Diagnostic Value of Cholinesterase Activity for the Development of Postoperative Delirium after Cardiac Surgery

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Abstract

Background Depression of cholinesterase (CHE) activity has been reported to lead to an amplified neuroinflammatory response, which clinically manifests as postoperative delirium (PD). This observational study investigates the association between CHE activity and the development of PD following elective cardiac surgery.

Methods Patients with preexisting neurologic deficits or carotid artery disease as well as patients undergoing reoperations or procedures under circulatory arrest have been excluded from this study. The Mini-Mental State Examination, the Confusion Assessment Method for the Intensive Care Unit, and the Intensive Care Delirium Screening Checklist were performed at regular intervals. CHE activity was estimated pre- and postoperatively until postoperative day (POD) 5 and at discharge.

Results A total of 107 patients were included. PD was diagnosed in 34 (31.8%) patients, who have been compared with those without PD. Time on ventilator, length of ICU, and hospital stay were longer in patients with PD ($p = 0.001$, $p < 0.001$, and $p = 0.004$, respectively). MMSE scores were lower in patients with PD ($p < 0.001$; $p = 0.015$). CHE activity on POD 1 to 4 as well as at discharge were lower in the delirium group ($p = 0.041$; $p = 0.029$; $p = 0.015$; $p = 0.035$; $p = 0.028$, respectively). A perioperative drop of CHE activity of more than 50% and a postoperative CHE activity below 4,800 U/L (on POD 0) were independently associated with an increased risk of development of PD ($p = 0.038$; $p = 0.008$, respectively).

Conclusion In addition to the established functional tests, routine estimation of CHE activity may serve as an additional diagnostic tool allowing for the timely diagnosis and treatment of PD in cardiac surgery patients.

Keywords
- postoperative delirium
- cholinesterase activity
- cardiac surgery

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Introduction

In one of the earliest works on delirium by Engel and Romano,[1] delirium was defined as an analogue to organ failure. This definition has evolved to the currently widely accepted Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria defining delirium as a transient and serious disturbance in attention and cognition developing over a short period of time, whose symptoms tend to fluctuate during the day and cannot be explained by a preexisting neurocognitive disorder.[2]

Postoperative delirium (PD) has been reported to occur in between 3 and 80% of patients after cardiac surgery.[2–4] It has been shown to be associated with prolonged hospital and intensive care unit (ICU) stay as well as poor outcomes.[4] PD after cardiac surgery is multifactorial, and its pathophysiology remains incompletely deciphered. There is ample evidence for a pronounced inflammatory response after cardiac surgery procedures, especially those on cardiopulmonary bypass. Therefore, it may be hypothesized that this inflammatory reaction may play a significant role in the etiology of PD. In this context, an imbalance in the "cholinergic anti-inflammatory pathway" has been shown to be one underlying mechanism.[5] Plasma cholinesterase (CHE) plays an important role in this pathway as it represents a converging point of immune and drug-metabolizing systems. This prospective observational study investigates the association between CHE activity in blood and the development of PD after cardiac surgery, thereby seeking to assess the diagnostic value of CHE activity for the development of PD in patients undergoing cardiac surgery.

Methods

All patients consented to participate in this prospective observational study. Postoperative treatment and data acquisition were performed as part of routine patient care. All procedures described in this study were in accordance with the Institutional Research Committee (application number: 26/4/19), National Data Safety Regulations, and the 1964 Helsinki declaration and its last amendment by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Data acquisition was based on our institutional database and was then de-identified. The EuroSCORE (European System for Cardiac Operative Risk Evaluation) II was calculated to estimate perioperative mortality.[6]

Inclusion and exclusion criteria have been outlined in ►**Fig. 1**. The preoperative anticholinergic burden was calculated using the Anticholinergic Cognitive Burden (ACB) Scale.[7–9] A Mini-Mental State Exam (MMSE) was performed at admission and at discharge.[10] On the ICU, PD was evaluated using the Confusion Assessment Method for the ICU (CAM-ICU) as well as the Intensive Care Delirium Screening Checklist (ICDSC)[11,12] on postoperative day (POD) 1 to 5. All examinations were performed by a single investigator to rule out bias. CHE (assay of butyrylcholinesterase, BChE) activity was determined preoperatively, immediately after surgery, on POD 1 to 5, and at discharge.

