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ORIGINAL ARTICLE

Novel mode of heart and lung machine for real-time identification of cerebral autoregulation impairments during cardiac surgery with cardiopulmonary bypass: prospective observational study

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ABSTRACT

BACKGROUND: Postoperative cognitive dysfunction (POCD) occurs in 20% to 80% of patients following cardiac surgical interventions. The incidence of delirium is from 20% to 50%. Impaired cerebral autoregulation (CA) during cardiopulmonary bypass (CPB) contributes to these issues. We investigated a novel method for real-time monitoring of CA during CPB. The study aimed to obtain real-time CA impairment data to demonstrate the timely arterial blood pressure (ABP) management for immediate restoration of intact CA and, potentially, to reduce the incidences of POCD and delirium.

METHODS: An observational pilot clinical trial involved 108 elective on-pump surgery patients of whom 78 were included in the final analysis. All patients were evaluated for cognitive function on the 7^{th} to 10^{th} postoperative day. A rectangular blood flow modulation technique was proposed and applied to facilitate real-time detection of CA status impairment by using CA(t) transient response analysis.

RESULTS: A single CA impairment event lasting longer than 241 seconds was statistically significantly associated with POCD (P=0.0178), while impairments exceeding 262 seconds were related to delirium (P=0.0315). It was demonstrated that CA impairment events and patient-specific lower and upper limits of CA can be identified with sub-minute delays during cardiac surgery.

CONCLUSIONS: The study demonstrated the feasibility of a novel heart and lung machine operation mode with rectangular blood flow modulation. Precise personal ABP(t) management can be performed during CPB to restore patient-specific optimal brain perfusion with sub-minute time resolution and, potentially, to reduce incidences of POCD and delirium.

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KEY WORDS: Coronary artery bypass; Cerebrovascular circulation; Cardiopulmonary bypass; Postoperative cognitive complications; Heart-lung machine.

Coronary artery bypass grafting (CABG) surgery with cardiopulmonary bypass (CPB) is a common elective surgery, comprising up to 30% of all cardiac surgeries. Studies indicate that cognitive dysfunction occurs in 20% to 80% of patients following cardiac surgery, such as coronary artery bypass grafting or heart valve replacement.[1, 2] The incidence of post-operative delirium can range from 20% to 50%.[3-6] Both neurological complications are associated with more extended hospital stays, different types of complications, and higher mortality risk.[1-6]

Pathophysiology of postoperative cognitive dysfunction is multifactorial, but adequate cerebral tissue perfusion plays the key role. Cerebral autoregulation (CA), which keeps cerebral blood flow stable during systemic fluctuations of ABP(t) or cerebral perfusion pressure (CPP(t)), is crucial for neurological outcomes.[7-10] Impaired CA during CPB is linked to cerebral ischemic or hyperemic injuries, leading to post-operative cognitive impairment and delirium.[10-14] Thus, monitoring of CA status in real-time is essential for personalized management of brain perfusion and enhancing patient outcomes.[11, 12] Clinically acceptable continuous CA monitoring requires invasive ABP(t) and intracranial pressure (ICP(t)) monitoring.[15, 16] Invasive ICP monitoring is inappropriate for cardiac surgery. Given that, as of today, we are unable to utilize all available CA monitoring methods – some due to the need for additional intervention (*e.g.*, ICP), and others due to limitations of applicability in operating room (*e.g.*, magnetic resonance imaging (MRI) or positron emission tomography [PET]). In the operating environment, current clinical practice allows CA assessment by monitoring "static" autoregulation solely through non-invasive methods.[9-11, 13, 17] "Static" CA assessment has too high a time delay (5 min or more) between start points in time of brain ischemic or hyperemic insults and the moment of such insult identification. "Dynamic" CA assessment with sub-minute time delay is needed for immediate restoration of individual patient-specific cerebral perfusion after identification of the start moment of brain insult.

