ROZPRAWA DOKTORSKA

Anna Kupiec

Czynniki ryzyka występowania majaczenia u pacjentów po operacjach kardiochirurgicznych

Risk factors for delirium in patients after cardiac surgery

Promotor: dr hab. n. med. Waldemar Goździk, prof. nadzw.

Katedra i Klinika Anestezjologii i Intensywnej Terapii
Kierownik: dr hab. n. med. Waldemar Goździk, prof. nadzw.
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Wrocław 2021

Składam serdeczne podziękowania
Panu Profesorowi Waldemarowi Goździkowi
oraz Pani Doktor Habilitowanej Barbarze Adamik
za Ich cierpliwość, nieustające wsparcie
i wszelką pomoc wniesioną w powstanie tej pracy.

Wykaz publikacji stanowiących pracę doktorską

Pracę doktorską stanowi opublikowany cykl prac poświęcony analizie okołooperacyjnych czynników ryzyka występowania majaczenia u pacjentów po operacjach kardiochirurgicznych.

1. Kupiec A, Adamik B, Kozera N, Gozdzik W. Elevated Procalcitonin as a Risk Factor for Postoperative Delirium in the Elderly after Cardiac Surgery-A Prospective Observational Study. J Clin Med. 2020 Nov 26;9(12):E3837. doi: 10.3390/jcm9123837. PMID: 33256084.
   IF: 3,303
   MNiSW: 140

2. Kupiec A, Adamik B, Forkasiewicz-Gardynik K, Goździk W. Intra-operative hyperoxia and the risk of delirium in elderly patients after cardiac surgery. Aging (Albany NY). 2020 Apr 19;12(8):7006-7014. doi: 10.18632/aging.103058. Epub 2020 Apr 19. PMID: 32305956; PMCID: PMC7202500.
   IF: 4,831
   MNiSW: 140

Spis treści

1.Wstęp

2. Cele pracy

3. Publikacje stanowiące pracę doktorską

4. Omówienie publikacji

5. Podsumowanie

6. Streszczenie

7. Summary

8. Piśmiennictwo

9. Oświadczenia współautorów

Wykaz skrótów użytych w pracy

CBP – cardiopulmonary bypass - krążenie pozaustrojowe
OIT – oddział intensywnej terapii
TAVI – transcatheter aortic valve implantation – przezskórna implantacja zastawki aortalnej
DMS – 5 - Diagnostic and Statistical Manual of Mental Disorders - Klasyfikacja zaburzeń psychicznych Amerykańskiego Towarzystwa Psychiatrycznego
ICD 10 - International Statistical Classification of Diseases and Related Health Problems - Międzynarodowej Statystycznej Klasyfikacji Chorób i Problemów Zdrowotnych
PCT – prokalcytonina
ADL - Activities of Daily Living - Skala Oceny Podstawowych Czynności Życia Codziennego wg Katza
IADL - Instrumental Activities of Daily Living - Skala Oceny Złożonych Czynności Życia Codziennego wg Lawtona
GDS-15 - Geriatric Depression Scale – 15 – punktowa Geriatryczna Skala Oceny Depresji wg Yesavage'a
MMSE - Mini Mental State Examination - Krótka Ocena Stanu Psychicznego
RASS - Richmond Agitation – Sedation Score - Skali Pobudzenia i Sedacji Richmond
IQR – interquartile range – rozstęp kwartylowy
CAM ICU - Confusion Assessment Method in Intensive Care Unit – Metoda Oceny Splątania na Oddziale Intensywnej Terapii
NYHA – New York Heart Association
PaO_2 – ciśnienie parcjalne tlenu we krwi tętniczej

1. WSTĘP

Pierwsze przypadki majaczenia po operacjach kardiochirurgicznych zostały opisane ponad sześćdziesiąt lat temu. W roku 1956 S. Gilman w New England Journal of Medicine opisał szereg negatywnych neuropoznawczych następstw operacji serca z użyciem krążenia pozaustrojowego (ang. *cardiopulmonary bypass* - CPB) takich jak: zaburzenia pamięci, dezorientację w czasie i przestrzeni, zaburzenia zachowania oraz brak współpracy z personelem. (1) W 1957 roku w The Surgical Clinics of North America R. Atkinson określił te zaburzenia jako majaczenie pooperacyjne. Już wtedy autor zwracał uwagę na wiele niekorzystnych konsekwencji – takich jak: gorsza jakość życia, przedłużona rekonwalescencja oraz zwiększona śmiertelność. (2) Od tego czasu, pomimo dokonanego istotnego postępu w technikach chirurgicznych i anestezjologicznych, delirium nadal pozostaje częstym powikłaniem pooperacyjnym, powodującym szczególnie duży niepokój zarówno u chorego jak i u jego rodziny. Majaczenie nie powoduje bólu fizycznego, jaki zwykliśmy łączyć z operacją, ale powoduje realne cierpienie psychiczne pacjentów i ich rodzin, widzących bliską osobę zachowującą się zupełnie odmiennie.

Majaczenie występuje u chorych hospitalizowanych zarówno w oddziałach niezabiegowych, sięgając w starszej populacji nawet 50%, (3) jak i na oddziałach chirurgicznych. Jest stwierdzane u 46-52% chorych po operacjach w zakresie aorty, u 16-44% chorych operowanych z powodu złamania biodra. (4) Jest również poważnym problemem u chorych hospitalizowanych w oddziale intensywnej terapii (OIT). Częstość występowania delirium w OIT waha się między 16% do nawet 80% u chorych wentylowanych mechanicznie. (5)

Raportowana częstość występowania u chorych po operacjach kardiochirurgicznych jest bardzo zróżnicowana. W dużej metaanalizie przeprowadzonej przez Y. Lin na podstawie 25 prac wahała się między 6% a 50%. Majaczenie opisywano również często u chorych po mniej inwazyjnej procedurze, jaką jest przezskórna implantacja zastawki aortalnej (ang. *transcatheter aortic valve implantation* - TAVI) z częstością sięgającą między 7% a 21% chorych. (6) Przyczynia się ono również do rozwoju konkretnych powikłań okołooperacyjnych – przedłuża czas hospitalizacji po operacji, zwiększa ryzyko ponownego przyjęcia do OIT, powoduje zwiększoną śmiertelność. Opisywano również wpływ majaczenia na długofalowe powikłania takie jak niższa jakość życia i długotrwałe obniżenie funkcji poznawczych. (7, 8)

Definicja majaczenia, czyli delirium znajduje się zarówno w klasyfikacji zaburzeń psychicznych Amerykańskiego Towarzystwa Psychiatrycznego DSM-5 (ang. *Diagnostic and Statistical Manual of Mental Disorders*), jak i w, obowiązującej w Polsce, Międzynarodowej Statystycznej Klasyfikacji Chorób i Problemów Zdrowotnych ICD 10 (ang. *International Statistical Classification of Diseases and Related Health Problems*). Obie definicje są podobne i opisują majaczenie jako "nieswoisty etiologicznie organiczny zespół mózgowy" którego cechami charakterystycznymi są: zaburzenia uwagi, świadomości oraz zaburzenia funkcji poznawczych. Zaburzenia uwagi dotyczą wszystkich aspektów: ukierunkowania, zogniskowania, przerzutności, utrzymania uwagi, a zaburzenia funkcji poznawczych obejmują: zaburzenia pamięci - głównie krótkotrwałej przy stosunkowo niezaburzonej pamięci długotrwałej, orientacji w miejscu, czasie, zaburzenia językowe, wzrokowo-przestrzenne, percepcji. Charakterystyczne jest, że majaczenie rozwija się w krótkim okresie czasu (zwykle w ciągu kilku godzin) i wykazuje zmienność w ciągu dnia. Dodatkowo mogą wystąpić: zaburzenia rytmu dobowego, bezsenność w nocy, drzemki w ciągu dnia, odwrócenie rytmu dzień-noc, koszmary senne, halucynacje lub iluzje, zwiększony czas reakcji oraz zwiększona lub zmniejszona prędkość mowy. Zaburzenia te nie mogą być wytłumaczone wcześniej istniejącymi zaburzeniami poznawczymi lub neurologicznymi, a u podłoża majaczenia leży stan chorego. (9, 10) Majaczenie może mieć postać hiperaktywną – chory jest wtedy pobudzony, niespokojny lub hipoaktywną, w której jest senny i spowolniały, lub też postać mieszaną, gdy obie te formy przechodzą jedna w drugą.

Mechanizmy patofizjologiczne, prowadzące do rozwoju majaczenia, pozostają w chwili obecnej tematem badań. Opisywano między innymi hipotezę stanu zapalnego mózgowia, gdzie za rozwój majaczenia odpowiedzialna jest aktywacja reakcji zapalnej. (11) Inna z teorii opisuje wpływ zaburzeń równowagi pomiędzy neuroprzekaźnikami, gdzie dochodzi do spadku stężenia acetylocholiny, która jest głównym neuroprzekaźnikiem w mózgu, wzrostu uwalniania dopaminy, norepinefryny, glutaminianu i serotoniny. (12) Według hipotezy neuroendokrynnej, do rozwoju majaczenia przyczynia się, występujący często w okresie okołooperacyjnym, stres psychologiczny i fizjologiczny. Powoduje on zwiększenie produkcji glikokortyosteroidów wpływających na zmianę w neurotransmisji glutaminianu w korze przedczołowej i hipokampie, prowadząc do upośledzenia funkcji poznawczych. (13, 14) Jeszcze inna teoria opisuje wpływ stresu oksydacyjnego. Według niej obniżona oksygenacja tkankowa powoduje spadek produkcji ATP i zaburzenia w kanałach jonowych. Prowadzi to do uwalniania neurotransmiterów - glutaminianu i dopaminy i kumulacji jonów wapnia, co w konsekwencji zapoczątkowuje procesy kataboliczne. (15) Dochodzić może również do zaburzenia równowagi pomiędzy produkcją wolnych rodników tlenowych a działaniem antyoksydantów, co w konsekwencji może prowadzić do śmierci komórek nerwowych. (16)

Opisywane w piśmiennictwie teorie powstania majaczenia wzajemnie się przenikają i uzupełniają. Liczne potencjalne zaburzenia homeostazy, które prowadzą do rozwoju tego powikłania i niejasny do końca patomechanizm sprawiają, że poszukiwanie przyczyn tego powikłania jest szczególnie trudne. Wszystko to sprawia, że ocena czynników ryzyka majaczenia musi uwzględniać zarówno staranny wywiad przed operacją, jak i analizę przebiegu operacji oraz towarzyszących jej komplikacji.

2. CELE PRACY

Celem przedstawionego cyklu prac była:

1. Analiza czynników ryzyka występowania majaczenia w grupie pacjentów hospitalizowanych w oddziale intensywnej terapii po operacjach kardiochirurgicznych z zastosowaniem krążenia pozaustrojowego, ze szczególnym uwzględnieniem wartości predykcyjnej oznaczeń stężenia prokalcytoniny w surowicy.
2. Analiza czynników śródoperacyjnych, ze szczególnym uwzględnieniem wpływu epizodów hiperoksji występujących w trakcie krążenia pozaustrojowego na częstość występowania majaczenia w bezpośrednim okresie pooperacyjnym.
3. Ocena wpływu majaczenia na czas hospitalizacji po operacji i rozwój powikłań pooperacyjnych takich jak ostra niewydolność nerek i przedłużony czas wentylacji mechanicznej.

3. Publikacje stanowiące pracę doktorską

Journal of
Clinical Medicine

MDPI

Article

Elevated Procalcitonin as a Risk Factor for Postoperative Delirium in the Elderly after Cardiac Surgery—A Prospective Observational Study

Anna Kupiec *, Barbara Adamik, Natalia Kozera and Waldemar Gozdzik

Department of Anesthesiology and Intensive Therapy, Wroclaw Medical University, Borowska 213, 50-556 Wroclaw, Poland; barbara.adamik@umed.wroc.pl (B.A.); natalia.kozera@student.umed.wroc.pl (N.K.); waldemar.gozdzik@umed.wroc.pl (W.G.)

* Correspondence: anna.kupiec@umed.wroc.pl

Received: 28 October 2020; Accepted: 24 November 2020; Published: 26 November 2020

check for updates

Abstract: One of the most common complications after cardiac surgery with cardiopulmonary bypass (CBP) is delirium. The purpose of this study was to prospectively investigate the risk of developing postoperative delirium in a group of elderly patients using a multivariate assessment of preoperative and intraoperative risk factors. A total of 149 elderly patients were included. Thirty patients (20%) developed post-operative delirium. Preoperative procalcitonin (PCT) above the reference range (>0.05 ng/mL) was recorded more often in patients who postoperatively developed delirium than in the non-delirium group (50% vs. 27%, $p = 0.019$). After surgery, PCT was significantly higher in the delirium than the non-delirium group: ICU admission after surgery: 0.08 ng/mL vs. 0.05 ng/mL $p = 0.011$), and for consecutive days (day 1: 0.59 ng/mL vs. 0.25 ng/mL, $p = 0.003$; day 2: 1.21 ng/mL vs. 0.36 ng/mL, $p = 0.006$; day 3: 0.76 ng/mL vs. 0.34 ng/mL, $p = 0.001$). Patients with delirium were older (74 vs. 69 years, $p = 0.038$), more often had impaired daily functioning (47% vs. 28%, $p = 0.041$), depressive symptoms (40% vs. 17%, $p = 0.005$), and anemia (43% vs. 19%, $p = 0.006$). In a multivariable logistic regression model, preoperative procalcitonin (odds ratio (OR) = 3.05), depressive symptoms (OR = 5.02), age (OR = 1.14), impaired daily functioning (OR = 0.76) along with CPB time (OR = 1.04) were significant predictors of postoperative delirium.

Keywords: delirium; procalcitonin; elderly; functional decline; depression; cardiac surgery

J. Clin. Med. **2020**, *9*, 3837; doi:10.3390/jcm9123837 www.mdpi.com/journal/jcm

1. Introduction

In recent decades, we have seen a significant aging of the population in developed countries. Over 70% of people above the age of 60 suffer from cardiovascular disease [1]. Consequently, the number of elderly and very elderly patients undergoing cardiac surgery is increasing [2]. As the elderly are more burdened with comorbidities, this group is at high risk of perioperative complications, including death [3]. Therefore, perioperative care for elderly patients subjected to cardiac surgery becomes a big challenge for everyone—the surgeon, anesthesiologist, and intensivist—as is taking care of the patient after surgery. One of the most common complications after on-pump cardiac surgery, with reported incidence rates ranging up to 50%, is postoperative delirium, defined as fluctuating attention and awareness disturbances. Perioperative factors and the type of cardiac surgery are associated with postoperative delirium. In our previously published study, it was shown that cardiopulmonary hyperoxia episodes might be a risk factor associated with the occurrence of postoperative delirium [4]. Three subtypes of delirium have been differentiated: hypoactive, hyperactive, and mixed [5]. All of them have been associated with prolonged hospitalization, increased death rate [6], increased risk of intensive care unit (ICU) and hospital readmission [7], and possible long-term consequences such as lower quality of life or cognitive decline after the operation [8].

It is difficult to determine the origin of this complication as there are many potential systemic homeostasis disorders which can lead to delirium. Several hypotheses have been described, including neuroinflammation, oxidative stress, neuroendocrine dysregulation, circadian dysregulation, and neuronal aging [9]. Our knowledge of perioperative delirium risk factors in heart surgery is continuously growing, but there is still much that is unknown. The activation of an inflammatory response after surgery has been suggested as one of the possible mechanisms of delirium [9]. The use of cardiopulmonary bypass leads to the activation of a systemic inflammatory response and is associated with increased production of various inflammatory mediators during and after surgery [10,11]. An inflammatory marker, procalcitonin (PCT), may be considered a good predictor of postoperative complications early after cardiac surgery with cardiopulmonary bypass. High levels of PCT have been associated with postoperative complications such as infection [12], organ dysfunction [13], and increased mortality [14,15]. The usefulness of procalcitonin as a predictor of postoperative delirium caused by surgery and cardiopulmonary bypass (CBP) has not yet been investigated. Therefore, we have prospectively studied the risk of developing postoperative delirium in a group of elderly patients undergoing cardiac surgery with CPB, using a multivariate assessment of perioperative risk factors.