Induction of anesthesia was performed according to a standardized protocol with remifentanil, propofol, and rocuronium in adjusted doses. On cardiopulmonary bypass, sevoflurane and remifentanil were used. In the ICU, sedation was continued with propofol and a standardized nurse-controlled analgesia protocol with oxycodone was implemented. Furthermore, in the ICU, a standardized antidelirium protocol was followed, which included early physiotherapy and mobilization, as well as natural daylight, to reestablish circadian rhythm.

Cerebrovascular adverse events were defined as new onset of postoperative neurologic symptoms and associated with a new cerebral lesion confirmed by computed tomography (CT).[13] Reexplorative surgery was performed in case of pericardial tamponade or surgical bleeding. Cardiogenic shock was defined as a persistent mean arterial pressure of less than

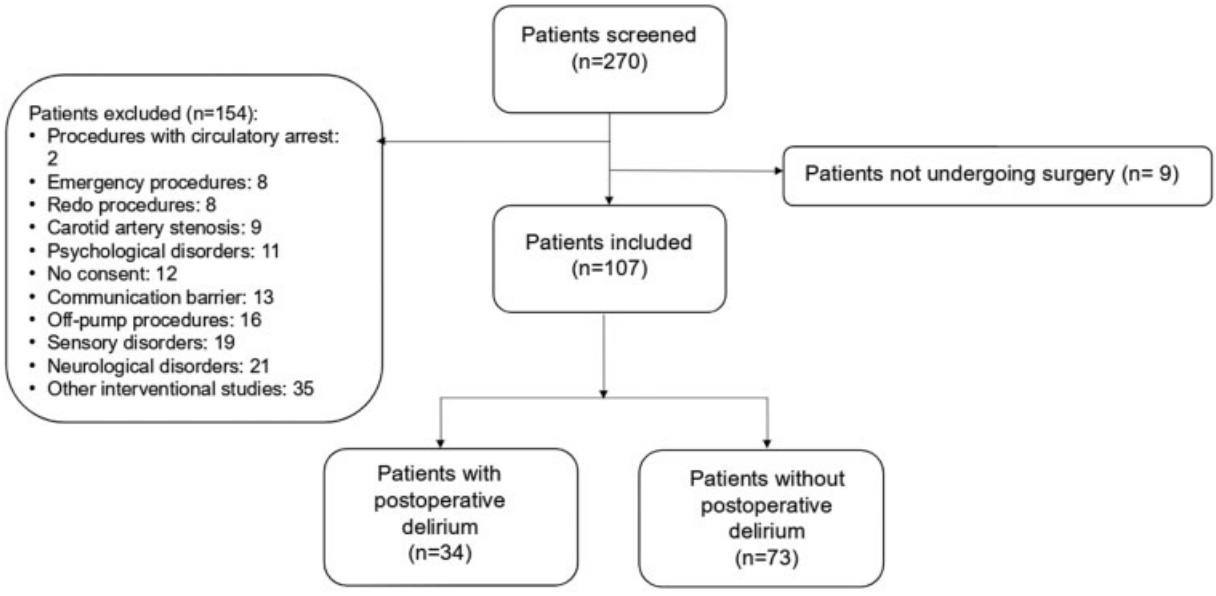

Fig. 1 Study design.

65 mm Hg despite inotropic support.[14] Nosocomial pneumonia (NP) was diagnosed according to clinical presentation, elevated leukocyte and C-reactive protein levels, and/or radiological evidence of pulmonary infiltrates.

Data were analyzed using the IBM SPSS Statistics Data Editor, version 20 (IBM Corp., Armonk, NY). They were tested for normal distribution using the Shapiro–Wilk test as well as the Kolmogorov–Smirnov test with Lilliefors correction. Categorical variables were evaluated using the Fisher exact test and continuous variables were evaluated using the Mann–Whitney *U* test. The null hypothesis was rejected, and a significant difference was assumed when *p*-values were ≤ 0.05. Multivariate analysis incorporated binary logistic regression using a forward stepwise (conditional) model, where significance for entry was set at $p < 0.05$, and significance for exit was $p < 0.10$. Results are presented as medians with interquartile ranges and percentages, respectively.