Studies have shown that a disruption in autoregulation lasting longer than 5 minutes can lead to cerebral tissue injury.[14] Non-invasive real-time dynamic CA assessment during CPB requires specific blood flow wave modulation from the heart-lung machine, which is essential for the reliable and timely detection of critical CA impairment events.[12-14, 18, 19]

Clinical trials tested a sinusoidal wave-modulated blood flow mode for continuous CA assessment, which monitors CA status through a sinusoidal ABP(t) wave.[13, 14] However, due to the need for data accumulation, a 5-minute or longer delay in triggering CA impairment alarms has been noted.[12] A randomized trial of personalized blood pressure management during cardiac surgery with transcranial Doppler cerebral autoregulation monitoring and 5-minute delay in triggering CA impairment demonstrated that 45% reduction in the frequency of clinically detected delirium can be achieved.[12] Brain neurons can be damaged or die because of CA impairments lasting 5 minutes or longer. Real-time CA impairment alarm triggering or triggering with sub-minute delay can save neurons from damage, and, potentially, can even more reduce the frequency of POCD and delirium.

In this study, a new heart and lung machine (HLM) operation mode with periodic rectangular blood flow modulation was proposed and applied to cardiac surgery patients for the first time. Such modulation, with a 15-30 second period, allows almost real-time tracking of intact or impaired CA responses and detection of CA impairment with sub-minute resolution. Identification of CA impairments is achieved by performing continuous analysis of transient CA responses reflected by cerebral blood flow velocity (CBFV(t)) changes.[20-25] We proposed a rectangular blood flow modulation to identify CA status (intact or impaired) by automatic analysis of CA response to two input step functions — rising front and falling front of rectangular arterial blood pressure pulses, which reflect rectangular blood flow pulses. Automatic rectangular blood flow modulation was implemented by connecting our HLM control plug-in device, BrainProtect, to the driver of the HLM pump speed. Rectangular pulses of blood flow were transformed into ABP(t) rectangular pulses in the patient's body. The mean ABP value was controlled by a professional perfusionist according to EACTS/EACTAIC/EBCP Guidelines on cardiopulmonary bypass in adult cardiac surgery.

This study investigates a novel rectangular blood flow modulation mode HLM aiming to implement real-time detection of critical cerebral autoregulation (CA) impairment events in individual patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

The study demonstrates the feasibility of a novel heart and lung machine operation mode with rectangular blood flow modulation. Precise personal ABP(t) management can be performed during CPB to restore patient-specific optimal brain perfusion with sub-minute time resolution and to reduce incidences of POCD and delirium.

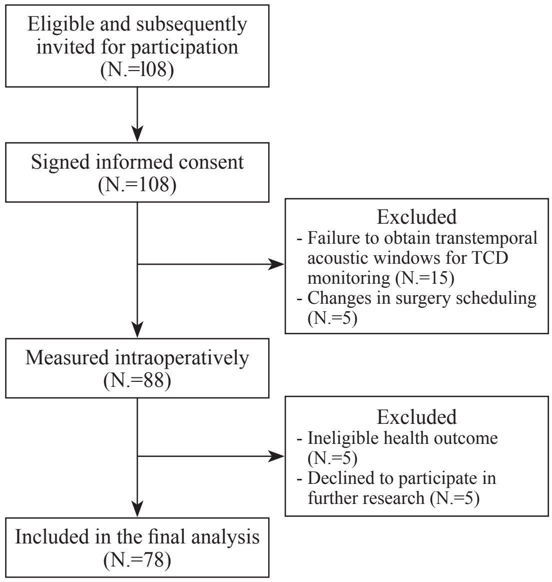

Figure 1.—The flow diagram of the patients enrolled in the study.