2. Experimental Section

The study was approved by the local Bioethics Committee (permission number 219/2016), and informed consent was collected from all patients participating in the study. Inclusion criteria were: planned cardiac surgery with CBP, age 65 years old or more, and full participation of the patient in the preoperative evaluation. Exclusion criteria were: inability to get informed consent, urgent operation, off-pump surgery, diagnosis of dementia before surgery, a different protocol of anesthesia (total venous anesthesia), or deep hypothermia procedures.

2.1. Procalcitonin Measurement

In all patients, the PCT concentrations were routinely measured one day before surgery (baseline) and on day 0 (ICU admission after surgery), 1, 2, and 3 after surgery. All measurements were performed in the hospital laboratory (normal serum values are below 0.05 ng/mL) by using a chemiluminescent microparticle immunoassay (ARCHITECT B·R·A·H·M·S PCT, Abbott, Chicago, IL, USA). The limit of quantification of the test was 0.01 ng/mL, and the analytical sensitivity was 0.00 ng/mL.

2.2. Preoperative Assessment

A preoperative assessment was performed the day before the operation by a trained anesthesiologist and included the following evaluation of the patient's ability to care for him- or herself with (I) an Activities of Daily Living scale (ADL); (II) an Instrumental Activities of Daily Living scale (IADL); an evaluation of the occurrence of cognitive decline using the (III) Mini-Mental State Examination score (MMSE); and an assessment of the occurrence of depression with an (IV) Geriatric Depression Scale (GDS-15).

(I) ADL and (II) IADL are both parts of a comprehensive geriatric assessment [16] and are used to assess functional decline. The ADL questionnaire consists of 6 questions assessing basic functional activities as: (1) using the toilet, (2) controlling urination and defecation, (3) bathing, (4) eating, (5) getting out of bed, and (6) dressing oneself [17]. The ADL scale ranges from 0 to 6 pts., with 0 being the worst and 6 pts. being the best. A score of 6 indicates the full function and a score below 6 pts. indicates compromised daily functioning. The IADL consists of 8 questions about everyday activities: (1) to use a phone, (2) to do shopping, (3) to do housekeeping, (4) to handle finances, (5) to use a mode of transportation, (6) to be responsible for one's own medication, (7) to prepare meals, and (8) to do laundry or craftwork [18]. The IADL score ranges from 8 to 24 points (1–3 pts. for each question), with 8 pts. being the worst and 24 pts. being the best. A score below 24 indicates compromised activities related to independent living.

As older populations are at risk of cognitive impairment, cognitive decline was measured with (III) the Mini-Mental State Examination (MMSE), one of the most common scores used for screening. It can also be easily used by physicians who are not psychiatrists. The MMSE assesses seven different cognitive domains: (1) orientation to time (range 0–5), (2) orientation to place (range 0–5), (3) word registration (range 0–3), (4) delayed recall (range 0–3), (5) working memory (range 0–5), (6) language (range 0–8), and (7) visuospatial (range 0–1). The total MMSE score ranges from 0 to 30 points. A score of 27–30 indicates no cognitive impairment and MMSE ≤ 26 indicates cognitive impairment [19].

In addition, we assessed depressive symptoms with (IV) a 15-point Geriatric Depression Scale GDS-15 with 0 pts. being the best and 15 pts. being the worst. A score ≥ 5 indicates depression with a sensitivity of 80% and specificity of 75% [20]. The GDS-15 score results were divided into two categories: no depression with GDS-15 < 5 and depressive symptoms present with GDS-15 ≥ 5. In addition, information on comorbidities was recorded. The European System for Cardiac Operative Risk Evaluation (Euroscore II) was used to predict the risk of death after heart surgery, as calculated by the available online Euroscore II calculator (euroscore.org). According to World Health Organization (WHO) criteria, preoperative anemia was defined, setting the hemoglobin cut off below 12 g/dL for females and 13 g/dL for males [21].

2.3. *Anesthesia and Surgery*

The induction of anesthesia was conducted with sufentanil, propofol, and rocuronium. Sufentanil and rocuronium infusion with inhaled sevoflurane was applied to maintain anesthesia. After administering heparin and achieving an activated clotting time longer than 480 s, CBP was initiated. A hollow fiber membrane oxygenator (Medtronic Affinity, Medtronic, Inc., Minneapolis, MN, USA) with an integrated polyester arterial line filter of 40 mm pore size and a roller pump with a non-pulsatile flow 2.4–2.5 L/min/m^2 (Stockert S3, Sorin Group, Munich, Germany) was used in all patients. All patients were normothermic (37 °C). After the operation, patients were transferred to the ICU. Sedation with propofol was continued, and patients were extubated if they were hemodynamically stable, with sufficient oxygenation and without excessive bleeding. Postoperative pain was treated with Paracetamol 1 g every 6 h and Oxycodone 3–4 mg every 4 h. Procedure parameters and postoperative complications were noted, including the type of operation, aorta cross-clamping, CBP and operation time, and ICU stay and hospitalization lengths. Acute kidney injury was diagnosed according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria [22].

2.4. *Delirium Assessment*

Patients were evaluated for delirium every 12 h, starting the morning after the operation for three subsequent days. We chose the Confusion Assessment Method for Intensive Care Unit (CAM ICU) to assess delirium. Its reported sensitivity is 83%, and specificity reaches up to 100% [23]. The CAM ICU is easy to perform and can be used by non-psychiatrists, physicians, and nurses. In our study, the CAM ICU assessment was performed by anesthesiologists trained for that purpose. The scale includes the evaluation of four features of delirium: fluctuating changes in mental status, inattention, an altered level of consciousness, and disorganized thinking.

The examination of consciousness was conducted with the Richmond Agitation-Sedation Scale (RASS). RASS is a 10-level score between −5 and +4 points, where −5 pts. indicates unarousable, 0 pts. indicates alert and calm, and +4 is combative. The CAM ICU can be used when the RASS ≥ −3. We used the RASS scale to identify subtypes of delirium. Hypoactive delirium was diagnosed in cases with −3 ≤ RASS ≤ 0 pts., and hyperactive delirium was diagnosed in patients with RASS > 0 pts. A mixed type of POD was diagnosed in the case of a hyper- and hypoactive type switching from one to another during the day.

2.5. Statistical Analysis

All analyses were performed with Statistica 13 software (StatSoft, Inc., Tulsa, OK, USA). Continuous variables were expressed as median (interquartile range between the 25th and 75th percentiles); categorical data were expressed as numbers and percentages. The distribution was not normal based on the Shapiro–Wilk test. Therefore, statistical analysis was performed using nonparametric tests. The Mann–Whitney U test was used for comparison of the continuous variables between study groups. A Friedman's ANOVA with post-hoc tests was used to analyze changes within groups in the course of procalcitonin over time. Categorical variables were analyzed using the chi-square test; contingency tables were used to summarize the relationship between several categorical variables. Multivariate logistic regression analysis was performed to create a model predicting the development of postoperative delirium. The association between procalcitonin and selected covariates (age, gender, ADL, IADL, MMSE and GDS-15 scale, Euroscore II, anemia before surgery, CPB time, aorta cross clamp (AoX) time) and the development of postoperative delirium was assessed; the results were reported as odds ratios (OR) with 95% confidence intervals (CI). The first prepared model included preoperative and postoperative PCTs and all selected covariates. The collinearity of the variables was tested; two of the covariates (gender and MMSE) were collinear so those features were excluded from the analysis. The choice of the best model was proposed based on the backward selection of the model. From the baseline PCT, the PCT recorded on day 0, and the eight covariates (age, ADL, IADL, GDS-15 scale, Euroscore II, anemia before surgery, CPB time, AoX time), the procedure chose the best model with the baseline PCT and four covariates (age, IADL, depressive symptoms, and CPB time). All the tests were conducted with a 5% significance level.

3. Results

3.1. Study Sample

A total of 534 consecutive patients who underwent cardiac surgery between January 2017 and December 2018 were screened for inclusion/exclusion criteria. Of this number, 271 patients met the inclusion criteria and were invited to the study. Finally, informed consent was obtained from 151 patients, but two patients withdrew their consent after the operation; 149 patients were included in the final analysis. The flow diagram of the study is presented in Figure 1.

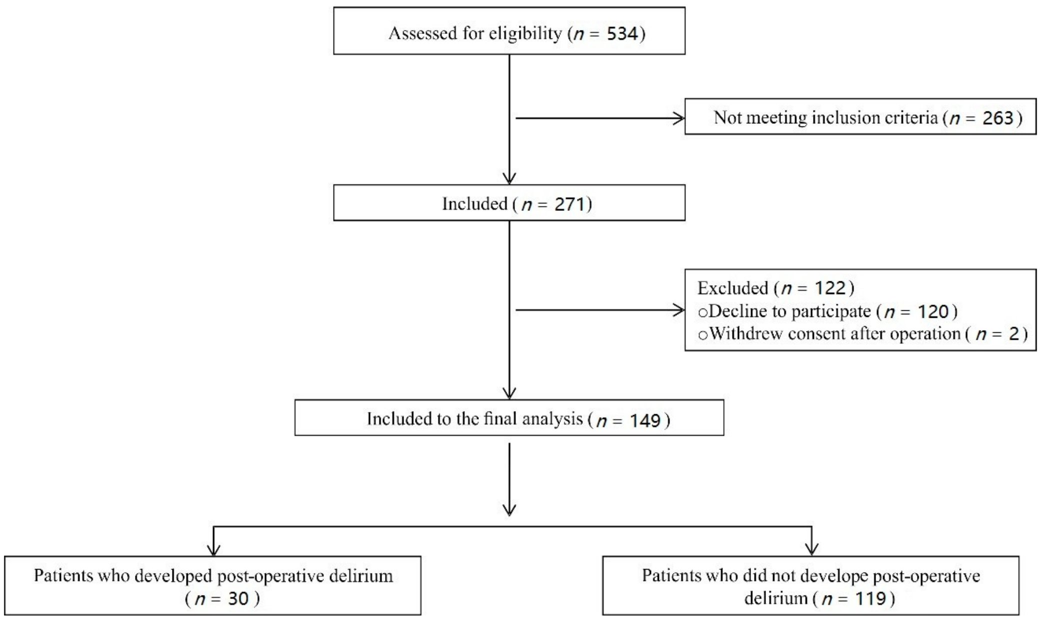

Figure 1. Flow diagram of the study.

None of the patients presented signs of infection before surgery, and the WBC count was within the reference range in both groups (with postoperative delirium: 7.37, interquartile range (IQR) 6.04–8.57 $10^3/mm^3$ vs. without delirium: 7.76, IQR 6.09–8.93 $10^3/mm^3$; p = 0.306).

Thirty patients developed postoperative delirium (20%), and 119 patients (80%) did not. Hypoactive delirium was the most prevalent and was diagnosed in 50% (15/30) of patients. Hyperactive delirium was diagnosed in 33% (10/30) of patients, and 17% (5/30) of patients developed a mixed type of delirium (Figure 2). Of all delirium cases, 23 patients experienced delirium lasting less than 12 h, four patients between 12 and 24 h, and three patients experienced longer delirium. The majority of delirium (19 incidences) occurred on the first day postoperatively. Nine incidences were recorded on the second day, and five on the third day (Figure 2).

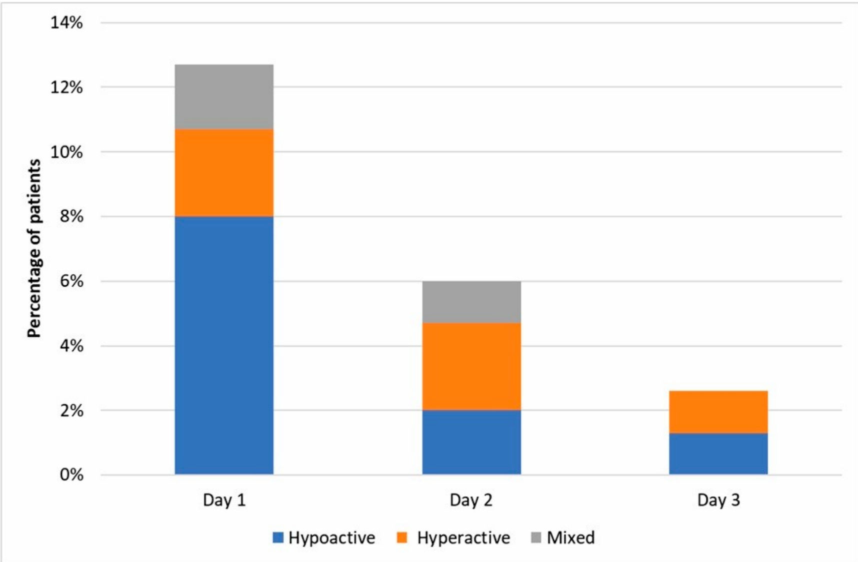

Figure 2. Postoperative delirium cases identified on days 1, 2, and 3 after surgery.

3.2. *Risk Factors for Delirium*

3.2.1. Procalcitonin

Preoperative (baseline) PCT levels above the reference range (>0.05 ng/mL) were found in 50% of patients who postoperatively developed delirium and in only 27% in the non-delirium group (p = 0.019). The comparison of PCT values between groups on each study day is presented in Figure 1. The median preoperative value of PCT was 0.05 ng/mL (IQR 0.01–0.08) in the delirium group and 0.03 ng/mL (IQR 0.01–0.06) in the non-delirium group (p = 0.207). After surgery, PCT levels were significantly higher in the delirium group than in patients without delirium on admission to the ICU (day 0: 0.08 ng/mL, IQR 0.03–0.15 vs. 0.05 ng/mL, IQR 0.02–0.09, p = 0.011) and for the consecutive days (day 1: 0.59 ng/mL, IQR 0.25–1.55 vs. 0.25 ng/mL, IQR 0.14–0.54, p = 0.003; day 2: 1.21 ng/mL, IQR 0.24–3.29 vs. 0.36 ng/mL, IQR 0.16–0.76, p = 0.006; day 3: 0.76 ng/mL, IQR 0.48–2.34 vs. 0.34 ng/mL, IQR 0.14–0.66, p = 0.001, respectively, in the delirium and non-delirium group), with a peak value on the second day after surgery (Figure 3).

The analysis of changes in PCT concentrations overtime within the groups showed significant changes in the delirious group (p < 0.001, Friedman's ANOVA test) and in the group without delirium (p = 0.021); post-hoc tests showed a significant increase of PCT on days 1 and 2 compared to the baseline in both groups.

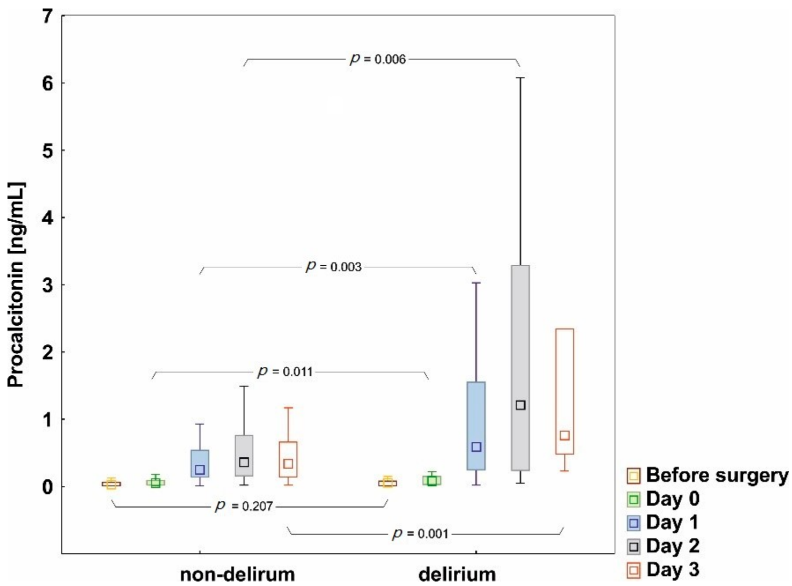

Figure 3. Procalcitonin concentrations in the group with and without postoperative delirium; *p*-values indicate statistically significant differences between groups; boxplot showing minimum and maximum (whiskers), median (middle point), and IQR values (box).