Results

A total of 270 patients were screened, among whom 107 have been included in this study. PD was diagnosed in 34 (31.8%) patients, who have been compared with those without PD.

Baseline Parameters

Patient characteristics are outlined in ►**Table 1**. Median age was significantly higher in the PD group (71 [62–77] versus 65 [58–71]; $p = 0.008$). All other baseline parameters were comparable. Regarding the whole cohort, a total of 19.6% of patients were female. Median EuroSCORE II was 1.6%. Median left ventricular ejection fraction was 55.0%. A total of 9 (8.4%) patients suffered from chronic obstructive pulmonary disease (COPD) and 14 (13.1%) from insulin-dependent diabetes mellitus. Concerning surgical procedures, 50 (46.7%) patients underwent isolated coronary artery bypass grafting, 28 (26.2%) underwent isolated valve surgery, and 29 (27.1%) underwent combined procedures.

Postoperative Delirium

A total of 34 (31.8%) patients were diagnosed with delirium postoperatively. Among them, 17 (50.0%) patients were diagnosed with hypoactive delirium, 1 (2.9%) suffered from hyperactive delirium, and 16 (47.1%) were diagnosed with mixed forms of delirium. The onset of PD was POD 1 in 15 (44.1%) patients, POD 2 in 10 (29.4%), POD 3 in 6 (17.6%), POD 4 in 1 (2.9%) and POD 5 in 2 (5.9%).

Table 1 Baseline characteristics and surgical details

	No delirium ($n = 73$)	Delirium ($n = 34$)	*p*-Value
Baseline characteristics			
Age (years)	65 (58–71)	71 (62–77)	0.008
Female (%)	12 (16.4)	9 (26.5)	0.296
BMI (kg/m^2)	27.2 (24.9–31.6)	27.0 (23.7–28.9)	0.312
EuroSCORE II (%)	1.6 (1.2–2.7)	1.8 (1.2–3.1)	0.560
LVEF (%)	55 (55–55)	55 (55–55)	0.541
Comorbidities			
Arterial hypertension (%)	51 (69.8)	21 (61.7)	0.406
Atrial fibrillation (%)	10 (13.7)	8 (23.5)	0.267
Insulin-dependent diabetes (%)	11 (15.1)	3 (8.8)	0.372
Chronic kidney disease (%)	5 (6.8)	4 (11.8)	0.461
Hyperlipidemia (%)	28 (38.4)	8 (23.5)	0.187
Hyperuricemia (%)	7 (9.6)	2 (5.9)	0.716
COPD (%)	6 (8.2)	3 (8.8)	1.000
Pulmonary hypertension (%)	3 (4.1)	1 (2.9)	1.000
Peripheral artery disease (%)	2 (2.7)	1 (2.9)	1.000
Coronary artery disease (%)	49 (67.1)	28 (82.4)	0.065
Surgical details			
Isolated CABG (%)	36 (49.3)	14 (41.2)	0.434
Single valve surgery (%)	18 (24.7)	10 (29.4)	0.604
Combined procedures (%)	19 (26.0)	10 (29.4)	0.715
Total duration of surgery (minute)	248 (215–291)	267 (220–307)	0.265
Duration of cardiopulmonary bypass (minute)	127 (91–158)	132 (106–176)	0.087
Duration of cross-clamping (minute)	78 (59–107)	91 (65–106)	0.301

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction.
Note: data are presented as medians (25th–75th percentiles) or as absolute numbers (percentages).