Materials and methods

Design of the clinical study

The pilot observational study was conducted at the Department of Cardiothoracic and Vascular Surgery in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics in 2021-2023. After signing an informed consent form, 108 patients undergoing standard elective CABG surgery with CPB were enrolled. The inclusion criteria were: carotid artery atherosclerosis ≤50%, 55-90 years, Mini mental score evaluation (MMSE) test score >24. Exclusion criteria included preoperative use of psychotropic agents (such as benzodiazepines or antidepressants), preoperative neurological or mental disorders, and uncontrolled diabetes. Thirty patients were excluded from the study because of changes in surgery scheduling of patients, decline of patients to participate in further cognitive tests, low transcranial Doppler (TCD) monitoring signals' quality, and artifacts in monitoring signals. The flow diagram of the patients enrolled in the study is shown in Figure 1. Table I and II present demographics. Clinical data collection was performed according to study protocols approved by the Kaunas Regional Biomedical Research Ethics Committees (Protocols No. BE-2-64, 2021-06-08, No. P1-BE-2-64/2021, P1-BE-2-64/2021). Participants signed a written informed consent to participate in the study and use their anonymized clinical data for analysis. The study protocol was registered at ClinicalTrials.gov Protocol Registration and Results System (Identifier: NCT04943458, Registered June 29, 2021).

Table I.—*Demographic and clinical data of cardiac surgery patients. Patients are grouped into those with no delirium and those with postoperative delirium.*

Parameter	No delirium (N.=70)	Delirium (N.=8)	TH	P value
F/M	13/57	2/6		0.646
Age, year	66 [62-74]	63 [57-70]	–	0.478
MAP, mmHg	61.9 [58.1-63.5]	66.9 [63.9-68.6]	65.7	0.0017
LCAI, s	181 [122-241]	311 [176-465]	262	0.0315

Data presented as median and IQR.
MAP: mean arterial blood pressure per group; IQR: interquartile range; LCAI: duration of longest cerebral autoregulation impairment event; P: probability of the Mann-Whitney U or Fisher's Exact Tests for detecting differences between the groups; TH: critical value that statistically significantly separates patients' outcome groups identified according to the Chi-square maximum value.

Table II.—*Demographic and clinical data of cardiac surgery patients. Patients are grouped into those who experienced POCD and/or delirium and those without signs of cognitive deterioration.*

Parameter	No deterioration (N.=51)	POCD and/or delirium (N.=27)	TH	P value
F/M	11/40	4/23	–	0.558
Age, year	66 [64-75]	63 [55-67.5]	64.9	0.002
MAP, mmHg	62.0 [57.9-63.7]	62.1 [60.6 65.8]	–	0.108
LCAI, s	178 [121-263]	263 [155-465]	241	0.018

Data presented as median and IQR.
MAP: mean arterial blood pressure per group; IQR: interquartile range; LCAI: duration of longest cerebral autoregulation impairment event; P: probability of the Mann-Whitney U or Fisher's Exact Tests for detecting differences between the groups; TH: critical value that statistically significantly separates patients' outcome groups identified according to the Chi-square maximum value.

Patient care

All patients underwent routine surgical and anesthetic techniques during the CABG surgery with CPB. Premedication included 1-2.5 mg of lorazepam the night before surgery and half the usual dose of metoprolol the following morning. Anesthesia was induced with fentanyl (1-2 µg/kg), propofol (2 mg/kg), and rocuronium (0.6 mg/kg) after preoxygenation with 80% oxygen. Anesthesia maintenance included sevoflurane (BIS 40-60), fentanyl (10-12 µg/kg), and muscle relaxants as needed. Ventilation with 50% oxygen maintained normocapnia (ETCO2 35-45 mmHg). A median sternotomy and standard anastomosis techniques were performed. Systemic heparinization (3 mg/kg) was administered for an activated clotting time ACT ≥400 s. The CPB was established using a roller pump Stockert S5 (LivaNova) and a hollow-fibre membranous oxygenator Compactflo D703 (Dideco, Mirandola, Italy). The CPB circuit was primed with 1500 ml Ringer's acetate and 1000 IU heparin, maintaining a cardiac index of 2.2-2.4. L/min/m^2 at 35-36 °C. Cold St. Thomas cardioplegia (1000 mL initially, 500 mL every 35-40 min) provided myocardial protection. Protamine sulfate (1.2 mL/kg) reversed anticoagulation, with ACT controlled at 120-140 s. Tranexamic acid was administered according to hospital protocol. Standard monitoring of vital signs included an electrocardiogram, heart rate, invasive arterial blood pressure, pulse oximetry, esophageal and body core temperature, central venous pressure, and urine output. The average duration of the surgery was 190 minutes. The average duration of the CPB procedure was 83 min. After surgery, all patients were transferred to the Intensive Care Unit (ICU) managed according to ICU protocols.