Three patients in the delirium group and two in the group without delirium had infection symptoms in the postoperative period; two patients were diagnosed with pneumonia, two with surgical-site infection, and one with pneumonia and a urinary tract infection. The other patients, despite an elevated PCT level after surgery, did not present any signs of infection.

3.2.2. Age

The median age in the group of patients with postoperative delirium was higher than in the non-delirium group (74 years, IQR 70–76 vs. 69 years, IQR 67–74; $p = 0.038$) (Table 1).

Table 1. Preoperative characteristics: an analysis comparing characteristics of subjects who developed delirium and those who did not.

Preoperative Characteristics	Delirium	Non-Delirium	*p*
	n = 30	*n* = 119	
Age	73.5 (70–76)	69 (67–74)	0.038
Gender, men, *n* (%)	18 (60)	79 (66)	0.511
BMI, (kg/m^2)	28.4 (24.2–29.4)	27.5 (25.3–31.0)	0.597
Euroscore II, (%)	2.5 (1.6–5.7)	1.8 (1.2–2.8)	0.009
Comorbidities, *n* (%)			
Cerebrovascular disease	7 (23)	13 (10)	0.138
Arterial hypertension	26 (86)	107 (89)	0.607
Diabetes mellitus	11 (36)	44 (36)	0.975
Continuous atrial fibrillation	2 (6)	11 (9)	0.654
Chronic renal insufficiency	8 (26)	20 (16)	0.216
Anemia, *n (%)*	13(43)	23 (19)	0.006
Ejection fraction, *n* (%)	60 (50–65)	60 (50–65)	0.471
Nicotine abuse, *n* (%)	6 (20)	26 (22)	0.825

Data are presented as median (interquartile range) or percentage. BMI: Body Mass Index.

3.2.3. Comorbidities

The distribution of comorbidities such as cerebrovascular disease, hypertension, atrial fibrillation, diabetes, or renal insufficiency was comparable in the study groups, and anemia was more than two times more common in the group of patients who experienced postoperative delirium compared to the group without delirium (43% vs. 19%, $p = 0.006$) (Table 1).

3.2.4. Euroscore II

As estimated by the pre-surgery Euroscore II risk model, the risk of death after cardiac surgery was higher in patients who eventually developed delirium postoperatively than in the non-delirious group (2.5% vs. 1.8%, $p = 0.009$). The observed mortality was 3.3% in the group with delirium and 0.8% in the non-delirium group ($p = 0.323$).

3.2.5. Preoperative Geriatric Assessment Scores

MMSE: the overall scores were not different among patients with or without postoperative delirium (median 25 pts. in each group). An analysis of the MMSE domains between patient groups revealed only a statistically significant difference for the orientation to place domain ($p = 0.020$); results in other domains (orientation to time, word recall, working memory, language, and visuospatial) were similar in both study groups. A total of 39% of patients did not show signs of cognitive impairment (27%, 8/30 in the delirium group; 42%, 50/119 in the non-delirium group); MMSE $\leq$ 26, which indicates cognitive impairment, was found in 73% of patients (22/30) in the delirious group and in 58% (69/119) in the non-delirium group ($p = 0.123$).

ADL: the majority of patients did not show signs of a decline in functional status (93%, 28/30 in the delirium group; 99%, 118/119 in the non-delirium group). Compromised daily functioning was detected in 2 patients in the delirious group (both cases with 2 pts.) and in 1 in the non-delirium group (5 pts.).

IADL: no sign of decline in functional status was recorded in only 53% of patients (16/30) in the delirium group and 72% (86/119) in the non-delirium group. Compromised daily functioning was detected in 47% of patients (14/30) in the delirium group and 28% (33/119) in the non-delirium group ($p = 0.046$). Among those with compromised daily functioning, patients with postoperative delirium were less independent in terms of shopping ($p = 0.041$), housekeeping ($p < 0.001$), using a mode of transportation ($p = 0.014$), being responsible for one's own medication ($p = 0.035$), preparing meals ($p = 0.022$), and doing laundry (0.001) compared to the non-delirium group.

GDS-15 score: GDS-15 $\geq$ 5, indicating depressive symptoms, was detected in 12 patients in the delirious group (40%) and in 20 in the non-delirious group (17%) ($p = 0.005$). The median value of GDS-15 was 5 pts. (IQR 3–7) in the delirious group and 3 pts. (IQR 2–5) in patients without delirium ($p = 0.003$).

An analysis comparing the preoperative geriatric characteristics of subjects who developed delirium and those who did not is presented in Table 2.

3.2.6. Surgery and Postoperative Indices

In the group with postoperative delirium, a complex procedure was used more often (40% vs. 14%, $p = 0.009$). As expected, cardiopulmonary bypass and aortic cross-clamp time were significantly longer in patients who eventually developed delirium than in the group without delirium, but anesthesia time was similar in both study groups (Table 3). The postoperative analysis showed that in the group of patients with delirium, respiratory support was significantly longer than in the group without delirium (290 vs. 200 min, $p = 0.002$), acute kidney injury was diagnosed three times more often (20% vs. 7%, $p = 0.025$), the hospital stay was longer (11 vs. 9 days, $p = 0.002$), and mortality was higher (3.3% vs. 0.8%, $p = 0.323$) (Table 3).

Table 2. Preoperative geriatric assessment: an analysis comparing the assessment of subjects who developed delirium and those who did not.

	Delirium	Non-Delirium	*p*
	n = 30	*n* = 119	
MMSE, *n* (%)			0.123
no cognitive impairment (≥27 pts.)	8 (27)	50 (42)	
cognitive impairment (≤26 pts.)	22 (73)	69 (58)	
ADL, *n* (%)			0.103
full functioning (6 pts.), *n* (%)	28 (93)	118 (99)	
compromised functioning (<6 pts.), *n* (%)	2 (7)	1(1)	
IADL, *n* (%)			0.046
full functioning (24 pts)	16 (53)	86 (72)	
compromised functioning (total score < 24 pts.):			
(1) use phone	2 (7)	3 (3)	0.471
(2) shopping	5 (16)	6(5)	0.041
(3) housekeeping	9 (30)	4 (4)	<0.001
(4) handle finances	7 (23)	23 (19)	0.235
(5) a mode of transportation	10 (33)	15(12)	0.014
(6) responsibility for own medication	5 (16)	5 (5)	0.035
(7) preparation of food	5 (16)	4 (3)	0.022
(8) doing laundry	7 (23)	5 (5)	0.001
GDS-15, *n* (%)			0.005
no depression (<5 pts.)	18 (60)	99 (83)	
depressive symptoms (≥5 pts.)	12 (40)	20 (17)	

Data are presented as median (interquartile range) or percentage. MMSE: Mini Mental State Examination; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; GDS-15: 15-Item Geriatric Depression Scale.

Table 3. Perioperative characteristics: an analysis comparing the characteristics of subjects who developed delirium and those who did not.

	Delirium	Non-Delirium	*p*
	n = 30	*n* = 119	
Intra-operative characteristics			
Type of operation, *n* (%)			0.009
CABG	16 (53)	84 (71)	
Valve only	2 (7)	18 (15)	
CABG + valve	12 (40)	17 (14)	
CBP time (min)	102 (81–127)	79 (67–94)	<0.001
AoX time (min)	57 (43–81)	43 (34–60)	0.004
Anesthesia time (min)	272 (240–305)	255 (235–280)	0.101
Post-operative characteristics			
Respiratory support (minutes)	290 (210–525)	200 (175–270)	0.002
AKI, *n* (%)	6 (20)	8 (7)	0.025
ICU stay (days)	3 (2–6)	3 (2–5)	0.133
Hospital stay (days)	11 (10–15)	9 (8–11)	0.002
In-hospital mortality, *n* (%)	1 (3.3)	1 (0.8)	0.323

Data are presented as median (interquartile range) or percentage. CBP: cardiopulmonary bypass; AoX: aorta cross clamp; AKI: acute kidney injury; ICU: intensive care unit.

3.3. Prediction Model of Postoperative Delirium

Multivariate logistic regression analysis was performed to create a model to predict the development of postoperative delirium. The model's backward selection determined the choice of the variables from the set of perioperative parameters (procalcitonin, age, gender, ADL, IADL, MMSE, and GDS-15 scale, Euroscore II, anaemia before surgery, CPB time, AoX time). The baseline procalcitonin (OR = 3.05; IQR 1.01–9.19), GDS-15 ≥ 5 indicating depressive symptoms (OR = 5.02, IQR

1.67–15.10), age (OR = 1.14; IQR 1.02–1.26), IADL score (OR = 0.76; 0.63–0.91), and CPB time (OR = 1.04; IQR 1.02–1.06) were significant predictors of postoperative delirium; other parameters did not enter the model. The results are presented in Table 4.

Table 4. Univariate and multivariate logistic regression analysis of the predictors of delirium.

	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	**95% CI**	***p***	**Odds Ratio**	**95% CI**	***p***
PCT baseline	2.70	1.15–6.32	0.022	3.05	1.01–9.19	0.048
IADL	0.81	0.70–0.92	0.002	0.76	0.63–0.91	0.003
Depressive symptoms	3.30	1.37–7.91	0.008	5.02	1.67–15.10	0.004
Age	1.08	1.01–1.17	0.031	1.14	1.02–1.26	0.016
CPB time	1.02	1.01–1.04	<0.001	1.04	1.02–1.06	<0.001
AoX time	1.02	1.01–1.04	0.003			
Euroscore	1.21	1.06–1.37	0.004			
Gender	0.75	0.33–1.73	0.511			
MMSE	0.96	0.84–1.09	0.595			
ADL	0.34	0.10–1.16	0.086			
Anemia before surgery	3.19	1.35–7.49	0.007			

CI: confidence interval; IADL: Instrumental Activities of Daily Living; CBP: cardiopulmonary bypass; PCT: procalcitonin; AoX: aortic cross clamp; MMSE: Mini Mental State Examination; ADL: Activities of Daily Living.

4. Discussion

The key finding of this study is that elevated preoperative procalcitonin, along with other preoperative factors such as age, depressive symptoms, and compromised daily functioning, accompanied by prolonged CBP time, are the most critical factors in the development of postoperative delirium after cardiac surgery. A multivariate logistic regression model was used to estimate the strength of the association of these parameters with the development of postoperative delirium. To our knowledge, this is the first study showing the usefulness of procalcitonin as a predictor of the development of postoperative delirium in patients undergoing cardiac surgery.

PCT is a peptide precursor of calcitonin and a biomarker of inflammation. In ICU patients, PCT has been used to identify bacterial infections and monitor antibiotic therapy as part of standard care for septic patients. However, there is growing evidence that pre-procedural PCT may be a marker that also predicts an adverse outcome in non-infectious diseases. Keranov et al. recently investigated the relationship between preoperative PCT and postoperative outcome in patients after transcatheter aortic valve implantation (TAVI). Multivariable analysis revealed that preoperative PCT was an independent predictor of 30-day mortality (HR 2.84) and 1-year mortality (HR 1.90); significantly higher mortality was observed in the group in which the preoperative PCT value was only slightly above the reference range (≥0.06 ng/mL) [24]. The importance of preoperative procalcitonin as a predictor of delirium has not yet been established. In the present study, it was observed that 50% of patients who developed postoperative delirium and only 27% of patients without delirium had procalcitonin above the reference range prior to surgery and according to the multivariate logistic regression analysis, preoperative PCT significantly increased the risk of postoperative delirium with an odds ratio of 3.05 ($p = 0.048$).

The causes of delirium are multifactorial and in our study the best multivariable model for predicting delirium development after cardiac surgery included the preoperative PCT concentration along with other factors such as IADL score, depressive symptoms, age, and the duration of CPB. The elderly are particularly sensitive to the development of postoperative delirium; in addition, delirium duration is longer in elderly patients than in younger patients subjected to cardiac surgery. Previously, Cereghetti et al. found that each year of life significantly increased postoperative delirium risk with an OR of 1.06 [25]. These results coincide with our research; according to the multivariate logistic regression analysis, the patient's age was a significant factor of the model that predicted postoperative delirium with an odds ratio of 1.13.

Depression is frequent in older people and seems to be another critical risk factor of postoperative delirium. We reported here that the GDS-15 ≥ 5, indicating depressive symptoms, was associated with a 5-fold increased risk of postoperative delirium. A study by Eshmawe et al. confirmed that a higher preoperative depression score was associated with an increased risk of postoperative delirium [26]. In another study, Oldham et al. demonstrated a relationship between the occurrence of preoperative depression and the development and severity of delirium after CABG. The authors used three different scales to diagnose depression, and only one scale (Patient Health Questionnaire 9) was predictive of delirium, while the results of two other scores (GDS-15 and HDRS) were shown to have little or no association with postoperative delirium [27]. Different scales have been used to measure depression and it remains unclear which measure of depression may be most predictive of outcome.

Advanced age is one of the most important risk factors for functional deterioration assessed by the IADL score. It was estimated that 40% of men and more than 50% of women were limited in at least one IADL activity [28]. A decline in physical activity such as doing housework, travel, and shopping were more age-dependent than cognitive activities such as using a telephone, managing finances, or taking one's medication [29]. In our research, patients who developed postoperative delirium had significantly compromised physical activities assessed with the IADL score. Moreover, in the multivariate logistic regression analysis, a lower IADL score estimated before surgery was a significant risk factor for postoperative delirium. These results confirm the importance of examining depression or the deterioration of physical and cognitive activity before an operation in an elderly patient. As part of a comprehensive geriatric assessment, tools such as the IADL and GDS-15 should be a routine part of managing an elderly population to help identify cases of increased risk of postoperative delirium.

In this study, we found other differences in the analyzed parameters between the delirious and non-delirious group, but these variables were not significant in the multivariable logistic regression model. One of these variables was the postoperative PCT concentration. We diagnosed postoperative infection in only 5 patients, but the increased PCT was significant in both the delirium and non-delirious groups. This can be explained by the fact that the concentration of procalcitonin may rise in the course of the inflammatory reaction in response to surgical trauma without infection, and a transient increase in the PCT concentration has been observed even during uncomplicated heart surgery [30]. In cardiac surgery, the systemic inflammatory response can be activated by many factors such as surgical trauma, CBP circuit, endotoxemia, and ischemia-reperfusion injury. Various inflammatory mediators, including PCT, are released and lead to systemic effects such as vasodilatation and disturbances in the microcirculation [10]. Long CBP is a powerful inductor of a systemic inflammatory reaction, and brain function may also be affected. Consistent with the neuroinflammatory hypothesis of postoperative delirium, inflammatory mediators released when the systemic inflammatory response has been activated cross the blood-brain barrier, activating microglial cells to produce inflammatory mediators. Consequently, damage to brain tissue, dysfunction of neuron activity, disturbances in the neurotransmitter system, impaired synaptic conduction, and leaking of intercellular connections of blood–brain barrier cells were detected [9,31].

Here, we assessed PCT because daily PCT measurements are readily available as part of routine in-hospital monitoring, and the predictive value of PCT for diagnosing complications after cardiac surgery had been previously confirmed. Clementi et al. presented results that the PCT measurement performed 48 h after the cardiac operation was a good predictor of postoperative renal and respiratory complications [14]. In another study, Klingele et al. showed that a single PCT measurement taken the day after surgery was a predictor of delayed complications such as prolonged hospitalization, ICU readmission, and hospital death [32].