Table 2 MMSE and cholinesterase activity

	No delirium ($n = 73$)	Delirium ($n = 34$)	p-Value
MMSE score			
MMSE score at admission	28 (27–29)	27 (25–28)	<0.001
MMSE score at discharge	29 (27–30)	28 (26–29)	0.015
ACB scale			
ACB scale	0 (0–1)	0 (0–1)	0.759
CHE activity			
Preoperative CHE (U/L)	9,728 (8,362–11,134)	9,205 (7,688–10,674)	0.194
CHE POD 0 (U/L)	5,876 (5,000–7,208)	5,655 (4,561–6,543)	0.092
CHE POD 1 (U/L)	6,116 (5,350–7,218)	5,478 (4,656–6,538)	0.041
CHE POD 2 (U/L)	5,277 (4,464–6,079)	4,588 (3,734–5,353)	0.029
CHE POD 3 (U/L)	4,923 (4,106–5,627)	4,245 (3,584–4,955)	0.015
CHE POD 4 (U/L)	4,838 (4,068–5,933)	4,212 (3,578–5,067)	0.035
CHE POD 5 (U/L)	4,980 (4,009–5,942)	5,359 (4,471–6,266)	0.064
CHE at discharge (U/L)	6,127 (5,100–7,163)	4,201 (3,533–5,623)	0.028
Postoperative drop in CHE > 50% (%)	2 (2.7)	7 (20.6)	0.002
CHE POD 0 < 4,800 U/L (%)	14 (19.2)	13 (38.2)	0.035

Abbreviations: ACB, anticholinergic burden; CHE, cholinesterase; MMSE, Mini-Mental State Examination; POD, postoperative day.
Data are presented as medians (25th – 75th percentiles) or absolute numbers (percentages).

Regarding the MMSE, scores at admission as well as at discharge were significantly lower in the PD group ($p < 0.001$ and $p = 0.015$, respectively). The ACB scale was comparable in both groups. CHE activity at admission and immediately after surgery did not differ; however, significant differences were observed in CHE activity on POD 1 to 4 ($p = 0.041$, $p = 0.029$, $p = 0.015$, $p = 0.035$, respectively), as well as at discharge ($p = 0.028$) (►**Table 2** and ►**Fig. 2**). Accordingly, independent risk factors for the development of PD identified by multivariate regression analysis were a low preoperative MMSE score (odds ratio [OR]: 0.732 [95% confidence interval, CI: 0.99–1.11]; $p = 0.017$), a drop in postoperative CHE activity (preoperative CHE compared with CHE on POD 0) of more than 50% (OR: 2.609; [95% CI: 1.01–6.44]; $p = 0.038$), and an early postoperative CHE activity (POD 0) below 4,800 U/L (OR: 9.20 [95% CI: 1.8–47.1]; $p = 0.008$).