Patient outcome

All patients underwent a neurocognitive evaluation with standardized neuropsychological tests on the eve of the surgery and 7-10 days after the surgery. The same qualified examiner performed all evaluations. The assessment included the Addenbrooke test (ACE–III) and the Hopkins Verbal Learning Test-Revised (HVLT-R) measures. ACE–III is sensitive to mild cognitive dysfunction and encompasses attention, orientation, memory, language, verbal fluency, and visuospatial skills, while HVLT-R test is specialized only for memory evaluation: reproduction, recognition, differentiation of memorized and new material, and the learning process. The Confusion Assessment Method for the Intensive Care Unit (CAM – ICU) was used to identify postoperative delirium in the ICU.

Novel mode of HLM machine for continuous real-time CA assessment

The novel mode of HLM operation – blood flow with rectangular modulation – was proposed by a team of the Health Telematics Science Institute at Kaunas University of Technology (Kaunas, Lithuania). The same team also developed plug-in device BrainProtect – hardware and software for HLM blood flow modulation and mean flow management, enabling real-time CA status monitoring during the CPB (Figure 2). HLM included a novel mechatronic plug-in device for continuous modulation of blood flow with rectangular pulses having a 30-second duration. Blood flow was modulated by not more than ±5% of the actual flow rate to automatically get the stable amplitude of APB(t) rectangular waves of up to ±5 mmHg. Draeger Infinity DeltaXL monitor was used to monitor invasive ABP(t) data. Ultra-

Figure 2.—The mechatronic plug-in device BrainProtect used during the clinical trial for implementing a novel mode of HLM (Stöckert S5) operation – rectangular modulation of blood flow for real-time CA status monitoring and blood flow control during the CPB.

sonic transcranial robotic two-channel Doppler (TCD) monitor (Viasonix Dolphin 4D) was used to monitor CBFV(t) in the left and right middle cerebral arteries to increase the signal-to-noise ratio of the output TCD signal compared with a single-channel TCD. ABP(t) rectangular modulation data and CA transient response expressed by CBFV(t) data were registered by using the Intensive Care Brain Monitoring System software tool ICM+ (Cambridge, UK).

Tieck's model was used to quantify CA status based on the different shapes of transient CA responses in the CBFV(t) signal when CA is intact (Figure 3) or impaired (Figure 4), quantifying such shapes by ARI autoregulation index values.[20] ARI index value equals 0 when CA is impaired and 9 when CA is fully intact. The transient response of an intact CA system reaches a steady level within 5 to 15 seconds.[20, 26] This is evidence that it is possible to identify CA status periodically if the blood flow velocity of the heart and lung machine has a rectangular periodical step function shape and the period of such continuous blood flow modulation process has a

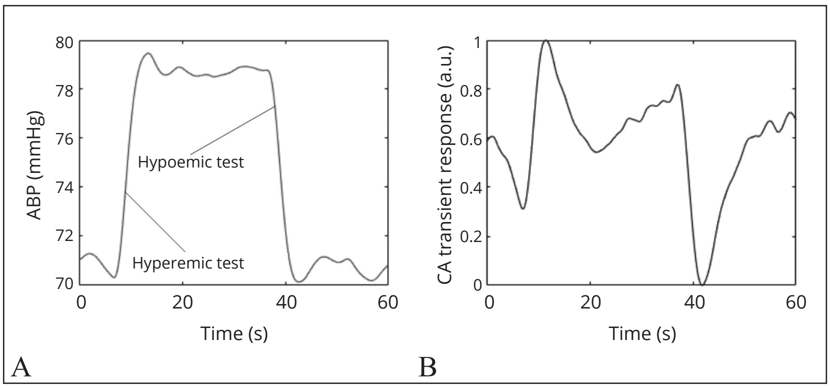

Figure 3.—A) Rectangular ABP(t) input signals of hyperemic (rising front) and hypoemic (falling front) tests of CA system in the case of intact CA. B) CA transient responses recorded by transcranial Doppler real-time monitoring device. Transient response (B) shows cerebral blood flow velocity reactions to input ABP(t) signal expressed in arbitrary units (a.u.) because only the shape of transient response is used for decision making on intact (B) or impaired CA (Figure 4).