The importance of postoperative procalcitonin as a predictor of delirium has not yet been established. Earlier, McGrane et al. demonstrated that in a population of non-cardiac ICU patients, high PCT values recorded on ICU admission predicted prolonged periods of acute brain dysfunction, linking inflammation as an essential mechanism in the pathophysiology of delirium [33]. In a later prospective study by Nemeth et al., the relationship between changes in the procalcitonin concentration measured on the first day after surgery and the occurrence of postoperative cognitive dysfunction was assessed in a population of elderly patients undergoing on-pump cardiac surgery, and no relationship was found between inflammatory response and cognitive dysfunction [34]. In this study, the median level of PCT was elevated after the operation with a peak value on the second day, and it was significantly higher in patients with postoperative delirium than in those without delirium. However, it should be emphasized, that while median PCT level was elevated in patients throughout the postoperative period, in multivariate logistic regression analysis only pre-operative PCT along with age, depression, daily functioning dysfunction, and CBP were significant in the delirium prediction model. As PCT tests are readily available (hospital laboratory, point of care testing), fast, and relatively cheap, it may be an additional indicator useful for the early identification of patients at risk for postoperative delirium.

Comorbidities are known risk factors for the development of postoperative delirium [35]. In our study, a majority of patients were diagnosed with arterial hypertension; diabetes and chronic renal insufficiency were common. Except for anemia, there was no difference in the distribution of comorbidities between groups. Anemia was diagnosed in 43% of patients in the group who developed postoperative delirium, and only 19% in the group without delirium. Previous studies have shown that preoperative anemia was considered a risk factor for the outcome in non-cardiac surgery; it was associated with a more extended hospital stay, a higher risk of perioperative complications, and higher mortality [36]. In a recent study of 800 patients undergoing elective non-cardiac surgery, anemia was associated with postoperative delirium and longer hospitalization [37]. The impact of preoperative anemia on postoperative delirium in the cardiosurgical population is not yet well understood, and the results published so far have often been contradictory. In a systematic review based on 34 studies, several studies identified anemia as an important risk factor for delirium following on-pump cardiac surgery, while others did not find an association [38]. In a recently published study by Smulter et al., the preoperative hemoglobin level was not associated with postoperative delirium [39]. In our study, preoperative anemia was more than twice as common in the group with postoperative delirium than in patients without delirium (43% vs. 19%, p = 0.006); however, in a multivariate logistic regression analysis, the presence of preoperative anemia was not included in the prediction model. It seems that this issue requires further evaluation in larger populations.

In the present study, more patients who postoperatively developed delirium required a complex procedure. This resulted in a significant prolongation of CBP time. Along with long aortic cross-clamping, prolonged CBP time has been one of the most important factors of postoperative delirium [6]. This observation was also confirmed in our study in the multivariate logistic regression analysis. The duration of CPB was a significant factor in the model predicting postoperative delirium with an odds ratio of 1.04. This observation leads to the conclusion that qualifying elderly patients for long and complex procedures require careful consideration and balancing the risks and potential benefits.

Our study has several limitations. First, we did not assess the long-term consequences of delirium, postoperative cognitive decline, or a reduced quality of life after the operation. Second, our model was based on patients in one center and the study sample was relatively small. Multi-centered research on the assessment of procalcitonin and other inflammatory markers is worth considering.

5. Conclusions

The multivariate logistic regression model shows that preoperative factors such as procalcitonin above a normal range, older age, depressive symptoms, impaired functional status, along with the intraoperative factor of a longer cardiopulmonary bypass time are associated with an increased risk of developing postoperative delirium. Further research is needed to confirm our observations on a larger cohort of patients.

Author Contributions: Conceptualization, W.G., A.K.; methodology, W.G., A.K.; validation, B.A.; formal analysis, B.A.; investigation, A.K., N.K.; resources, A.K., N.K.; data curation, B.A., writing—original draft preparation, A.K.,

B.A.; writing—review and editing, A.K., B.A., W.G., N.K.; visualization, A.K., B.A.; supervision, W.G.; project administration, W.G.; funding acquisition, B.A. All authors have read and agreed to the published version of the manuscript.

Funding: The authors acknowledge funding support from Wroclaw Medical University, Poland (grant No. ST.A170.18.024).

Acknowledgments: The authors wish to thank Lukasz Stróżecki for performing statistical analysis of the data.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Benjamin, E.J.; Virani, S.S.; Callaway, C.W.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; de Ferranti, S.D.; Floyd, J.; Fornage, M.; Gillespie, C.; et al. Heart Disease and Stroke Statistics—2017 Update. *Circulation* **2017**, *135*, e146–e603. [CrossRef]
2. Iung, B.; Baron, G.; Butchart, E.G.; Delahaye, F.; Gohlke-Bärwolf, C.; Levang, O.W.; Tornos, P.; Vanoverschelde, J.-L.; Vermeer, F.; Boersma, E.; et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on valvular heart disease. *Eur. Heart J.* **2003**, *24*, 1231–1243. [CrossRef]
3. Ranucci, M.; Castelvecchio, S.; Menicanti, L.; Frigiola, A.; Pelissero, G. Risk of assessing mortality risk in elective cardiac operations: Age, creatinine, ejection fraction, and the law of parsimony. *Circulation* **2009**, *119*, 3053–3061. [CrossRef]
4. Kupiec, A.; Adamik, B.; Forkasiewicz-Gardynik, K.; Goździk, W. Intra-operative hyperoxia and the risk of delirium in elderly patients after cardiac surgery. *Aging* **2020**, *12*, 7006–7014. [CrossRef]
5. Lin, Y.; Chen, J.; Wang, Z. Meta-analysis of factors which influence delirium following cardiac surgery. *J. Card. Surg.* **2012**, *27*, 481–492. [CrossRef]
6. Bakker, R.C.; Osse, R.J.; Tulen, J.H.M.; Kappetein, A.P.; Bogers, A.J.J.C. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. *Eur. J. Cardio Thorac. Surg.* **2012**, *41*, 544–549. [CrossRef]
7. Koster, S.; Hensens, A.G.; Schuurmans, M.J.; Van Der Palen, J. Consequences of delirium after cardiac operations. *Ann. Thorac. Surg.* **2012**, *93*, 705–711. [CrossRef]
8. Sauër, A.C.; Veldhuijzen, D.S.; Ottens, T.H.; Slooter, A.J.C.; Kalkman, C.J.; Van Dijk, D. Association between delirium and cognitive change after cardiac surgery. *Br. J. Anaesth.* **2017**, *119*, 308–315. [CrossRef]
9. Maldonado, J.R. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *Int. J. Geriatr. Psychiatry* **2018**, *33*, 1428–1457. [CrossRef]
10. Paparella, D.; Yau, T.M.; Young, E. Cardiopulmonary bypass induced inflammation: Pathophysiology and treatment. An update. *Eur. J. Cardio Thorac. Surg.* **2002**, *21*, 232–244. [CrossRef]
11. Gozdzik, W.; Adamik, B.; Gozdzik, A.; Rachwalik, M.; Kustrzycki, W.; Kübler, A. Unchanged plasma levels of the soluble urokinase plasminogen activator receptor in elective coronary artery bypass graft surgery patients and cardiopulmonary bypass use. *PLoS ONE* **2014**, *9*, e98923. [CrossRef]
12. Li, Q.; Zheng, S.; Zhou, P.Y.; Xiao, Z.; Wang, R.; Li, J. The diagnostic accuracy of procalcitonin in infectious patients after cardiac surgery: A systematic review and meta-analysis. *J. Cardiovasc. Med.* **2020**. [CrossRef]
13. Brocca, A.; Virzì, G.M.; de Cal, M.; Giavarina, D.; Carta, M.; Ronco, C. Elevated Levels of Procalcitonin and Interleukin-6 are Linked with Postoperative Complications in Cardiac Surgery. *Scand. J. Surg.* **2017**, *106*, 318–324. [CrossRef]
14. Clementi, A.; Virzì, G.M.; Muciño-Bermejo, M.J.; Nalesso, F.; Giavarina, D.; Carta, M.; Brocca, A.; de Cal, M.; Danesi, T.H.; Zanella, M.; et al. Presepsin and Procalcitonin Levels as Markers of Adverse Postoperative Complications and Mortality in Cardiac Surgery Patients. *Blood Purif.* **2019**, *47*, 140–148. [CrossRef]
15. Clementi, A.; Brocca, A.; Virzì, G.M.; De Cal, M.; Giavarina, D.; Carta, M.; Muciño-Bermejo, M.-J.; Danesi, T.H.; Salvador, L.; Ronco, C. Procalcitonin and Interleukin-6 Levels: Are They Useful Biomarkers in Cardiac Surgery Patients? *Blood Purif.* **2017**, *43*, 290–297. [CrossRef]
16. Partridge, J.S.L.; Harari, D.; Martin, F.C.; Dhesi, J.K. The impact of pre-operative comprehensive geriatric assessment on postoperative outcomes in older patients undergoing scheduled surgery: A systematic review. *Anaesthesia* **2014**, *69*, 8–16. [CrossRef]
17. Katz, S. Assessing self-maintenance: Activities of daily living, mobility, and instrumental activities ofdaily living. *J. Am. Geriatr. Soc.* **1983**, *31*, 721–727. [CrossRef]
18. Vittengl, J.R.; White, C.N.; McGovern, R.J.; Morton, B.J. Comparative validity of seven scoring systems for the instrumental activities of daily living scale in rural elders. *Aging Ment. Health* **2006**, *10*, 40–47. [CrossRef]
19. Foley, T.; McKinlay, A.; Warren, N.; Stolwyk, R.J. Assessing the sensitivity and specificity of cognitive screening measures for people with Parkinson's disease. *NeuroRehabilitation* **2019**, *43*, 491–500. [CrossRef]

20. Wancata, J.; Alexandrowicz, R.; Marquart, B.; Weiss, M.; Friedrich, F. The criterion validity of the geriatric depression scale: A systematic review. *Acta Psychiatr. Scand.* **2006**, *114*, 398–410. [CrossRef]
21. WHO. *Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Vitamin and Mineral Nutrition Information System*; World Health Organization: Geneva, Switzerland, 2011; pp. 1–6. Available online: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Haemoglobin+concentrations+for+the+diagnosis+of+anaemia+and+assessment+of+severity#1 (accessed on 26 November 2020).
22. Kellum, J.A.; Lameire, N.; Aspelin, P.; Barsoum, R.S.; Burdmann, E.A.; Goldstein, S.L.; Herzog, C.A.; Joannidis, M.; Kribben, A.; Levey, A.S.; et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int. Suppl.* **2012**, *2*, 1–138.
23. Chanques, G.; Ely, E.W.; Garnier, O.; Perrigault, F.; Eloi, A.; Carr, J.; Rowan, C.M.; Prades, A.; de Jong, A.; Moritz-Gasser, S.; et al. The 2014 updated version of the Confusion Assessment Method for the Intensive Care Unit compared to the 5th version of the Diagnostic and Statistical Manual of Mental Disorders and other current methods used by intensivists. *Ann. Intensive Care.* **2018**, *8*, 33. [CrossRef] [PubMed]
24. Keranov, S.; Kim, W.K.; Arsalan, M.; Renker, M.; Keller, T.; Bauer, T.; Dörr, O.; Nef, H.M.; Gaede, L.; Möllmann, H.; et al. Predictive value of preprocedural procalcitonin for short- and long-term mortality after transfemoral transcatheter aortic valve implantation. *Heart Vessels* **2019**, *34*, 1993–2001. [CrossRef] [PubMed]
25. Cereghetti, C.; Siegemund, M.; Schaedelin, S.; Fassl, J.; Seeberger, M.D.; Eckstein, F.S.; Steiner, L.A.; Goettel, N. Independent Predictors of the Duration and Overall Burden of Postoperative Delirium After Cardiac Surgery in Adults: An Observational Cohort Study. *J. Cardiothorac. Vasc. Anesth.* **2017**, *31*, 1966–1973. [CrossRef]
26. Eshmawey, M.; Arlt, S.; Ledschbor-Frahnert, C.; Guenther, U.; Popp, J. Preoperative Depression and Plasma Cortisol Levels as Predictors of Delirium after Cardiac Surgery. *Dement Geriatr. Cogn. Disord.* **2020**, *48*, 207–214. [CrossRef]
27. Oldham, M.A.; Hawkins, K.; Lin, I.; Deng, Y.; Hao, Q.; Scoutt, L.M.; Yuh, D.D.; Lee, H.B. Depression predicts delirium after coronary artery bypass graft surgery independent of cognitive impairment and cerebrovascular disease: An analysis of the NOAHS study. *HHS Public Access.* **2020**, *27*, 476–486.
28. Scheel-Hincke, L.L.; Möller, S.; Lindahl-Jacobsen, R.; Jeune, B.; Ahrenfeldt, L.J. Cross-national comparison of sex differences in ADL and IADL in Europe: Findings from SHARE. *Eur. J. Ageing* **2020**, *17*, 69–79. [CrossRef]
29. Bleijenberg, N.; Zuithoff, N.P.A.; Smith, A.K.; de Wit, N.J.; Schuurmans, M.J. Disability in the individual ADL, IADL, and mobility among older adults: A prospective cohort study. *J. Nutr. Health Aging* **2017**, *21*, 897–903. [CrossRef]
30. Sponholz, C.; Sakr, Y.; Reinhart, K.; Brunkhorst, F. Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: A systematic review of the literature. *Crit. Care* **2006**, *10*, R145. [CrossRef]
31. Cascella, M.; Muzio, M.R.; Bimonte, S.; Cuomo, A.; Jakobsson, J.G. Postoperative delirium and postoperative cognitive dysfunction: Updates in pathophysiology, potential translational approaches to clinical practice and further research perspectives. *Minerva Anestesiol.* **2018**, *84*, 246–260.
32. Klingele, M.; Bomberg, H.; Schuster, S.; Schäfers, H.J.; Groesdonk, H.V. Prognostic value of procalcitonin in patients after elective cardiac surgery: A prospective cohort study. *Ann. Intensive Care* **2016**, *6*, 116. [CrossRef] [PubMed]
33. McGrane, S.; Girard, T.D.; Thompson, J.L.; Shintani, A.K.; Woodworth, A.; Ely, E.W.; Pandharipande, P.P. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. *Crit. Care* **2011**, *15*, R78. Available online: http://ccforum.com/content/15/2/R78 (accessed on 26 November 2020). [CrossRef] [PubMed]
34. Nemeth, E.; Vig, K.; Racz, K.; Koritsanszky, K.B.; Ronkay, K.I.; Hamvas, F.P.; Borbély, C.; Eory, A.; Merkely, B.; Gal, J. Influence of the postoperative inflammatory response on cognitive decline in elderly patients undergoing on-pump cardiac surgery: A controlled, prospective observational study. *BMC Anesthesiol.* **2017**, *17*, 113. [CrossRef] [PubMed]

35. Guenther, U.; Theuerkauf, N.; Frommann, I.; Brimmers, K.; Malik, R.; Stori, S.; Scheidemann, M.; Putensen, C.; Popp, J. Predisposing and precipitating factors of delirium after cardiac surgery: A prospective observational cohort study. *Ann. Surg.* **2013**, *257*, 1160–1167. [CrossRef]
36. Fowler, A.J.; Ahmad, T.; Abbott, T.E.F.; Torrance, H.D.; Wouters, P.F.; De Hert, S.; Lobo, S.M.; Rasmussen, L.S.; della Rocca, G.; Beattie, W.S.; et al. Association of preoperative anaemia with postoperative morbidity and mortality: An observational cohort study in low-, middle-, and high-income countries. *Br. J. Anaesth.* **2018**, *121*, 1227–1235. [CrossRef]
37. Kunz, J.V.; Spies, C.D.; Bichmann, A.; Sieg, M.; Mueller, A. Postoperative anaemia might be a risk factor for postoperative delirium and prolonged hospital stay: A secondary analysis of a prospective cohort study. *PLoS ONE* **2020**, *15*, e0229325. [CrossRef]
38. Gosselt, A.N.C.; Slooter, A.J.C.; Boere, P.R.Q.; Zaal, I.J. Risk factors for delirium after on-pump cardiac surgery: A systematic review. *Crit. Care* **2015**, *19*, 1–8. [CrossRef]
39. Smulter, N.; Engström, K.G.; Appelblad, M.; Gustafson, Y.; Lingehall, H.C.; Svenmarker, S.; Svenmarker, S. Disturbances in Oxygen Balance During Cardiopulmonary Bypass: A Risk Factor for Postoperative Delirium. *J. Cardiothorac. Vasc. Anesth.* **2017**, *32*, 684–690. [CrossRef]

