arterial pressure, TCD, and NIRS signals were further high-pass filtered with a DC cut-off set at 0.003 Hz to remove slow drifts associated with haemodilution at the onset of bypass, blood transfusions, cooling, and re-warming. A continuous, moving Pearson's correlation coefficient was calculated between the MAP and CBF velocity, and between MAP and NIRS data, rendering the variables Mx (mean velocity index) and COx (cerebral oximetry index).^{6–9, 10} Consecutive, paired, 10 s averaged values from 300 s' duration were used for each calculation, incorporating 30 data points for each index. When autoregulation is intact, there is no correlation between CBF and MAP, and Mx and COx approach 0; when autoregulation is impaired, Mx and COx values approach 1.

Data analysis

Mx values were categorized in 5 mm Hg bins of MAP for each patient. The Mx value indicating impaired autoregulation is not known, but based on our prior work and data from neurosurgical patients, it is likely to be between 0.3 and 0.5.^{4–6, 10} Mx can increase if arterial pressure decreases below the lower limit of autoregulation or if processes that mediate microcirculatory autoregulatory compensations to arterial pressure changes are impaired. For the former, an increase in Mx with decreasing or increasing arterial pressure would be evident with a plateau of Mx approaching zero over a range of MAPs (Fig. 1A). For the purpose of this analysis, impaired autoregulation was defined as an Mx value of ≥ 0.40 at all recorded MAPs during CPB (Fig. 1B).

Based on the Mx cut-off of 0.40, we categorized patients into those with and those without impaired autoregulation. In addition to this categorization, time-averaged Mx and COx data from both hemispheres were averaged and included in the analysis. Differences between the groups in patient characteristic, operative, and physiological characteristics during surgery were compared by using analysis of variance for continuous data and Fisher's exact test for dichotomous data. Non-parametric data were log transformed before analysis. Linear regression was performed between the average Mx and factors that could influence CBF, including Pa_{CO_2} , CBF velocity, and prior stroke. Multivariate logistic regression was performed to identify variables

Fig 1 Monitoring results from a patient with (A) intact CBF autoregulation and (B) impaired CBF autoregulation during CPB. In A and B, the top graph is MAP, and the middle two graphs are the mean velocity index (Mx) for the right and left brain hemispheres. The bottom graph is the percentage of time during the recording at each 5 mm Hg bin of arterial pressure. When arterial pressure is within the autoregulation range, Mx approaches zero. When arterial pressure is outside the autoregulatory range, Mx increases toward 1 as CBF and arterial pressure become correlated. Using an Mx cut-off of ≥ 0.40 , arterial pressure of the patient shown in (A) approaches the lower limit of autoregulation at around 75 mm Hg, while the upper limit of autoregulation is approached at an MAP of 100 mm Hg. In contrast, the patient in (B) demonstrates impaired autoregulation at all arterial pressure readings.

that were independently associated with impaired autoregulation. Variables that differed between the groups at $P < 0.2$ based on univariate analysis and also patient age, history of stroke, and P_{aCO_2} were included in the model. A receiver operator characteristic (ROC) curve was constructed for the multivariate model. Statistical analysis was performed with Stata software version 11 (StataCorp LP, College Station, TX, USA).

Results

Of 234 patients included in this analysis, 47 (20%) met the definition of impaired CBF autoregulation. Patient and operative characteristics are listed in Table 1. Compared with patients who had preserved autoregulation during CPB, patients with impaired autoregulation were more likely to be male and less likely to have a history of chronic

Table 1 Patient characteristic and operative data for patients with and without impaired CBF autoregulation during CPB. *Values are listed as number with percentage in parentheses unless otherwise noted. †Impaired autoregulation was defined as a mean velocity index of ≥ 0.40 for all 5 mm Hg MAP bins. ACE, angiotensin-converting enzyme; AVR, aortic valve replacement; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; MVR, mitral valve replacement