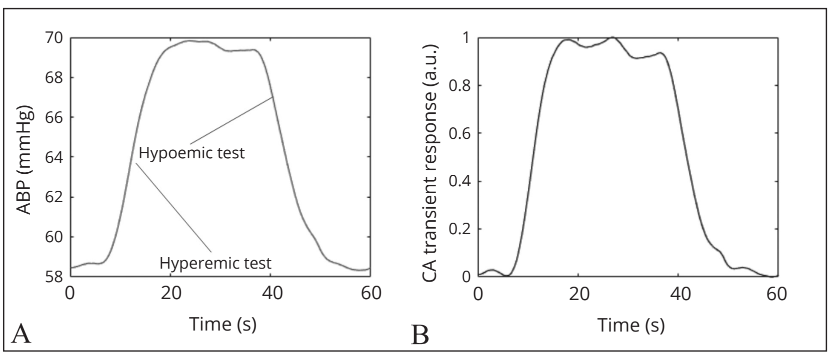

Figure 4.—A) Rectangular ABP(t) input signals of hyperemic and hypoemic tests of CA system; B) CA transient response (in arbitrary units, a.u.) in the case of impaired CA.

pulse repetition period of 15 seconds or longer. We proposed an algorithm and software solutions to enable immediate adjustments of mean ABP(t) by regulating the mean blood flow of HLM, aiming to stop ischemic and hyperemic events in the individual patient's brain and to restore near-optimal cerebral perfusion. This methodology represents an introduction of the personalized medicine concept into CPB surgery practice.

Statistical analysis

The patients were grouped into those who experienced POCD (POCD group), including delirium *vs.* without cognitive deterioration (no-deterioration group), and those who experienced postoperative delirium (delirium group) *vs*. without delirium (no-delirium group).

The Mann-Whitney U Test was applied to identify associations between patients' outcomes and the duration of longest CA impairment (LCAI) events estimated using critical ARI=3 value by testing the statistical significance of differences between factors among groups. Fisher's Exact Test was used to test statistical significance for binary data (gender) among outcome groups. Other demographic data (age, sex) were also included in the analysis. Statistically significant differences were assumed when the Mann-Whitney U Test results were P<0.05. Critical threshold (TH) values of analyzed factors that significantly separated outcome groups were identified according to the Chi-square maximum value. The point estimate and data distribution among groups were expressed by the median and interquartile range (IQR).

Results

Figure 3 and Figure 4 show the transient responses of the normalized CBFV(t) signal as reactions on rectangular pulses in the ABP (t) signal after the rising and falling fronts in the cases of intact and impaired CA. The durations of transient responses are at most 15 s. This evidence suggests that it may be possible to reduce the time delay between the onset of cerebral ischemic or hyperemic events and the activation of an alarm, enabling an immediate response in ABP management to restore intact CA and prevent brain ischemia or hyperemia.

The final data analysis was performed on 78 patients (Figure 1). All patients experienced episodes of CA impairment. POCD was detected in 34.62% (N.=27) of the patients. The patients' data in the delirium *vs*. no-delirium and POCD *vs.* No-deterioration groups are presented in Table I and II. There was no statistically significant difference in the median value of mean arterial blood pressure (MAP) between the groups. However, the median duration of LCAI was significantly longer in the POCD group (263 *vs*. 278 s).

The rate of delirium in our study was 10.26% (eight patients). Patients in the Delirium group had a statistically significantly higher median MAP (66.9 *vs*. 61.9 mmHg) and experienced significantly longer duration of LCAI (311 *vs*. 181 s).

The relation between the duration of the longest CA impairment event and the occurrence of postoperative delirium and POCD is presented in Figure 5A and B. The duration of CA impairment events longer than 241 s and 262 s was associated with postoperative cognitive dysfunction, P=0.0178 and delirium P=0.0315, respectively.