Research Paper

Intra-operative hyperoxia and the risk of delirium in elderly patients after cardiac surgery

Anna Kupiec[1], Barbara Adamik[1], Katarzyna Forkasiewicz-Gardynik[1], Waldemar Goździk[1]

[1]Department of Anesthesiology and Intensive Therapy, Wroclaw Medical University, Wroclaw 50-556, Poland

Correspondence to: Anna Kupiec; **email:** anna.kupiec@umed.wroc.pl
Keywords: hyperoxia, elderly, delirium, cardiac surgery, cardiopulmonary bypass
Received: October 10, 2019 **Accepted:** March 29, 2020 **Published:** April 19, 2020

ABSTRACT

Delirium is a common complication after cardiac surgery. The aim of our study was to determine the impact of hyperoxia episodes occurring during cardiopulmonary bypass (CBP) on the rate of delirium episodes in the postoperative period. 93 patients, aged ≥ 65, who underwent elective cardiac surgery (CBP <90 minutes) were enrolled. The occurrence of delirium episodes was examined every 12 hours for three days after surgery. Eleven patients (11.8%) developed postoperative delirium (POD (+)) and 83 did not (POD (-)). More incidences of severe hyperoxia (PaO2 ≥ 26.6kPa) during CBP were observed in the POD (+) group: 64% had ≥ 2 episodes of hyperoxia, 27% ≥ 3, and 18% ≥ 4, while in the POD (-) group: 42%, 13% and 1%, respectively (P=0.02). Patients in the POD (+) group had a higher maximum PaO_2 during CBP than the POD (-) group (37 ± 5.8 vs 31.6 ± 6.6 kPa; P=0.01) and a higher mean PaO_2 (30.1 ± 4.5 vs 26.1 ± 5.6 kPa; P=0.01). The optimal maximum PaO_2 cut-off point for the occurrence of delirium was 33.2 kPa (AUC 0.72, P=0.001, sensitivity 75%, specificity 38%). We conclude that CBP hyperoxia episodes may be a risk factor associated with the occurrence of postoperative delirium.

INTRODUCTION

Delirium is one of the most common complications after cardiac surgery. The incidence rates range from 11% up to 52% [1]. The presence of delirium after cardiac surgery is associated with a higher mortality rate, increased length of Intensive Unit (ICU) stay [2], higher hospitalization costs [3] and a risk of readmission [4]. Furthermore, the occurrence of delirium during the postoperative period correlates with the development of long-term consequences after surgery such as cognitive decline and functional impairment, which in turn results in the deterioration of the patient's quality of life [5].

The etiology of delirium is multifactorial and it is always a combination of predisposing and precipitating risk factors [6]. Several pathophysiological mechanisms that contribute to the development of postoperative delirium have been presented, such as inflammation, disturbances in cerebral autoregulation, aortic plaque disruption, microemboli, Alzheimer-like cerebral pathology, and the neurotoxicity of anesthetics [7].

The role of low oxygen concentration in the development of delirium has been previously described. Severe hypoxia during CPB is one of the risk factors for postoperative delirium [8] and intraoperative cerebral oxygen desaturation and disturbances in the oxygen supply-demand balance may contribute to acute brain failure [7, 9]. One of the main tasks for the anesthesiologist during cardiac surgery is to prevent cellular hypoxia and high concentrations of oxygen are often administered. As a consequence, hyperoxia episodes may occur that are as dangerous to the patient as the occurrence of hypoxia. Increasing amounts of data are demonstrating worse clinical outcomes related to hyperoxia. The presence of hyperoxia episodes were reported in over 43% of emergency department patients [10], 36% of patients after cardiac arrest [11] and up to 70% of patients hospitalized in the ICU [12].The role of hyperoxia as a risk factor for the development of delirium in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) has not yet been determined. The aim of this study was to determine the impact of hyperoxia episodes occurring during CBP on the incidence of delirium in the immediate postoperative period.

RESULTS

The characteristics of the study population are shown in Table 1. Out of 93 patients included in the study, 11 (11.8%) developed postoperative delirium (group POD (+)) and 82 did not (group POD (-)). There were no significant differences between groups in age, gender, or in factors related to the patient's clinical condition assessed with the Euroscore II and Charlson Comorbidity Index. There was no statistical difference between the study groups in the incidence of comorbidities such as recent myocardial infarction, lung disease, peripheral vascular disease, history of atrial fibrillation, diabetes mellitus or cerebral vascular disease (Table 1). There were no significant differences in the incidence of postoperative complications such as bleeding, need for re-thoracotomy, need for red blood cell transfusions, or acute kidney injury. 2 patients (18%) in the POD (+) group and 5 patients (6%) in the POD (-) group received milrinone infusion (P=0.15). No one needed adrenaline infusion and noradrenaline infusion was given to 6 patients (54.5%) in the POD (+) group and 40 patients (48.7%) in the POD (–) group (P=0.71). The highest dose of noradrenaline was similar in both groups (P=0.65) (Table 2).
The mean ICU length of stay was 3 days in both groups. There were no significant differences between groups in factors related to the operation such as CBP time, aortic cross clamping time, and mean hemoglobin level and cardiac index during CBP (Table 2). There was no significant difference between groups in blood loss or red blood cell transfusions and detailed information is provided in Table 2. No patient was given steroids perioperatively. After terminating sedation all patients were extubated on the day of surgery and the mean mechanical ventilation time was 292 minutes in group POD (+) and 231 minutes in the POD (-) group (n.s.). The hospital survival rate was 100% in both groups.

Hyperoxia and delirium incidences

The Confusion Assessment Method for the Intensive Care Unit (CAM ICU) conducted before surgery indicated that delirium was absent in all patients included in the study. 81% of all delirium episodes occurred on the first postoperative day, 18% on the second, and 18% on the third day. The cumulativenumber of delirium episodes was greater than 100% because some patients had delirium episodes diagnosed more than once during the study period.

Arterial blood gases were controlled every 20-30 minutes during CBP and a total of 256 of samples were analyzed. Severe hyperoxia defined as the highest $PaO_2 \geq 26.6$ kPa was recorded in 100% (11/11) of patients in the POD (+) group and in 78% (64/82) of patients in the POD (-) group. Mild hyperoxia defined as a PaO_2 between 16 and 26.5 kPa was not observed in any patient in the POD (+) group but it was present in 21.9% (18/82) of the patients in the POD (-) group. During CBP, the incidence rate of severe hyperoxia was significantly higher in the POD (+) group than in the POD (-) group. The median number of episodes of severe hyperoxia was 2 (IQR 1-3) in the POD (+) group and 1 (IQR 1-2) in the POD (-) group. (P=0.02, Figure 1).

The value of the maximum PaO2 during CBP was significantly higher in the POD (+) group than in the POD (-) group (37 kPa vs 31.6 kPa; P=0.01). Similarly, the value of the mean PaO2 during CBP was significantly higher in the POD (+) group than in the POD (-) group (30.1 kPa vs. 26.1 kPa; P=0.01) (Table 3). There was no difference in the minimum PaO2 between groups (24.1 kPa vs. 21.2 kPa; P=0.06). Using the ROC curve, it can be concluded that the optimal maximum PaO2 cut-off point for the occurrence of delirium in the postoperative period was 33.2 kPa with an area under the curve 0.72 (P=0.001, sensitivity of 75%, specificity of 38%). Postoperative delirium was not associated with longer mechanical ventilation (292 min vs. 231 min, respectively, in the POD (+) and POD (-) group, P=0.31) or longer hospitalization after operation (10 vs. 9.8 days, respectively, in the POD (+) and POD (-) group, P=0.1).

DISCUSSION

The study showed that despite the short time of CPB and without complications during surgery and during the ICU stay, up to 11.8% of patients experienced delirium in the period immediately after the surgery.

In the group of patients with delirium, the incidence rate of severe hyperoxia during CPB was significantly higher than in patients with an uneventful postoperative course. Thus, CBP hyperoxia episodes may be a risk factor associated with the occurrence of postoperative delirium.

Table 1. Demographic characteristics of the study population.

	POD (+) N=11 (11.8%)	POD (-) N=82 (88.2%)	p
Gender, male [N, (%)]	6 (54.5%)	57 (69.5%)	.33
Age [years]	74 ± 6 (65 - 87)	71 ± 5 (65 - 83)	.13
BMI [kg/m²]	28 ± 3.2 (22.5 - 33.6)	28.5 ± 4.4 (20.8 - 38.2)	.87
BSA [m²]	1.86 ± 0.19 (1.54 - 2.23)	1.92 ± 0.19 (1.53 - 2.37)	.38
Euroscore II [%]	6.0 ± 9.6 (0.8 - 33.1)	2.4 ± 2 (0.5 - 9.4)	.38
Charlson Comorbidity Index	5.7 ± 2 (3 - 10)	4.7 ± 2 (2 - 10)	.15
CCS IV [N, (%)]	1 (9)	2 (2.4)	.24
NYHA III/ IV [N, (%)]	4 (36.3)	13 (15.8)	.09
Comorbidities [N, (%)]			
Recent myocardial infarction	3 (27.7)	19 (23.2)	.76
Lung disease	0 (0)	4 (4.9)	-
Peripheral vascular disease	1 (9)	10 (12.2)	.76
History of atrial fibrillation	2 (18.1)	11 (13.4)	.66
Diabetes mellitus	6 (54.5)	31 (37.8)	.28
Cerebrovascular disease	3 (27.2)	10 (12.2)	.17
Chronic kidney disease	3 (27.2)	16 (19.5)	.54
Ejection fraction [%]	54 ± 12 (25-65)	57 ± 8 (30-68)	.80
Mechanical ventilation time [min]	292 ± 177 (90 - 690)	231 ± 94 (95 - 555)	.31
ICU length of stay [days]	3 ± 1.6 (2 - 7)	3 ± 1.6 (2 - 9)	.68
Length of hospitalization [days]	10 ± 1.6 (8 - 13)	9.8 ± 2.7 (7 - 24)	.10

POD: Postoperative delirium; BMI: Body Mass Index; BSA: Body Surface Area; ICU: Intensive Care Unit; CCS: Canadian Cardiovascular Society Angina Grading Scale; NYHA: New York Heart Association Functional Classification; Data are presented as mean ± SD (minimum - maximum) or percentage.

Data on the negative consequences of hyperoxia are becoming more widely known. The results of previously published studies indicate that in a wide range of medical conditions such as myocardial injury, cardiac arrest, stroke, and respiratory failure requiring mechanical ventilation, hyperoxia is associated with increased morbidity and hospital mortality [11, 13, 14]. In our study, the occurrence of hyperoxia during surgery did not change mortality, and the survival rate in the hospital was 100%. However, this study group was a low risk population; all patients could be extubated on the day of surgery, without the need for a prolonged ICU stay.
The influence of hyperoxia on brain activity has been the subject of preclinical and clinical studies; however, the results of these studies are often contradictory. The results of preclinical studies indicate that prolonged hyperoxia induces a disturbance in the balance between the production of reactive oxygen species (ROS) and antioxidant defense [15, 16]. As a consequence, neuron apoptosis and cerebral tissue ROS increase, leading to persistent cerebral damage. In a clinical study investigating the effect of hyperoxia in patients with severe traumatic brain injury, a PaO_2 above 19.9 kPa was shown to contribute to an increase in the glutamate level in brain tissue, suggesting secondary brain damage [17]. These results were not confirmed in a recently published retrospective analysis of over 24,000 patients after traumatic brain injury; hyperoxia > 39.8 kPa during the first 24 hours in the ICU, although present in 13% of patients, was not associated with a worse outcome [18]. In another study, Rincon et al. demonstrated the detrimental effect of hyperoxia in ventilated ICU patients after stroke; a PaO_2 above 39.9 kPa was associated with higher in-hospital mortality and hyperoxia was even more harmful than hypoxia below 7.9 kPa [19]. These data underline the need for studies of controlled oxygenation in ventilated ICU patients.
To date, the impact of hyperoxia on the brain activity of patients undergoing cardiac surgery with CPB has been the subject of very few studies and this problem

Table 2. Surgical parameters.

	POD (+) N=11	POD (-) N=82	p
CBP time [min]	71.6 ± 12.3 (48 - 89)	70 ± 12.4 (37 - 90)	.75
AoX time [min]	39.4 ± 13.6 (20 - 68)	39.1 ± 11.7 (19 - 69)	.98
Cardiac Index on CBP [L/min/m2]	2.5 ± 0.3 (2.0 - 3.0)	2.5 ± 0.1 (2.1 - 2.9)	.69
Mean Hb level on CBP [g/dl]	9.3 ± 1.8 (7.2 - 12.8)	9.4 ± 1.0 (7.4 - 11.6)	.48
Type of surgery [N, (%)]			.52
Isolated CABG	9 (81.8)	67 (81.7)	
Isolated valve surgery	1 (9.0)	13 (15.8)	
Combined procedure	1 (9.0)	2 (2.4)	
Perioperative vasopressors [N, (%)]	6 (54.5)	40 (48.7)	.71
Noradrenaline, highest [µg/kg/min]	0.05 ± 0.08 (0 - 0.22)	0.03 ± 0.04 (0 – 0.18)	.65
Milrinone infusion [N, (%)]	2 (18)	5 (6)	.15
Perioperative RBC transfusion [ml]	305 ± 292 (0 – 840)	198 ± 347 (0 – 1960)	.15
Postoperative blood loss [ml]	365 ± 177 (200 – 750)	414 ±182 (150 – 1050)	.27
Acute kidney injury [N, (%)]	1 (9.0)	7 (8.5)	.95
Lactate [mmol/L]	1.02 ± 0.29 (0.75 – 1.8)	1.02 ± 0.35 (0.4 – 2.46)	.99
pH	7.36 ± 0.04 (7.3 – 7.41)	7.37 ± 0.04 (7.23 – 7.46)	.92
Electrolyte balance [mmol/L]			
Na^+	138.4 ± 5.2 (125.2 – 145.6)	139.2 ± 2.1 (135.6 – 150.3)	.92
K^+	5.1 ± 0.4 (4.5 – 5.8)	5.1 ± 0.4 (3.9 – 6.3)	.33
Ca^{2+}	1.18 ± 0.08 (1.06 – 1.38)	1.17 ± 0.05 (1.06 – 1.36)	.77
Re-thoracotomy [N, (%)]	0	2 (2,5)	-

POD: Postoperative delirium; CBP: Cardiopulmonary Bypass; AoX time: aorta cross-clamp time; Hb: hemoglobin; RBC: Red Blood Cells; CABG: coronary artery bypass graft, Combined procedure: valve surgery + coronary artery bypass graft; Data are presented as mean ± SD (minimum - maximum) or percentage.

requires thorough analysis. The results of our study indicate a direct relationship between the high intraoperative PaO_2 level and the occurrence of delirium in the immediate postoperative period in elderly patients. During CBP, severe arterial hyperoxia ($PaO_2 \geq 26.6$ kPa) was recorded in all patients who postoperatively developed delirium, and the incidence rate of severe hyperoxia recorded during CPB was significantly higher in patients with delirium than in those with an uneventful postoperative course.

In a study by Lopez et al., cerebral oxygenation was measured with oximetry monitors in cardiac surgery patients. The results indicated that prolonged cerebral hyperoxia during CBP was responsible for the occurrence of delirium following surgery in 30% of patients. What is more, the risk of developing delirium significantly increased when an episode of hypoxia was followed by prolonged hyperoxia [20]. In a recently published study by Thudium et al. a relationship was found between cerebral hyperperfusion and post cardiac surgery delirium. In the study the authors examined right middle cerebral artery blood flow during CBP using the transcranial Doppler [21]. In our study we did not plan to measure cerebral blood flow, but the cardiac index during CBP was similar in both groups, with and without postoperative delirium (mean CI=2,5 $l/min/m^2$, P=0.69).