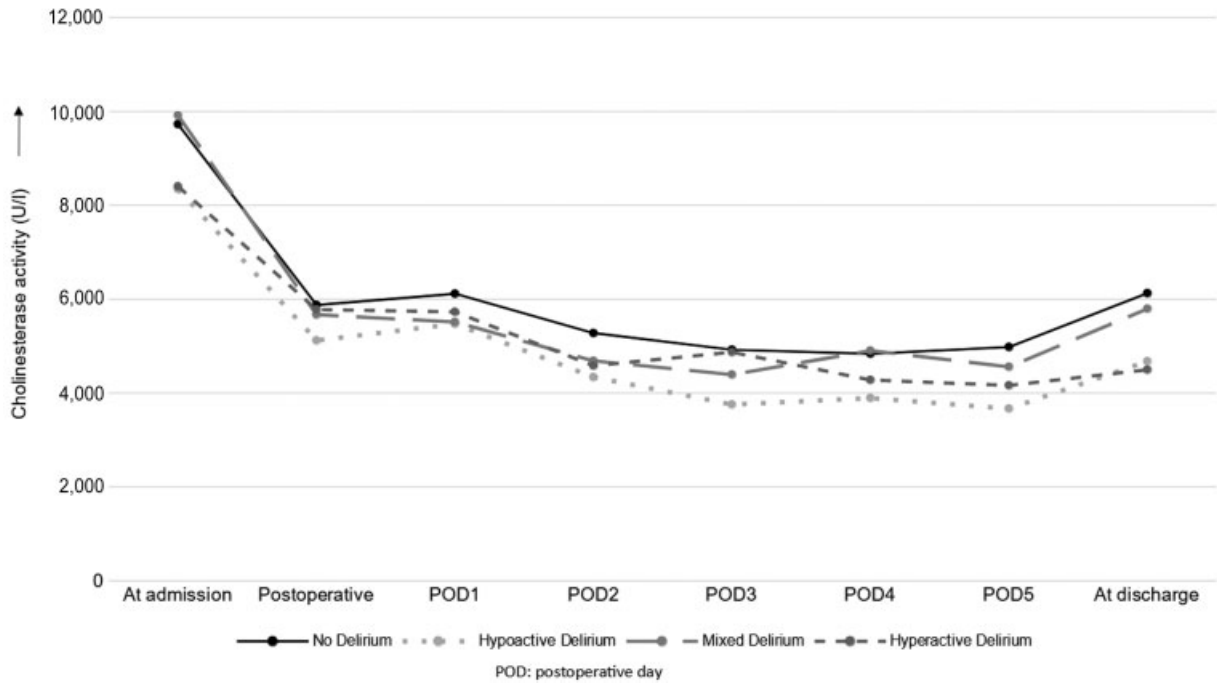

Fig. 2 Perioperative cholinesterase activity. POD, postoperative day.

Table 3 Postoperative complications and outcome

	No delirium ($n = 73$)	Delirium ($n = 34$)	p-Value
Adverse events			
Reexplorative surgery (%)	1 (1.4)	0 (0.0)	1.000
Pacemaker implantation (%)	1 (1.4)	0 (0.0)	1.000
Surgical site infection (%)	0 (0.0)	1 (2.9)	0.318
Nosocomial pneumonia (%)	9 (12.3)	8 (23.5)	0.162
Tracheostomy (%)	0 (0.0)	1 (2.9)	0.318
ICU readmission (%)	1 (1.4)	2 (5.9)	0.236
Outcomes			
In-hospital mortality (%)	0 (0.0)	0 (0.0)	–
Length of hospital stay (days)	12 (10–15)	14 (12–20)	0.004
Length of ICU stay (days)	2 (2–4)	4 (3–7)	<0.001
Length of PMV (hours)	10 (7–14)	14 (10–27)	0.001

Abbreviations: ICU, intensive care unit; PMV, postoperative mechanical ventilation.
Note: data are presented as medians (25th– 5th percentiles) or as absolute numbers (percentages).

Outcome

Data on adverse events and outcome are presented in ►**Table 3**. The incidence of adverse events was comparable between both groups. The most frequent complication was NP, which was diagnosed in a total of 17 (15.9%) patients. No cerebrovascular events were observed. Reexplorative surgery was performed in one (0.9%) patient. A total of 3 (2.8%) patients were readmitted to the ICU. All patients survived to discharge. Median time on mechanical ventilation was longer in the delirium group (14 [10–27] vs. 10 [7–14] hours; $p = 0.001$). Accordingly, length of ICU stay (4 [3–7] vs. 2 [2–4] days; $p < 0.001$) as well as total hospital stay (14 [10–27] vs. 12 [10–15] days; $p = 0.004$) were longer in patients with PD.

Discussion

Based on the results of the CESARO[15] trial, which was the first multicentre observational study on the association between CHE activity and the development of PD in surgical patients, this study focuses on patients after cardiac surgery. Due to the high incidence of PD in cardiac surgery and its negative impact on postoperative outcome, the prevention of PD is of high clinical relevance.[4] Reliable diagnostic tools such as reproducible functional tests or biomarkers, allowing for early diagnosis and treatment, are still scarce.

As expected, a significant drop of CHE activity was observed in all patients after cardiac surgery as a result of the inflammatory reaction discussed [previously (►**Fig. 2** and ►**Table 2**). Among the investigated patients, postoperative CHE activity was significantly lower in the delirium group. Accordingly, a postoperative drop of CHE activity of more than 50% as well as an early postoperative CHE activity of less than 4,800 U/L have been identified as an independent risk factor for PD. As the onset of PD occurred on POD 1 and 2 in the majority of patients (73.5%, $n = 25$), CHE activity may serve as a suitable marker for early diagnosis of PD. However, there were several limitations. Its diagnostic value was limited to POD 1 to 4 as well as to discharge. It was neither a suitable parameter for preoperative discrimination of patients at risk nor immediately or late after surgery (POD 5). In sum, routine estimation of CHE activity, that is, by point-of-care tests, may be recommended for early diagnosis and further monitoring of PD within the limitations discussed previously.