Discussion

Many studies have suggested that ABP targets in general anesthesia should be personalized. Our results confirmed this. In addition, by implementing rectangular blood flow modulation and blood flow control in the HLM machine, our study demonstrated the feasibility of almost real-time identification of CA impairment events, which could allow the management of mean blood flow with a minimal delay (in seconds) as well as to restore brain perfusion promptly after the alarm signal of CA impairment is generated (Figure 6). The personalized restoration of optimal brain perfusion physiologically means a restoration of an individual patient-specific optimal perfusion in all his vital organs and especially in the brain.

We hypothesized that impairment of CA during surgery with CPB might be a factor associated with POCD and postoperative delirium. Our analysis confirmed the associations between the longest duration of CA impairment (LCAI) and POCD and delirium. These results are consistent

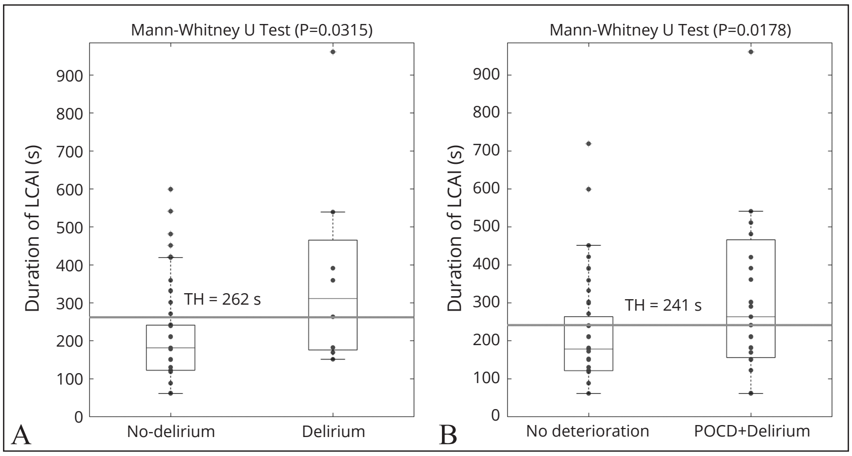

Figure 5.—Associations between the duration of the longest CA impairment event and postoperative delirium and POCD, including delirium. Patients were grouped into those who experienced postoperative delirium *vs*. those without delirium (A) and those who experienced POCD, including delirium *vs*. those without signs of cognitive deterioration (B). The duration of single CA impairment events longer than 262 and 241 s are associated with delirium (A) and POCD (B), respectively. TH: critical LCAI duration.

with the data from studies of traumatic brain injury patients, demonstrating that patients experiencing more extended CA impairment events are at higher risk of unfavorable outcomes.[27-29] In our study, the duration of cerebral autoregulation impairment events exceeding 241 s and 262 s was associated with POCD and delirium, respectively (Figure 5).

A statistically significant difference was also found in age between POCD and No-Deterioration groups, with patients with developed POCD being significantly younger. Our results seem counterintuitive initially, as older individuals are traditionally considered at higher risk for these complications. However, some studies show that younger patients might experience greater psychological and emotional stress related to undergoing major surgery.[30] Also, it is known that these stressors could lead to a heightened risk of delirium and cognitive disorders post-operatively. Also, younger people might have a stronger psychological response to surgery, including anxiety and fear about their health or the long-term effects of the surgery.[30]

MAP management during CPB is proposed for patient-specific continuous optimal cerebral perfusion control.[31] According to CPB guidelines, which follow an evidence-based medicine concept, many cardiac centers maintain MAP within 50-60 mmHg.[31-33] This target is based on the identification of 50 mmHg as the universal evidence-based lower limit of autoregulation (LLCA), below which CA is impaired.[31, 32]

LLCA and ULCA are patient-specific and vary widely. Figure 6 presents examples of CA status monitoring and identification of CA impairment events detected in individual patients using the proposed rectangular blood flow modulation approach in HLM during CPB. These examples also demonstrate that the value of LLCA could differ from the values recommended by evidence-based guidelines. In these examples, identified values for different patients range from 53 to 70 mmHg. Figure 6 also demonstrates the cases in which CA status is recovered by ABP management.