Although data on the negative effects of hyperoxia are increasing, toxic oxygen levels can still be found in the operating room. The safety of maintaining near- physiological levels of oxygenation during CPB was confirmed in a randomized clinical trial. It was demonstrated that the procedure of using an almost physiological level of oxygenation during CPB did not increase the level of lactate and troponin after surgery and did not increase the frequency of hypoxic episodes [22]. Delirium is always a result of many factors the majority of which are unpreventable. One important risk factor is prolonged CBP time. A detailed analysis of 1863 cardiac surgery procedures indicated that CPB time ≥90 minutes was considered to be prolonged and was associated with a longer hospital stay and a higher mortality rate [26]. In another study CPB ≥90 was associated with an increased release of the biomarkers of ischemia/reperfusion intestinal damage and endotoxemia [27]. Since we have no influence on CBP duration, careful attention to even the smallest details during surgery that may potentially have an impact on the postoperative course, are therefore, very important. Control and prevention of perioperative hyperoxia can be one such task. In our study, samples of blood-gases were controlled every 20-
30 minutes and gas flow settings were corrected accordingly. The implementation of real-time PaO_2 measuring devices can help reduce both hypoxia and hyperoxia episodes.

We are aware of our study limitations. The study was deliberately limited to elderly patients, a population at higher risk of postoperative delirium. We did not plan to analyze the long-term consequences of hyperoxia during CPB on brain injury. However, in a recently published retrospective analysis of 1018 patients undergoing cardiac surgery with CPB no association was found between hyperoxia >26.6 kPa or >39.9 kPa during surgery and neurocognitive dysfunction 6 weeks after surgery [23].Additional research conducted on a larger population, with the assessment of cerebral oximetry and cerebral blood flow, and an examination of the immediate and long-term consequences of hyperoxia, will shed light on the question of the effects of hyperoxia on brain function after cardiac surgery. Future research in this area is needed and should also include the impact of hyperoxia on brain damage and the release of brain- specific biomarkers. Changes in biomarkers in patients experiencing hyperoxia episodes could be associated with cognitive decline and delirium after surgery.
Considering the lack of statistically significant differences between groups in the values of the other parameters studied in the perioperative period, it can be assumed with high probability that intraoperative hyperoxia may be the cause of postoperative delirium.

Delirium is always a result of many factors. As we have no influence on many of them, preventing delirium is always a difficult task. Since hyperoxia during CBP is an important risk factor for developing postoperative delirium, avoiding hyperoxia above 26.6 kPa during CBP, along with avoiding large variations in oxygen tension, seems an easy and safe measure to lower the risk of this complication.

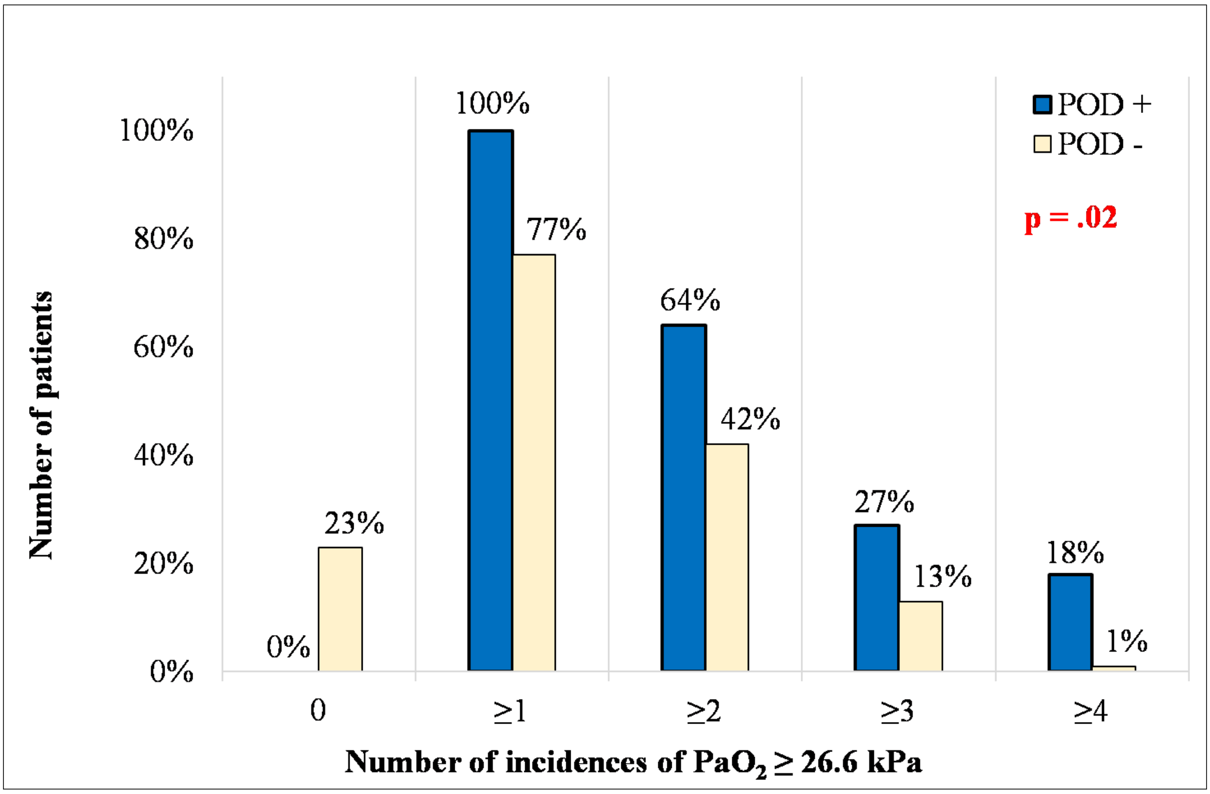

Figure 1. Number of incidences of $PaO_2 \geq 26.6$ kPa in the studied groups. The given p value represents the difference in the frequency of hyperoxia incidences for all data in figure 1. POD: postoperative delirium; PaO_2: Partial pressure of oxygen.

Table 3. Results of data analysis.

	POD (+)	POD (-)	p
	N=11	N=82	
Mild hyperoxia (PaO_2 16-26.5 kPa) [N (%)]	0/11 (0.0)	18/82 (21.9)	.18
Severe hyperoxia (PaO_2 ≥26.6 kPa) [N (%)]	11/11 (100.0)	64/82 (78.1)	.18
PaO_2 max [kPa]	37 ± 5.8 (29.8 - 45)	31.6 ± 6.6 (19.8 – 52.6)	.01
PaO_2 mean [kPa]	30.1 ± 4.5 (24.2 – 37.7)	26.1 ± 5.6 (15.3 – 41.6)	.01
PaO_2 min [kPa]	24.1 ± 4.5 (18.2 – 33.8)	21.2 ± 5.9 (9.9 – 39.1)	.06

POD: Postoperative delirium; PaO_2 max: maximum value of partial pressure of oxygen within CBP; PaO_2 mean: mean value of partial pressure of oxygen within CBP; PaO_2 min: minimal value of partial pressure of oxygen within CBP; CBP: Cardiopulmonary Bypass; Data are presented as mean ± SD (minimum; maximum).

MATERIALS AND METHODS

This retrospective study was conducted at the 6-bed cardiosurgical ICU at the Department of Anesthesiology and Intensive Therapy, Wroclaw Medical University in Poland between December 2016 and March 2018. The Bioethics Committee of Wroclaw Medical University approved the study (permission no. 219/2016). Inclusion criteria were: age ≥ 65 years and elective on- pump cardiac surgery. Exclusion criteria were: CBP time ≥ 90 minutes, emergency procedure, a different type of anesthesia (TIVA, total intravenous anesthesia), or refusal to provide written informed consent.

Delirium assessment

Each patient was examined for delirium before surgery (baseline) and then every 12 hours for three consecutive days, starting in the morning on the first day after surgery. The Confusion Assessment Method for the Intensive Care Unit (CAM ICU) was used for to identify the presence or absence of delirium. CAM ICU is a validated and commonly used score to assess delirium in ICU patients. With CAM ICU four features of delirium are assessed: 1) acute onset and a fluctuating course, 2) inattention, 3) disorganized thinking, and 4) an altered level of consciousness. To diagnose delirium, feature 1, 2, and either 3 or 4 should be recognized as positive. As a part of CAM ICU evaluation, the Richmond Agitation-Sedation Scale is used to assess altered levels of consciousness and fluctuations of mental status [24]. The score is recommended as a screening tool for postoperative delirium by the European Society of Anesthesiology [25]. All physicians involved in the study were trained on how to perform the CAM ICU delirium screening.

Every episode of hyperoxia that occurred during CPB was recorded; mild hyperoxia was defined as a value of the PaO_2 between 16 and 26.5 kPa and severe hyperoxia as $PaO_2 \geq 26.6$ kPa. These cut-offs of hyperoxia are based on the results from previous studies [13]. Delirium is always a result of a combination of patient- related and operation-related factors. One important risk factor is prolonged CBP time. Detailed analysis of 1863 cardiac surgery procedures indicated that CPB time ≥90 minutes was considered to be prolonged and was associated with a longer hospital stay and a higher mortality rate [26]. In another study CPB ≥90 minutes was associated with an increased release of the biomarkers of ischemia-reperfusion intestinal damage and endotoxemia [27]. Therefore, to eliminate the impact of this factor and to gain better homogeneity of the sample group, we excluded patients with CBP time
≥ 90 minutes.

Surgery

The induction of general anesthesia was achieved using sufentanil, propofol and rocuronium. During surgery the anesthesia was maintained using sevoflurane and a continuous infusion of sufentanil and rocuronium. Sevoflurane MAC was kept between 0.7 and 1.0. As a routine procedure, an open bypass circuit composed of uncoated polyvinylchloride tubing, a hard-shell venous reservoir, a hollow fiber membrane oxygenator (Medtronic Affinity, Medtronic, Inc. Minneapolis USA) with an integrated polyester arterial line filter of 40 µm pore size, and a roller pump with a nonpulsatile flow 2.4–2.5 $l/min/m^2$ (Stockert S3, Sorin Group, Germany) was used in all patients. Anticoagulation was attained by administering 300 IU/kg of heparin to achieve an activated clotting time longer than 480 seconds. Perfusion pressure was kept at 60 to 80mmHg. After aortic cross-clamping, cold blood cardioplegia Del Nido was used. Normothermia (37° C) was maintained during the entire procedure. Partial pressure of carbon dioxide ($PaCO_2$) was kept in a normal range between 4.6 – 5.9 kPa. During CBP, sevoflurane was administered to the extracorporeal circuit. Blood gas samples were taken by the perfusionist from the arterial line of the oxygenator every 20-30 minutes during CBP. According to our routine procedure, while on CBP, after every blood-gas result, gas flow settings were corrected on a regular basis: if the blood-gas result indicated a PaO_2 below 20 kPa, the oxygen concentration was increased. Fresh gas flow was changed according to the $PaCO_2$ blood gas result to keep the $PaCO_2$ value within a normal range 4.6 – 5.9 kPa.

According to our routine procedure, mean arterial pressure (MAP) was measured continuously through an arterial catheter inserted to a radial or femoral artery. The lowest acceptable MAP was 65 mmHg. In the case of hypotension, patients were given a noradrenaline infusion.

Each patient was transferred to the ICU immediately after surgery. Sedation with propofol 0.5 - 1.0 mg/kg/h was continued until the patient was able to be weaned from the ventilator and extubated. Postoperative pain management was controlled using Paracetamol 1 g every 6 hours and Oxycodon 3-4 mg every 4 hours. Patients were extubated if they were hemodynamically stable with only a small amount of inotropic agents or catecholamines and with sufficient oxygenation.

Statistical analysis

Data are expressed as mean values ± SD (minimum - maximum) or a number and percentage. The distribution of the variables was not normal based on a Shapiro–Wilk test. Therefore, statistical analysis of the data was performed using nonparametric tests. For continuous variables the Mann-Whitney U test was used to compare differences in maximal, minimal and mean PaO_2 during CPB between two independent groups. Categorical variables were analyzed using a Yates's chi-squared test. Receiver operating characteristics were analyzed to find the optimal maximum PaO_2 cut- off point for the occurrence of delirium in the postoperative period and these results are presented as the area under the curve (AUC), standard error, and 95% confidence interval. The Mann–Whitney U test was used to compare differences between 2 independent groups. All statistical measurements were carried out with *Statistica* 13.1 (StatSoft Inc., Tulsa, USA). Statistical significance was determined as a P value less than < 0.05.

ACKNOWLEDGMENTS

The authors wish to thank Lukasz Stróżecki, MSc, for performing statistical analysis of the data.

CONFLICTS OF INTEREST

The authors declare no actual or potential conflicts of interest.

FUNDING

The authors acknowledge funding support from Wroclaw Medical University, Poland (grant No. ST.A170.18.024).

REFERENCES

1. Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. J Card Surg. 2012; 27:481–92. https://doi.org/10.1111/j.1540-8191.2012.01472.x PMID:22784203
2. Bakker RC, Osse RJ, Tulen JH, Kappetein AP, Bogers AJ. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. Eur J Cardiothorac Surg. 2012; 41:544–49. https://doi.org/10.1093/ejcts/ezr031 PMID:22345177
3. Brown CH 4th, Laflam A, Max L, Lymar D, Neufeld KJ, Tian J, Shah AS, Whitman GJ, Hogue CW. The impact of delirium after cardiac surgical procedures on postoperative resource use. Ann Thorac Surg. 2016; 101:1663–69. https://doi.org/10.1016/j.athoracsur.2015.12.074 PMID:27041454
4. Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Consequences of delirium after cardiac operations. Ann Thorac Surg. 2012; 93:705–11. https://doi.org/10.1016/j.athoracsur.2011.07.006 PMID:21992939
5. Sauër AC, Veldhuijzen DS, Ottens TH, Slooter AJ, Kalkman CJ, van Dijk D. Association between delirium and cognitive change after cardiac surgery. Br J Anaesth. 2017; 119:308–15. https://doi.org/10.1093/bja/aex053 PMID:28854542
6. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA. 1996; 275:852–57. https://doi.org/10.1001/jama.1996.03530350034031 PMID:8596223Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF, Mathew JP. Neurocognitive function after cardiac surgery: from phenotypes to mechanisms. Anesthesiology. 2018; 129:829–51. https://doi.org/10.1097/ALN.0000000000002194 PMID:29621031
7. Liu Z, Pang X, Zhang X, Cao G, Fang C, Wu S. Incidence and risk factors of delirium in patients after type-A aortic dissection surgery. J Cardiothorac Vasc Anesth. 2017; 31:1996–99. https://doi.org/10.1053/j.jvca.2016.11.011 PMID:28109683
8. Smulter N, Lingehall HC, Gustafson Y, Olofsson B, Engström KG, Appelblad M, Svenmarker S. Disturbances in oxygen balance during cardiopulmonary bypass: a risk factor for postoperative delirium. J Cardiothorac Vasc Anesth. 2018; 32:684–90. https://doi.org/10.1053/j.jvca.2017.08.035 PMID:29153931
9. Page D, Ablordeppey E, Wessman BT, Mohr NM, Trzeciak S, Kollef MH, Roberts BW, Fuller BM.