Parameter	Intact autoregulation* (n=187)	Impaired autoregulation*† (n=47)	P-value
Age [(mean (range))]	66 (52–88)	66 (46–89)	0.645
Male/female gender	142 (76)/45 (24)	46 (98)/1 (2)	<0.0001
Prior stroke	15 (8)	6 (13)	0.392
Hypertension	141(75)	31(66)	0.362
Diabetes	57 (30)	16 (34)	0.724
COPD	24 (13)	1 (2)	0.034
Current tobacco abuse	30 (16)	8 (17)	1.0
Peripheral vascular disease	22 (12)	7 (15)	0.616
Congestive heart failure	32 (17)	4 (8)	0.177
Left ventricular ejection fraction <30%	22 (12)	6 (12)	1.0
Prior myocardial infarction	60 (32)	14 (30)	0.861
Prior cardiac surgery	9 (5)	4 (8)	0.307
Left carotid artery stenosis			0.878
<50%	79 (42)	20 (42)	
50–69%	10 (5)	2 (4)	
70–99%	2 (1)	1 (2)	
>99%	0	0	
Right carotid artery stenosis			0.263
<50%	83 (44)	21 (45)	
50–69%	8 (4)	1 (2)	
70–99%	1 (1)	1 (2)	
>99%	0	1 (2)	
Medications			
Aspirin	120 (64)	36 (76)	0.164
β -Blockers	110 (59)	27 (57)	0.868
Statin drugs	118 (63)	29 (62)	0.866
Calcium channel blockers	27 (14)	10 (21)	0.261
ACE inhibitors	56 (30)	18 (38)	0.300
Type of surgery			0.656
CABG	113 (60)	35 (74)	
CABG/AVR	21 (11)	3 (6)	
CABG/MVR or repair	5 (3)	0	
AVR	29 (15)	6 (13)	
MVR or repair	11 (6)	1 (2)	
Ascending aorta replacement	3 (2)	1 (2)	
Valve-sparing aortic root replacement	5 (3)	1 (2)	
Cardiopulmonary bypass duration (min)	114 (44)	110 (42)	0.537
Aortic cross-clamp duration (min)	76 (31)	71 (26)	0.333

Table 2 MAP, arterial blood gas, and other physiological data during CPB for patients with and without impaired CBF autoregulation. Results are given as means (sd). Mx, mean velocity index; COx, cerebral oximetry index; CPB, cardiopulmonary bypass; MCA CBF, middle cerebral artery cerebral blood flow. *Right- and left-sided Mx and COx are combined and averaged for the entire duration of CPB

Variable	Intact autoregulation (n=187)	Impaired autoregulation (n=47)	P-value
Mean arterial pressure (mm Hg)	73 (8)	75 (11)	0.563
Average Mx*	0.27 (0.12)	0.52 (0.08)	<0.0001
Average COx*	0.24 (0.16)	0.37 (0.16)	<0.0001
pH	7.38 (0.02)	7.39 (0.04)	0.777
PaCO ₂ (kPa)	5.3 (0.5)	5.3 (0.5)	0.215
PaO ₂ (kPa)	34.9 (5.8)	35.0 (7.0)	0.897
Lowest haemoglobin (g dl ⁻¹)	8.7 (1.3)	8.9 (1.4)	0.271
Average middle cerebral artery CBF velocity (cm s ⁻¹)			
Left	33.5 (11.8)	39.0 (9.9)	0.009
Right	31.9 (10.5)	37.3 (10.5)	0.003
Frontal cerebral O ₂ saturation			
Left	55.6 (9.1)	58.6 (8.7)	0.046
Right	55.9 (9.9)	60.1 (8.9)	0.0009
Average temperature during CPB re-warming (°C)	35.0 (1.7)	35.2 (1.9)	0.636
Peak temperature during CPB re-warming (°C)	36.8 (1.1)	36.8 (0.9)	0.698

obstructive pulmonary disease. Patient age, the frequency of prior cerebral vascular accident, diabetes, hypertension, and duration of CPB and aortic cross-clamping did not differ between the two groups.

Physiological variables and cerebral measurements during CPB are listed in Table 2. Compared with patients who had preserved autoregulation during CPB, those with impaired autoregulation had a higher average Mx and COx during CPB and also higher CBF velocity and rScO₂. MAP and other listed variables, including average temperature and peak temperature during re-warming, were similar between the two groups. The average CBF velocity during CPB was correlated with the average Mx ($r^2=0.125$, $P<0.0001$). There was no correlation between the average Mx during CPB and PaCO₂ ($P=0.5446$), age ($P=0.401$), or history of stroke ($P=0.545$).

Variables independently associated with impaired autoregulation are listed in Table 3. Time-averaged COx during CPB,

Table 3 Adjusted risk factors for impaired autoregulation during CPB. COx, cerebral oximetry index; CBF, cerebral blood flow velocity measured with TCD

Variable	Odds ratio	P-value	95% confidence interval
Average COx	1.04	<0.001	1.02–1.07
Average middle cerebral artery CBF velocity	1.05	0.003	1.02–1.09
Male gender	10.61	0.024	1.36–82.8
PaCO ₂	2.13	0.054	0.99–1.07
Preoperative aspirin	2.24	0.059	0.97–5.19

average CBF velocity, PaCO₂, and preoperative aspirin use were independently associated with risk for impaired CBF autoregulation during CPB. Male gender also identified risk for impaired autoregulation, but this variable may have been overfitted in the light of the small number of women with this condition. The area under the ROC curve was 0.799.