Maintaining mean arterial blood pressure within the ranges recommended by guidelines might be sub-optimal for specific individuals, potentially leading to perioperative cerebral injury.[10-14] For elderly patients or those at high risk (*e.g*., those with hypertension, pre-existing cerebrovascular disease, or diabetes), some studies recommend maintaining mean arterial blood pressure above 70 mmHg.[18, 34] Conversely, higher mean arterial blood pressure could exceed an individual's upper limit for CA, resulting in cerebral hyperemia, which has been linked to postoperative delirium.[18, 34] Our findings also show that elevated ABP was associated with an increased risk of postoperative delirium (P=0.0017, Table I).

Proposed almost real-time CA status monitoring technology potentially has to minimize the duration of ischemic and hyperemic insults during cardiac bypass surgery. We expect the reduction of POCD and post-operative delirium rates by applying the proposed technology. A multicenter randomized controlled trial is warranted in order to evaluate the effectiveness of the

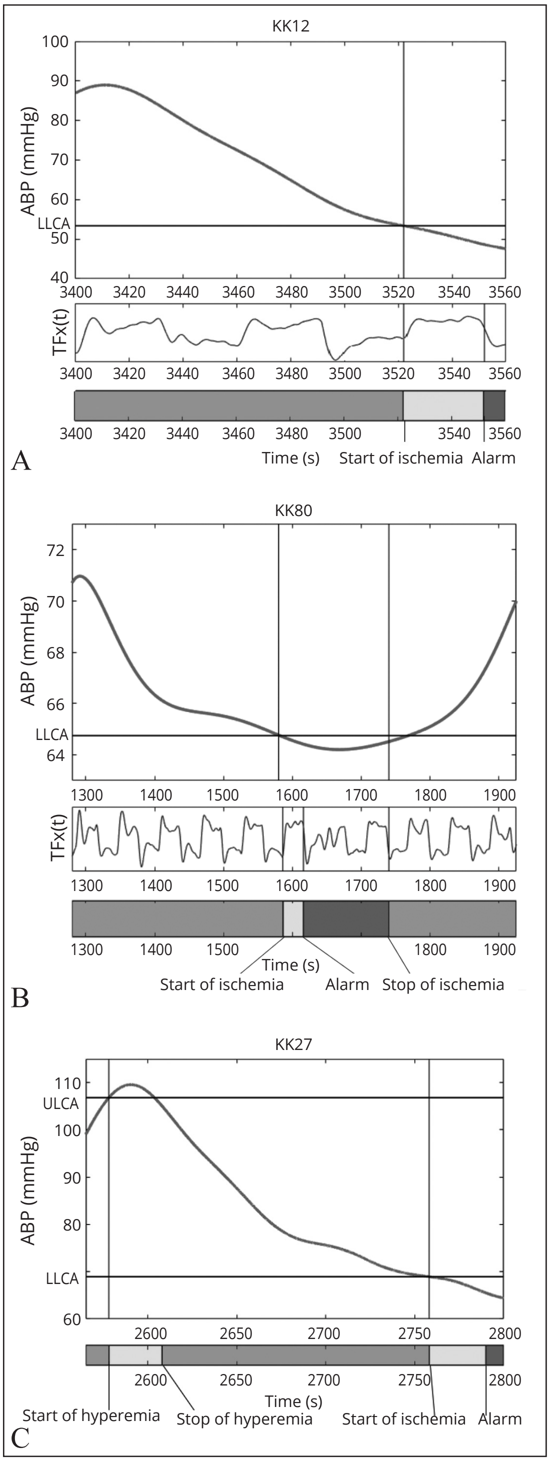

Figure 6.—A-C) Real-time identification of lower (LLCA) and upper (ULCA) limits of cerebral autoregulation, which represents the ABP values at which CA status starts to be impaired.
TFx(t): transient responses of CA system.

proposed technology in reducing postoperative complications.