Emergency department hyperoxia is associated with increased mortality in mechanically ventilated patients: a cohort study. Crit Care. 2018; 22:9. https://doi.org/10.1186/s13054-017-1926-4 PMID:29347982

10. Elmer J, Scutella M, Pullalarevu R, Wang B, Vaghasia N, Trzeciak S, Rosario-Rivera BL, Guyette FX, Rittenberger JC, Dezfulian C, and Pittsburgh Post-Cardiac Arrest Service (PCAS). The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database. Intensive Care Med. 2015; 41:49–57.
https://doi.org/10.1007/s00134-014-3555-6 PMID:25472570

11. Vincent JL, Taccone FS, He X. Harmful effects of hyperoxia in postcardiac arrest, sepsis, traumatic brain injury, or stroke: the importance of individualized oxygen therapy in critically ill patients. Can Respir J. 2017; 2017:2834956. https://doi.org/10.1155/2017/2834956 PMID:28246487

12. Helmerhorst HJ, Arts DL, Schultz MJ, van der Voort PH, Abu-Hanna A, de Jonge E, van Westerloo DJ. Metrics of arterial hyperoxia and associated outcomes in critical care. Crit Care Med. 2017; 45:187–95. https://doi.org/10.1097/CCM.0000000000002084 PMID:27763912

13. Kim TY, Kim DH, Kim SC, Kang C, Lee SH, Jeong JH, Lee SB, Park YJ, Lim D. Impact of early hyperoxia on 28-day in-hospital mortality in patients with myocardial injury. PLoS One. 2018; 13:e0201286. https://doi.org/10.1371/journal.pone.0201286 PMID:30086143

14. Terraneo L, Paroni R, Bianciardi P, Giallongo T, Carelli S, Gorio A, Samaja M. Brain adaptation to hypoxia and hyperoxia in mice. Redox Biol. 2017; 11:12–20. https://doi.org/10.1016/j.redox.2016.10.018 PMID:27835780

15. Doppenberg EM, Rice MR, Di X, Young HF, Woodward JJ, Bullock R. Increased free radical production due to subdural hematoma in the rat: effect of increased inspired oxygen fraction. J Neurotrauma. 1998; 15:337–47.
https://doi.org/10.1089/neu.1998.15.337 PMID:9605348

16. Quintard H, Patet C, Suys T, Marques-Vidal P, Oddo M. Normobaric hyperoxia is associated with increased cerebral excitotoxicity after severe traumatic brain injury. Neurocrit Care. 2015; 22:243–50. https://doi.org/10.1007/s12028-014-0062-0 PMID:25168744

17. Ó Briain D, Nickson C, Pilcher DV, Udy AA. Early hyperoxia in patients with traumatic brain injury admitted to intensive care in Australia and New Zealand: a retrospective multicenter cohort study. Neurocrit Care. 2018; 29:443–51. https://doi.org/10.1007/s12028-018-0553-5 PMID:29949002

18. Rincon F, Kang J, Maltenfort M, Vibbert M, Urtecho J, Athar MK, Jallo J, Pineda CC, Tzeng D, McBride W, Bell
R. Association between hyperoxia and mortality after stroke: a multicenter cohort study. Crit Care Med. 2014; 42:387–96. https://doi.org/10.1097/CCM.0b013e3182a27732 PMID:24164953

19. Lopez MG, Pandharipande P, Morse J, Shotwell MS, Milne GL, Pretorius M, Shaw AD, Roberts LJ 2nd, Billings FT 4th. Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. Free Radic Biol Med. 2017; 103:192–98. https://doi.org/10.1016/j.freeradbiomed.2016.12.039 PMID:28039082

20. Thudium M, Ellerkmann RK, Heinze I, Hilbert T. Relative cerebral hyperperfusion during cardiopulmonary bypass is associated with risk for postoperative delirium: a cross-sectional cohort study. BMC Anesthesiol. 2019; 19:35. https://doi.org/10.1186/s12871-019-0705-y PMID:30851736

21. Smit B, Smulders YM, de Waard MC, Boer C, Vonk AB, Veerhoek D, Kamminga S, de Grooth HJ, García-Vallejo JJ, Musters RJ, Girbes AR, Oudemans-van Straaten HM, Spoelstra-de Man AM. Moderate hyperoxic versus near-physiological oxygen targets during and after coronary artery bypass surgery: a randomised controlled trial. Crit Care. 2016; 20:55.
https://doi.org/10.1186/s13054-016-1240-6 PMID:26968380

22. Fontes MT, McDonagh DL, Phillips-Bute B, Welsby IJ, Podgoreanu MV, Fontes ML, Stafford-Smith M, Newman MF, Mathew JP, and Neurologic Outcome Research Group (NORG) of the Duke Heart Center. Arterial hyperoxia during cardiopulmonary bypass and postoperative cognitive dysfunction. J Cardiothorac Vasc Anesth. 2014; 28:462–66. https://doi.org/10.1053/j.jvca.2013.03.034 PMID:23972739

23. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM- ICU). JAMA. 2001; 286:2703–10. https://doi.org/10.1001/jama.286.21.2703 PMID:11730446

24. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, Cherubini A, Jones C, Kehlet H, MacLullich A, Radtke F, Riese F, Slooter AJ, et al. European Society of Anaesthesiology evidence-based and consensus- based guideline on postoperative delirium. Eur J Anaesthesiol. 2017; 34:192–214. https://doi.org/10.1097/EJA.0000000000000594 PMID:28187050

25. Chalmers J, Pullan M, Mediratta N, Poullis M. A need for speed? Bypass time and outcomes after isolated aortic valve replacement surgery. Interact Cardiovasc Thorac Surg. 2014; 19:21–26. https://doi.org/10.1093/icvts/ivu102 PMID:24722513

26. Adamik B, Kübler A, Gozdzik A, Gozdzik W. Prolonged cardiopulmonary bypass is a risk factor for intestinal ischaemic damage and endotoxaemia. Heart Lung Circ. 2017; 26:717–23. https://doi.org/10.1016/j.hlc.2016.10.012 PMID:27956161

4. OMÓWIENIE PUBLIKACJI STANOWIĄCYCH PRACĘ DOKTORSKĄ

Ad 1

Pierwsza z prezentowanych publikacji opisuje wpływ czynników ryzyka przed- i śródoperacyjnych na wystąpienie majaczenia, ze szczególnym uwzględnieniem roli prokalcytoniny (PCT).

Majaczenie pozostaje powikłaniem o niejasnej etiologii. Opisywano różne potencjalne zaburzenia homeostazy, które mogą prowadzić do rozwoju tego powikłania. Jednym nich jest hipoteza stanu zapalnego mózgowia. Według tej teorii za rozwój majaczenia odpowiedzialny jest powstający obwodowo uraz tkanek, w tym również uraz chirurgiczny, powodujący aktywację reakcji zapalnej. Uwalniane cytokiny prozapalne, przenikając barierę krew-mózg, prowadzą do aktywacji komórek mikrogleju. Dochodzi do rozwoju reakcji zapalnej w mózgu, dysfunkcji aktywności neuronów, zaburzeń w układzie neurotransmiterów, uszkodzenia przewodzenia synaptycznego oraz rozszczelnienia połączeń międzykomórkowych komórek bariery krew-mózg, (14) co objawia się u chorych wystąpieniem zaburzeń neuropoznawczych. Krążenie pozaustrojowe i sam uraz chirurgiczny są znanymi aktywatorami reakcji zapalnej. (17) W wyniku tego u chorych po operacjach kardiochirurgicznych obserwujemy wzrost parametrów zapalnych, w tym również prokalcytoniny (PCT). Podwyższone stężenia PCT często obserwuje się u pacjentów z komplikacjami po operacji, takimi jak niewydolność nerek, niewydolność oddechowa, a w konsekwencji z przedłużonym czasem hospitalizacji i wyższą śmiertelnością. (18, 19) Pojawiają się również doniesienia o zaletach oznaczania PCT przed planową operacją, co jest często stosowaną praktyką kliniczną. Nawet nieznacznie podniesione stężenia PCT wiązały się z większym ryzykiem zgonu u pacjentów poddanych przezskórnej implantacji zastawki aortalnej (TAVI). (20)

Ocena stężeń PCT jako predyktora wystąpienia majaczenia w populacji kardiochirurgicznej nie została do tej pory zbadana.

Celem prezentowanej pracy była analiza czynników ryzyka występowania majaczenia w grupie pacjentów hospitalizowanych w oddziale intensywnej terapii po operacjach kardiochirurgicznych z zastosowaniem CPB, ze szczególnym uwzględnieniem wartości predykcyjnej oznaczeń stężenia prokalcytoniny.

Do badania zakwalifikowano chorych powyżej 65 roku życia, którzy pomiędzy styczniem 2017 i grudniem 2018 przebyli planowy zabieg kardiochirurgiczny z zastosowaniem krążenia pozaustrojowego. Uzyskano zgodę Komisji Bioetycznej na przeprowadzenie badania (numer zgody 219/2016). Przed operacją u chorych przeprowadzona została ocena geriatryczna obejmująca skale: ADL (ang. *Activities of Daily Living* - Skala Oceny Podstawowych Czynności Życia Codziennego wg Katza), IADL (ang. *Instrumental Activities of Daily Living* - Skala Oceny Złożonych Czynności Życia Codziennego wg Lawtona), GDS-15 (ang. *Geriatric Depression Scale* – 15 – punktowa Geriatryczna Skala Oceny Depresji wg Yesavage'a) oraz MMSE (ang. *Mini Mental State Examination* - Krótka Ocena Stanu Psychicznego). Odnotowane zostały również choroby towarzyszące, parametry śródoperacyjne i powikłania pooperacyjne. Dodatkowo chorzy mieli zbadany poziom prokalcytoniny przed operacją, przy przyjęciu do OIT i przez trzy kolejne dni po operacji. Wystąpienie majaczenia ocenione zostało w skali CAM ICU (ang. *Confusion Assessment Method in Intensive Care Unit* – Metoda Oceny Splątania na Oddziale Intensywnej Terapii) co 12 godzin przez trzy dni, rozpoczynając od następnego dnia po operacji rano. Przy wykonywaniu badania w skali CAM ICU, należy również wykonać ocenę w Skali Pobudzenia i Sedacji Richmond (RASS, ang. *Richmond Agitation – Sedation Score*), a chorych uznaje się do zdolnych do oceny majaczenia, jeśli w skali RASS mają przynajmniej -3 punkty. Majaczenie zostało określone jako hipoaktywne, jeśli wartość RASS stwierdzona u chorych wynosiła pomiędzy -3 a 0, hiperaktywne, jeśli wartość RASS wynosiła więcej niż 0, a mieszane, jeśli obie formy przechodziły jedna w drugą.

Kryteria włączenia do badania spełniało 271 chorych. Z tej grupy świadomą zgodę uzyskano od 151 chorych, ale dwoje pacjentów wycofało w trakcie badania swoją zgodę. Do ostatecznej analizy włączono 149 chorych. Z tej grupy - 20% rozwinęło majaczenie w okresie pooperacyjnym (N = 30). Najczęściej - u 50% pacjentów (15/30) - rozpoznano formę hipoaktywną, u 33% formę hiperaktywną (10/30), a u 17% - mieszaną (5/30). W 23 przypadkach majaczenie trwało poniżej 12 godzin, w 4 przypadkach – pomiędzy 12 a 24 godzin, a u 3 chorych wystąpiło przedłużone majaczenie powyżej 24 godzin. Większość incydentów rozpoznano w pierwszej dobie po operacji.

Chorzy, którzy rozwinęli majaczenie byli starsi (mediana wieku 73,5, IQR 70 – 76 vs 69, IQR 67 – 74; p = 0,038), częściej występowała u nich przed operacją anemia (43% vs 19%; p = 0,006) oraz mieli wyższe ryzyko zgonu okołooperacyjnego w skali Euroscore II (2,5% vs 1,8%; p = 0,009). Nie wykazano różnic w częstości występowania chorób towarzyszących takich jak: naczyniopochodne uszkodzenie mózgu (23% chorych z majaczeniem vs 10% bez majaczenia; p = 0,138), nadciśnienie tętnicze (86% vs 89%; p = 0,607), cukrzyca (36% vs 36%; p = 0,975), utrwalone migotanie przedsionków (6% vs 9%; p = 0,654), przewlekła niewydolność nerek (26% vs 16%; p = 0,216), nikotynizm (20% vs 22%; p = 0,825).

Analiza stężenia prokalcytoniny przed i po operacji wykazała następujące zależności:

przed zabiegiem PCT powyżej normy występowało u 50% (15/30) chorych z grupy z majaczeniem i u 27% (32/119) chorych w grupie bez majaczenia (p = 0,019). Nie stwierdzono cech infekcji u żadnego chorego przed operacją, a poziom leukocytozy pozostawał w granicach normy w obu grupach pacjentów. Po zabiegu stężenia PCT były znacząco wyższe u chorych majaczących zarówno przy przyjęciu do OIT (mediana 0,08 ng/mL, IQR 0,03 – 015 vs 0,05 ng/mL, IQR 0,02 – 0,09; p = 0,011), jak i w kolejnych dniach (dzień pierwszy po operacji: 0,59 ng/mL, IQR 0,25 – 1,55 vs. 0,25 ng/mL, IQR 0,14 – 0,54, p = 0,003; dzień drugi: 1,21 ng/mL, IQR 0,24 – 3,29 vs. 0,36 ng/mL, IQR 0,16 – 0,76, p = 0,006; dzień trzeci: 0,76 ng/mL, IQR 0,48 – 2,34 vs. 0,34 ng/mL, IQR 0,14 – 0,66, p = 0,001). W okresie pooperacyjnym trzech pacjentów w grupie z majaczeniem i dwóch w grupie bez majaczenia rozwinęło cechy infekcji – u dwójki zdiagnozowano zapalenie płuc, u kolejnych dwóch – infekcję rany pooperacyjnej, a u jednego – zapalenie płuc i infekcję dróg moczowych.

Wyniki przedoperacyjnej oceny geriatrycznej były następujące: obniżone funkcjonowanie w zakresie podstawowych czynności życia codziennego stwierdzono u 2 chorych w grupie pacjentów z majaczeniem i u 1 w grupie pacjentów bez majaczenia. W ocenie złożonych czynności życia codziennego, upośledzenie funkcjonowania stwierdzono aż u 47% (14/30) pacjentów z majaczeniem i 28% (33/119) pacjentów bez majaczenia (p = 0,046). Różnice istotne statystycznie dotyczyły głównie czynności związanych z: samodzielnym robieniem zakupów (p = 0,041), wykonywaniem prac domowych (p < 0,001), przyjmowaniem leków (p = 0,035), przygotowaniem posiłków (p = 0,022), wykonywaniem prania (p = 0,001) oraz zdolnością do samodzielnego podróżowania (p = 0,014). Objawy depresji stwierdzono u 40% (12/30) wśród chorych, którzy rozwinęli majaczenie i u 17% (20/119) chorych bez majaczenia (p = 0,005). Mediana wartości punktacji GDS-15 była istotnie wyższa u chorych z majaczeniem (mediana 5, IQR 3 – 7 vs 3, IQR 2 – 5; p = 0,003). Mediana wartości MMSE wyniosła 25 punktów w obu grupach pacjentów. Zaburzenia poznawcze stwierdzono u 73% w grupie chorych z majaczeniem i u 58% chorych w grupie bez majaczenia (p = 0,123).

Po przeanalizowaniu parametrów śród- i pooperacyjnych, stwierdzono, że chorzy z majaczeniem częściej wymagali procedury złożonej (p = 0,009), z dłuższym czasem krążenia pozaustrojowego (mediana 102 vs 79 minut; p < 0,001) i czasem zaklemowania aorty (mediana 57 vs 43 minuty; p = 0,004). Obserwowano u nich również różnice w przebiegu pooperacyjnym – wymagali dłuższego czasu wentylacji mechanicznej (mediana 290 vs 200 minut; p = 0,002), częściej występowała u nich ostra niewydolność nerek (20% vs 7%; p = 0,025), a czas hospitalizacji po operacji był istotnie dłuższy (mediana 11 vs 9 dni; p = 0,002).

W wykonanej wieloczynnikowej analizie metodą regresji logistycznej następujące parametry zwiększały istotnie ryzyko wystąpienia majaczenia po operacji: podniesione stężenia PCT przed operacją (OR 3,05; p = 0,048), obniżona wartość skali IADL (OR 0,76; p = 0,003), stwierdzone objawy depresji (OR 5,02; p = 0,004), wiek (OR 1,14; p = 0,016) oraz czas krążenia pozaustrojowego (OR 1,04; p < 0,001).