Six of the 47 (12.8%) patients with impaired autoregulation experienced a new stroke after surgery compared with five of the 187 (2.7%) patients with preserved autoregulation ($P=0.011$). Eight of the strokes were detected within 1 day of surgery, while the remaining strokes were detected after the second postoperative day. Five of the six strokes in patients with impaired autoregulation were detected within 1 day of surgery. Two strokes in patients without impaired autoregulation were detected within 1 day of surgery. Based on clinical indications, six patients underwent computed tomography scanning and four patients underwent magnetic resonance imaging. In patients with brain imaging, all strokes appeared to be embolic in origin, but a definitive aetiology could not be ascertained since there was no standardized imaging protocol.

Discussion

In this study, we observed impaired CBF autoregulation in 20% of patients during CPB. Based on multivariate logistic regression analysis, time-averaged COx during CPB, average CBF velocity, PaCO₂, preoperative aspirin use, and male gender were independently associated with impaired CBF autoregulation. Perioperative stroke was more common in patients with impaired autoregulation than in those with preserved autoregulation.

Perioperative brain injury, manifest as stroke, cognitive decline, or delirium, continues to negatively impact survival, quality of life, and healthcare costs of patients undergoing cardiac surgery.¹¹ Of particular concern is the potential for increased frequency of these complications, given the increasing proportion of surgical patients who are aged and have preexisting cerebral vascular disease.^{12 13} Impaired CBF autoregulation might contribute to brain ischaemic injury when arterial pressure is low such as during CPB. Further, impaired autoregulation could lead to brain

hyperaemia with high arterial pressure that could increase cerebral embolic load and promote cerebral oedema in the setting of systemic inflammation from CPB.¹⁴ Cerebral hyperaemia is a proposed mechanism of acute delirium in patients with hypertensive emergency.¹⁵

Prior studies of autoregulation during CPB upon which the fundamentals of patient arterial pressure management are derived used intermittent assessments of CBF using ¹³³Xe washout or N₂O dilution methods.^{16–19} The statistical approach to some of these studies has been questioned, including their use of regression analysis from pooled discrete data from multiple patients.²⁰ Rather than using intermittent autoregulation testing, our study used continuous CBF autoregulation monitoring that is better able to detect individual dynamics of this physiological process. In this regard, this cohort provides details of CBF autoregulation during CPB not previously examined. Our approach to autoregulation monitoring is accomplished by continuously assessing the relationship between slow waves (0.003–0.04 Hz) in CBF and cerebral perfusion pressure.^{4 6 7} The many haemodynamic fluctuations during surgery, and the presence of arterial pressure and CBF velocity slow waves even during non-pulsatile CPB, allows for the application of this method in cardiac surgical patients.⁷ Since vacuum-assisted CPB venous drainage causes wide fluctuations in central venous pressure, we report MAP and not cerebral perfusion pressure (calculated as the difference between MAP and intracranial pressure or central venous pressure, whichever is higher).

Although TCD has been validated as a clinically reliable means for assessing autoregulation, it has limitations that preclude its routine use for continuous autoregulation monitoring.^{21–23} These limitations include artifact from electrocautery and patient movement that are particularly common during the initial phases of surgery, including internal mammary artery harvest. Our group has recently validated the use of NIRS for autoregulation monitoring in laboratory and clinical investigations. In a piglet laboratory model, we found that COx ≥ 0.36 was as accurate as laser Doppler flux for identifying loss of autoregulation; COx had 92% sensitivity, 63% specificity, and an area under the ROC curve of 0.89.⁶ In a study of adult patients undergoing CPB, we found that COx was correlated with TCD-derived Mx ($r=0.55$, $P=0.0001$) and had good agreement [bias, 0.08 (0.18); limits of agreement, 0.27–0.43].⁷ In that study, there was a high coherence [0.72 (0.11)] between slow waves of CBF velocity in the middle cerebral artery and slow waves of cerebral oximetry.