Limitations of the study

It is important to acknowledge that this study, conducted at a single institution with a relatively small sample size, may have some limitations that could be addressed in future research. The target sample size of at least 100 patients for this pilot observational study was determined to explore potential trends and effect sizes, intending to inform the design and sample size calculations for future larger-scale studies. This decision was based on preliminary knowledge from prior studies, which reported that the prevalence of POCD and delirium in cardiac surgery patients ranges from 20% to 70%, and up to 30% of participants may be excluded due to incomplete cognitive testing or poor-quality monitoring signals. Considering these factors, we anticipated that enrolling at least 100 patients would ensure a final dataset of approximately 70 evaluable patients, sufficiently representing POCD and/or delirium and No-POCD/No-delirium groups to enable meaningful statistical comparisons of CA-related characteristics.

A multicenter study with a larger sample size would provide more precise results. Additionally, we did not aim to assess long-term neurocognitive disorders. A longer follow-up period to assess long-term neurocognitive disorders would provide a more comprehensive understanding of the study's implications. Our study only monitored arterial blood pressure and cerebral autoregulation during surgery. Many risk factors in the intensive care unit could influence cerebral autoregulation. Ideally, cerebral autoregulation should be monitored not only in the operating room but also in the ICU. This could be the subject of further research in our clinic. We looked at univariable analysis of clinical trial results. Multifactorial analysis has to be included in further studies.

Conclusions

A prospective observational clinical trial performed on patients undergoing cardiac surgery with CPB demonstrates the feasibility of a novel mode of heart-lung machine operation with rectangular blood flow modulation. It has been shown for the first time that an individual patient-specific lower and upper limits of cerebral blood flow autoregulation can be identified in real-time. It also has been shown that the start and stop moments of brain injury caused by excursions of ABP outside the patient-specific limits of cerebral autoregulation can also be identified in almost real-time with a potentially minimal 15-second delay of the alarm signal. Precise personal ABP(t) management can be performed during CPB to restore patient-specific optimal brain perfusion with sub-minute time resolution and reduce the incidence of postoperative cognitive dysfunction and delirium.

A multicenter randomized controlled clinical trial is warranted to demonstrate the effectiveness of the proposed methodology and technology in reducing the incidences of postoperative cognitive dysfunction and delirium.

What is known

- Cerebral autoregulation (CA) is one of the key factors influencing the patient outcome following cardiac surgery with CPB.
- The duration of CA impairment events during cardiac surgery with CPB longer than 5 minutes is associated with a risk of postoperative cognitive dysfunction and delirium.

What is new

- A novel mode of heart-lung machine operation with rectangular blood flow modulation enables the identification of CA impairment with a sub-minute delay.
- Managing mean blood flow with a minimal delay (in seconds) and restoring brain perfusion is possible during cardiac surgery with CPB promptly when CA impairment is detected.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Vytautas Petkus, Edvinas Chaleckas and Arminas Ragauskas are co-authors of inventing the method and apparatus for human brain neuroprotection during cardiopulmonary bypass surgery. Study conception and design: Vilma Putnynaite, Edvinas Chaleckas, Vytautas Petkus, Edmundas Sirvinskas, Rimantas Benetis, Arminas Ragauskas. Acquisition of data: Greta Kasputyte, Birute Kumpaitiene, Laimonas Bartusis, Vilma Putnynaite, Rolandas Zakelis, Yasin Hamarat, Milda Svagzdiene, Arunas Gelmanas, Judita Andrejaitiene. Analysis and interpretation of data: Birute Kumpaitiene, Vytautas Petkus, Edvinas Chaleckas, Vilma Putnynaite, Greta Kasputyte. Drafting of manuscript: Vilma Putnynaite, Vytautas Petkus, Greta Kasputyte: Critical revision: Virginija Adomaitiene, Tadas Lenkutis, Arminas Ragauskas, Rimantas Benetis. All authors reviewed and approved the final version of the manuscript, with the exception of the deceased co-author, Rolandas Zakelis, whose contributions were made prior to his passing.

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