As patients with preexisting risk factors for delirium have been excluded from this study (►**Fig. 1**), the more pronounced postoperative drop of CHE activity in the delirium group supports the thesis that CHE is not only a diagnostic parameter but also involved in the pathomechanism of PD. Based on this knowledge, the use of CHE inhibitors (e.g., physostigmine), which reduce the degradation of synaptic acetylcholine (ACh), has been investigated for pharmacological treatment.[16–18]

Patients after cardiac surgery are at a particularly high risk of the development of PD as the use of cardiopulmonary bypass leads to a pronounced inflammatory response due to several factors such as the blood–air interface, the surface area of the tubing, and cell damage due to suction. Another contributor to the inflammatory cascade is ischemia–reperfusion injury due to additional proinflammatory mediators as a response to the reintroduction of oxygen to tissues.[19] As a result, a systemic inflammatory response syndrome of varying severity is observed in a substantial number of patients after cardiac surgery. Further precipitating factors include prolonged duration of surgery, microemboli, air embolisms, systemic inflammation, sedative agents, and mechanical ventilation.[20]

Focusing on the association between inflammation and CHE activity, the underlying pathomechanism has been referred to as the "cholinergic anti-inflammatory pathway." It is supposed to play an important role in the neuroinflammatory pathway of delirium.[21] An increased burden of serum anticholinergic activity along with suppressed plasma activity of acetylcholinesterase and BChE leads to the inactivation of circulating ACh.[21] Along with the oxidative metabolism of several drugs, ACh plays an important role in the homeostatic control of the immune response. Furthermore, in this state of

systemic inflammation, alterations in the blood–brain barrier (BBB) have been reported. Additional factors affecting the BBB include hypoxia, ischemia, and pain.[22] As a result, inflammatory agents may pass the BBB, causing functional and structural changes and thus inducing cognitive impairment.[22]

In this context, preoperative anticholinergic cognitive burden plays an important role and has, therefore, been evaluated in this study. The ACB scale provides a ranking of anticholinergic effects of different drugs, predicting the risk of adverse effects such as delirium.[23] The mechanism of action of several medications involves several ACh receptor subtypes. It has been reported that muscarinic receptor antagonism was associated with impaired capability concerning memory and attention.[9] In the investigated study population, ACB scores of both groups were comparable.

Furthermore, PD needs to be differentiated from postoperative cognitive dysfunction (POCD). Although several risk factors are common in both clinical entities, POCD refers to deterioration in cognition, temporally associated with surgery, whereas PD is caused by the inflammatory response associated with the stress of surgery.[24] Patients with PD may appear lucid following emergence from anesthesia and are usually then diagnosed with classical symptoms such as disorientation and hallucinations. In the investigated study population, MMSE has been performed, with patients in the delirium group having lower baseline and discharge scores. A low baseline MMSE score has been identified as an independent risk factor for the development of PD and may, thus, serve as a predictive diagnostic tool. In accordance with the transient nature of PD, a gradual postoperative increase in CHE activity was observed.

It has been reported that PD has been associated with poor outcomes in patients after cardiac surgery.[4] Accordingly, we observed significantly longer times on mechanical ventilation, a longer stay in ICU, and a longer total inhospital stay in the delirium group. The incidence of other adverse events was comparable between both groups (►**Table 3**).

Delirium is subdivided into three clinical subtypes: hyperactive, hypoactive, and mixed form.[20] Hypoactive delirium is characterized by reduced alertness, sedation, and reduction of motor activity, whereas hyperactive delirium is associated with hypervigilance, psychotic features (e.g., hallucinations and delusions), and agitation. Mixed forms represent the most common clinical presentation, which is characterized by overlapping symptoms of hyper- and hypoactive delirium.[22] In the investigated patient cohort, hypoactive and mixed forms were the predominant entities.

Conclusions

Our results indicate that routine estimation of CHE activity may serve as an additional diagnostic tool allowing for early diagnosis and treatment of PD in patients after cardiac surgery. In addition, our data support the neuroinflammatory etiology of PD in this setting. Further studies are required, with a focus on preoperative identification of patients at risk as well as on corresponding therapeutic approaches.

Conflicts of Interest
The authors of this manuscript declare that they have no conflicts of interest, had full control of the design and methods of the study, data analysis, and production of the written report, and that no funding supported this study.

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