In prior analysis of this cohort of patients, we found that the average lower limit of autoregulation during CPB was 66 mm Hg, but this value ranged from 40 to 90 mm Hg.¹⁰ We found no relationship between patient age, history of diabetes, hypertension, or stroke and the MAP at the lower limit of autoregulation. Preoperative MAP did not accurately predict MAP at the autoregulation threshold; however, there was a relationship between systolic arterial pressure measured before surgery and the lower limit of

autoregulation but only for patients with a systolic arterial pressure of ≤ 160 mm Hg. The strongest predictor of MAP at the autoregulation threshold was a COx value of >0.5 ($P=0.022$). These data indicate that the range of MAPs at the lower limit of autoregulation is wide and difficult to predict accurately based on clinical assessments. Hence, empiric targeting of arterial pressure is likely to result in MAP below or possibly above the CBF autoregulation limits in many patients. Real-time COx monitoring may provide a means for individualizing MAP during CPB.

We have previously noted that perturbed autoregulation during CPB can cause CBF to become arterial pressure passive in some patients.⁹ Here, we found that patient susceptibility to impaired autoregulation was identified with COx monitoring. This finding supports the potential clinical value of this NIRS-derived modality. We are not able to elucidate mechanisms for impaired autoregulation based on this analysis. Notably, there was no association between age, prior stroke, diabetes, hypertension, average temperature on CPB, or peak temperature during re-warming and this condition. We are further unable to determine any causal relationship between our findings of an association between CBF velocity and Mx and also risk factor for impaired autoregulation. Undiagnosed cerebral arterial stenosis could lead to higher CBF velocity distal to the lesion and the presence of such disease may lead to impaired autoregulation.²⁴ Although PaCO₂ was not correlated with the average Mx, this variable was independently associated with impaired autoregulation. During CPB, PaCO₂ was continuously monitored and maintained within a normal range. Our findings suggest that, perhaps, CBF is very sensitive to PaCO₂ in patients with impaired autoregulation. Preoperative aspirin use was associated with impaired autoregulation during CPB. This finding may simply indicate that patients receiving aspirin therapy are more likely to have widespread vascular disease that predisposes them to altered cerebral microcirculatory function. In whole-animal laboratory experiments, increased CBF at MAPs above the upper limit of autoregulation appeared to be mediated by increased prostanoid production.²⁵ Perhaps, patients receiving aspirin treatment have altered prostaglandin metabolism that produces dysfunctional microcirculatory control of autoregulation. We cannot speculate on why male gender was predictive of impaired autoregulation in the light of the small number of women in our study. Others have noted that females are better able to maintain CBF in the face of postural changes.²⁶

We found that perioperative stroke occurred in 12.8% of patients with impaired autoregulation during CPB but in only 2.7% of patients with intact autoregulation ($P=0.011$), extending our findings from earlier studies.⁹ In our prior study, we defined impaired autoregulation based on time-averaged Mx during surgery. Elevated averaged Mx could result from a combination of averaged MAP lower than the autoregulation threshold or impairment in vascular mechanisms that normally maintain autoregulation. In the current study, we defined impaired autoregulation based on elevated

Mx values at all recorded MAPs during CPB. This approach would exclude MAP below the autoregulation threshold as a cause of high Mx. Since there was no predefined brain imaging protocol in this study, we cannot ascertain whether impaired autoregulation contributed to cerebral hypoperfusion and brain injury. Most strokes in our study appeared to be embolic in origin. Conditions of cerebral hypoperfusion, though, often coexist in patients with embolic stroke, particularly for blood flow to the vulnerable ischaemic penumbra.²⁷ Regardless, acute stroke is known to result in impaired CBF autoregulation.²³ Thus, our monitoring methods may have identified patients with stroke during surgery. It is also possible that we simply identified patients with cerebral vascular disease and impaired cerebral vasoreactivity who are at high risk for stroke.²⁸ Finally, we did not continuously record isoflurane concentration from the membrane oxygenator exhaust to quantify its effects on autoregulation. Volatile anaesthetics may alter CBF autoregulation but mostly in doses >1.0 MAC.²⁹ In the light of the age-dependence of MAC, it is possible that some aged patients received ≥ 1 MAC of isoflurane.³⁰ Others have shown that small differences in Mx in elderly patients compared with younger patients were not explained by end-tidal sevoflurane concentrations.³¹ Insofar that age was not independently associated with impaired autoregulation, the effect of higher brain sensitivity to isoflurane in elderly patients on our findings would likely be minimal.

In conclusion, we have identified impaired CBF autoregulation in 20% of patients during CPB. Our findings suggest that COx monitoring may provide an accurate means to predict this condition. The observation that perioperative stroke was more common in patients with impaired autoregulation may facilitate early identification of affected patients and thereby promote strategies for early neuroprotective interventions.

Declaration of interest

K.B. has consulted for Somanetics, Inc., in a relationship that was managed by the committee for outside interests at the Johns Hopkins University School of Medicine; C.W.H. received research funding from Somanetics.

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