Z przeprowadzonej analizy wynika wniosek, że etiologia majaczenia pooperacyjnego jest wieloczynnikowa. Starszy wiek i dłuższy czas krążenia pozaustrojowego pozostają jednymi z najważniejszych czynników ryzyka. Można w uogólnieniu stwierdzić, że istnieje tutaj linijna zależność - każdy rok życia więcej i każda przedłużona minuta krążenia pozaustrojowego, zwiększają istotnie ryzyko wystąpienia majaczenia. Dodatkowo w ocenie przedoperacyjnej u chorych powyżej 65 roku życia wskazane jest wykonywanie badania geriatrycznego z oceną w skalach funkcjonowania i oceną występowania depresji, jako że te dwa parametry zostały potwierdzono w prezentowanej pracy jako istotne elementy zwiększające ryzyko wystąpienia majaczenia. Badanie stężenia prokalcytoniny może być dodatkowo pomocne w identyfikacji chorych narażonych na ryzyko wystąpienia tego powikłania. Wyodrębnienie tych chorych jako grupy ryzyka powinno skutkować wprowadzeniem dla nich szczególnych protokołów postępowania okołooperacyjnego, co w konsekwencji może prowadzić do zmniejszenia częstości występowania majaczenia i przyczynić się do poprawy jakości leczenia pacjentów kardiochirurgicznych.

Ad 2.

Drugi z prezentowanych artykułów koncentruje się na wpływie hiperoksji śródoperacyjnej na wystąpienie majaczenia.

Dotychczasowe publikacje opisywały różne czynniki ryzyka wystąpienia majaczenia – przedoperacyjne, związane z wyjściowym stanem pacjenta i śródoperacyjne – związane z przebiegiem operacji i jej ewentualnymi powikłaniami. Jednym z takich czynników jest hipoksja śródoperacyjna, która może prowadzić do ostrych zaburzeń neuropoznawczych spowodowanych niewystarczającym dostarczaniem tlenu do mózgu. (21) Wpływ hiperoksji na funkcje mózgu pozostaje tematem badań. Dotychczasowe doniesienia podkreślają rolę zwiększonego uwalniania reaktywnych form tlenu i w konsekwencji zwiększonej apoptozy komórek mózgowych. (22) Rola hiperoksji w czasie krążenia pozaustrojowego, jako czynnika, który może prowadzić do rozwoju majaczenia, nie została do tej pory zbadana. Celem pracy była ocena wpływu podwyższonego ciśnienia parcjalnego tlenu we krwi tętniczej w czasie krążenia pozaustrojowego na wystąpienie majaczenia.

Do analizy włączono 93 chorych, którzy przebyli zabieg kardiochirurgiczny z zastosowaniem CPB. Przedłużone krążenie pozaustrojowe jest dobrze znanym czynnikiem zwiększającym ryzyko wystąpienia majaczenia, wiąże się także z przedłużoną hospitalizacją po operacji i większą śmiertelnością. Z tego powodu do analizy włączono jedynie chorych u których czas krążenia był krótszy niż 90 minut. Gazometria krwi tętniczej pobierana była przez perfuzjonistę co 20 – 30 minut i łącznie oceniono ich 256. Majaczenie oceniano w skali CAM ICU przez trzy kolejne dni co 12 godzin, rozpoczynając rano od pierwszego dnia po operacji.

Wśród 93 chorych majaczenie stwierdzono u 11 pacjentów (11,8%). W obu grupach chorych nie stwierdzono istotnej różnicy statystycznej pomiędzy takimi czynnikami jak: wiek (średnio u chorych z majaczeniem 74 ± 6 vs 71 ± 5 lat u chorych bez majaczenia; p = 0,13), ryzyko zgonu w skali Euroscore II (6 ± 9,6 vs 2,4 ± 2%; p = 0,38), wskaźnik Charlsona (5,7 ± 2 vs 4,7 ± 2; p = 0,15), wartość frakcji wyrzutowej lewej komory (54 ± 12 vs 57 ± 8%; p = 0,80), obecność chorób towarzyszących takich jak: świeży zawał serca (27,7 vs 23,2 %; p = 0,76), niestabilna dławica piersiowa (9 vs 2,4%; p = 0,24), ciężka niewydolność krążenia - III lub IV w skali NYHA (36,3 vs 15,8%; p = 0,09), choroby płuc (0 vs 4,9%), miażdżyca naczyń obwodowych (9 vs 12,2 %; p = 0,76), migotanie przedsionków (18,1 vs 13,4%; p = 0,66), cukrzyca (54,5 vs 37,8%; p = 0,28), zmiany naczyniopochodne mózgu (27,2 vs 12,2%; p = 0,17), przewlekła choroba nerek (27,2 vs 19,5%; p = 0,54). Nie było również różnicy w parametrach śródoperacyjnych – obie grupy chorych miały podobną długość krążenia pozaustrojowego (u chorych z majaczeniem 72,1 ± 12,3 vs 70 ± 12,4 minut; p = 0,75), zakleszczenia aorty (39,4 ± 13,6 vs 39,1 ± 11,7 minut; p = 0,98), średni poziom hemoglobiny (9,3 ± 1,8 vs 9,4 ± 1,0 g/dL; p = 0,48) i indeks sercowy w czasie krążenia pozaustrojowego (2,5 ± 0,3 vs 2,5 ± 0,1 L/min/m^2; p = 0,69). Nie stwierdzono również różnicy statystycznej w parametrach pooperacyjnych takich jak: konieczność podaży noradrenaliny (54,5% u chorych z majaczeniem vs 48,7% u chorych bez majaczenia; p = 0,71), maksymalna dawka noradrenaliny (0,05 ± 0,08 vs 0,03 ± 0,04 µg/kg/min; p = 0,65), konieczność podaży milrynonu (18% vs 6%; p = 0,15), pooperacyjna utrata krwi (365 ± 177 vs 414 ± 182 ml; p = 0,27), przetoczenia koncentratu krwinek czerwonych (305 ± 292 vs 198 ± 347 ml; p = 0,15), częstość występowania ostrej niewydolności nerek (9% vs 8,5%; p = 0,95) lub potrzeba re-torakotomii (0% vs 2,5%). U chorych z majaczeniem i bez, podobny był czas wentylacji mechanicznej (292 ± 177 vs 231 ± 94 min; p = 0,31) i czas hospitalizacji w OIT (3 ± 1,6 vs 3 ± 1,6 dni; p = 0,68). Pooperacyjne delirium nie przedłużało hospitalizacji po operacji (10 ± 1,6 vs 9,8 ± 2,7 dni; p = 0,10).

Jedyną stwierdzoną różnicą u pacjentów, u których wystąpiło majaczenie, była różnica w ciśnieniu parcjalnym tlenu krwi tętniczej w czasie krążenia pozaustrojowego. U chorych, którzy rozwinęli majaczenie zarówno maksymalna jak i średnia wartość PaO_2 były znacząco wyższe niż u chorych bez majaczenia (maksymalne PaO_2 - 277,5 vs 237 mmHg; p = 0,01, średnie - 226 vs 196 mmHg; p = 0,01). Nie stwierdzono różnicy w minimalnych wartościach PaO_2 (181 vs 159 mmHg; p = 0,06). Po wykonanej analizie krzywej ROC (ang. Receiver Operating Characteristic) określono optymalny punkt odcięcia maksymalnej wartości PaO_2 jako 249 mmHg (AUC 0,72; p = 0,001) z czułością wynoszącą 75% i specyficznością 38%. Dodatkowo u chorych, którzy rozwinęli majaczenie w okresie pooperacyjnym stwierdzono znacząco więcej epizodów ciężkiej hiperoksji, definiowanej jako $PaO_2 \geq 200$ mmHg (mediana 2 [IQR 1 – 3] vs 1 [IQR 1 – 2]; p = 0,02). U 64 % chorych z majaczeniem stwierdzono ≥ 2 incydenty ciężkiej hiperoksji, u 27 % ≥ 3, a u 18 % ≥ 4, podczas gdy u 42 % chorych bez majaczenia stwierdzono ≥ 2 incydenty, u 13 % ≥ 3 i u 1 % ≥ 4 incydenty ciężkiej hiperoksji (p = 0,02).

W przedstawionej pracy wykazano, że hiperoksja śródoperacyjna może być czynnikiem ryzyka majaczenia pooperacyjnego. Szczególnie ciśnienia parcjalne tlenu powyżej 249 mmHg i przedłużony czas ekspozycji na jego wysokie stężenia, mogą się przyczynić do rozwoju tego powikłania. Obserwacje te niosą za sobą ważne konsekwencje praktyczne. Majaczenie może być wynikiem współwystępowania różnych czynników ryzyka. Na wiele z nich nie mamy wpływu. Unikanie hiperoksji śródoperacyjnej wydaje się być prostym i bezpiecznym sposobem na zmniejszenie częstości występowania tego powikłania, co w konsekwencji może przyczynić się do poprawy wyników leczenia chorych po operacjach serca.

4. PODSUMOWANIE

Obie przedstawione publikacje koncentrują się na problematyce majaczenia pooperacyjnego w chirurgii serca. Wyniki prac wskazują, że jest to częste powikłanie w starszej populacji, a jego etiologia jest wieloczynnikowa. Znajomość potencjalnych czynników ryzyka wywołujących majaczenie niesie ze sobą praktyczne korzyści. Pozwala na identyfikację chorych z grup ryzyka, którzy mogą wymagać zwiększonej uwagi lekarskiej i ścisłej opieki pielęgniarskiej w okresie pooperacyjnym. Może być również doskonałym materiałem do opracowania i wdrożenia programów opieki nad starszymi chorymi zagrożonymi wystąpieniem delirium. Szersza wiedza o problemach majaczenia pozwoli również rozważnie kwalifikować chorych z grup ryzyka do rozległych operacji kardiochirurgicznych, z uwzględnieniem bilansu ryzyka i potencjalnych korzyści.

Najważniejsze wnioski z prezentowanego cyklu prac są następujące:

- Majaczenie w okresie pooperacyjnym jest powikłaniem częstym u pacjentów kardiochirurgicznych
- Najczęstszą rozpoznawaną formą jest postać hipoaktywna i w większości występuje w ciągu pierwszej doby po operacji
- Hiperoksja w czasie krążenia pozaustrojowego, w szczególności powyżej 249 mmHg, może sprzyjać wystąpieniu majaczenia po operacji
- Podniesione stężenia prokalcytoniny w surowicy powyżej normy przed operacją mogą być pomocne w wyodrębnieniu chorych z grupy ryzyka majaczenia
- Pacjenci powyżej 65 roku, w ramach oceny przedoperacyjnej, powinni być zbadani pod kątem występowania depresji oraz obniżonego funkcjonowania w skali IADL, ponieważ czynniki te sprzyjają wystąpieniu majaczenia
- Pacjenci, u których wystąpiło delirium po operacji, są bardziej narażeni na wystąpienie ostrej niewydolności nerek, częściej wymagają dłuższego czasu wentylacji mechanicznej oraz czas ich hospitalizacji jest istotnie dłuższy

6. STRESZCZENIE

Wstęp

Majaczenie jest jednym z najczęstszych powikłań po operacjach kardiochirurgicznych. Wiąże się z szeregiem niekorzystnych następstw takich jak zwiększona śmiertelność i dłuższy czas hospitalizacji po operacji. Celem badania była wielokierunkowa analiza czynników ryzyka sprzyjających wystąpieniu majaczenia, uwzględniająca parametry przedoperacyjne i śródoperacyjne oraz ocena wpływu majaczenia na długość hospitalizacji i powikłania pooperacyjne.

Materiał i metody

Do badania zakwalifikowano chorych leczonych pomiędzy 12.2016 a 12.2018 w Klinice Anestezjologii i Intensywnej Terapii po operacjach kardiochirurgicznych z zastosowaniem krążenia pozaustrojowego. Wystąpienie majaczenia oceniane było przy pomocy skali CAM ICU (Confusion Assessment Method in Intensive Care Unit) co 12 godzin przez trzy kolejne dni po operacji.

Wyniki

W przedoperacyjnej ocenie pacjentów, istotne statystycznie były następujące czynniki ryzyka: starszy wiek, anemia, wyższa wartość Euroscore II, podniesiony poziom prokalcytoniny powyżej normy, upośledzone codzienne funkcjonowanie w skali IADL (Instrumental Activities of Daily Living) oraz objawy depresji. Chorzy z majaczeniem częściej wymagali operacji złożonej, z dłuższym czasem krążenia pozaustrojowego i czasem zaklemowania aorty. W czasie krążenia pozaustrojowego, chorzy z majaczeniem częściej byli narażeni na wysokie ciśnienia parcjalne tlenu – zarówno maksymalne jak i średnie PaO_2 było wyższe u chorych, którzy rozwinęli delirium pooperacyjne. Dodatkowo istotnie częściej stwierdzano u nich epizody ciężkiej hiperoksji. Obserwowano również różnice w przebiegu pooperacyjnym – chorzy w których wystąpiło majaczenie mieli dłuższy czas wentylacji mechanicznej i czas hospitalizacji po operacji, częściej występowała również u nich ostra niewydolność nerek.

Wnioski

Etiologia majaczenia po operacjach kardiochirurgicznych jest wieloczynnikowa i wiąże się z niekorzystnymi następstwami w okresie pooperacyjnym. Unikanie potencjalnych czynników wyzwalających, takich jaki hiperoksja śródoperacyjna, może przyczynić się do zmniejszenia częstości występowania tego powikłania.

7. SUMMARY

Introduction

Delirium is one of the most common complications after cardiac surgery. It is associated with adverse consequences such as increased mortality and longer hospitalization after surgery. The aim of the study was to identify risk factors of delirium including preoperative and intraoperative indices, and to assess the relationship between delirium and postoperative complications.

Material and Methods

Patients treated in the Department of Anaesthesiology and Intensive Therapy between December 2016 and December 2018 who underwent elective cardiac surgery with cardiopulmonary bypass CBP. The occurrence of delirium was assessed using CAM ICU (Confusion Assessment Method in Intensive Care Unit) score every 12 hours for three consecutive days after surgery.

Results

The following preoperative risk factors were confirmed as statistically significant: older age, anaemia, higher Euroscore II, elevated procalcitonin level above normal value, impaired daily functioning assessed by the IADL (Instrumental Activities of Daily Living) score and symptoms of depression. Patients with delirium more often required complex surgery, with longer CBP and aortic cross clamping time. Patients with delirium had higher maximum and mean PaO_2 (partial pressure of oxygen) during CPB. The incidence rate of severe hyperoxia was higher in patients with delirium. The postoperative analysis showed that in patients with delirium time of mechanical ventilation and length of hospitalization were longer and acute kidney injury was diagnosed more often

Conclusions

The aetiology of delirium is multifactorial and it is associated with adverse consequences in the postoperative period. Avoiding potential trigger such as intraoperative hyperoxia may help to reduce the incidence rate of this complication.

8. PIŚMIENNICTWO

1. Gilman S. Cerebral disorders after open-heart operations. N Engl J Med. 1965 Mar;272:489–98.
2. Atkinson RP. Postoperative psychosis. Surg Clin North Am. 1957 Jun;37(3):835–44.
3. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet (London, England). 2014 Mar;383(9920):911–22.
4. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: A systematic review. J Am Geriatr Soc. 2006;54(10):1578–89.
5. Gusmao-Flores D, Figueira Salluh JI, Chalhub RT, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. Crit Care. 2012;16(4):R115.
6. Abawi M, Pagnesi M, Agostoni P, Chiarito M, van Jaarsveld RC, van Dongen CS, et al. Postoperative Delirium in Individuals Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2018;66(12):2417–24.
7. Koster S, Hensens AG, Schuurmans MJ, Van Der Palen J. Consequences of delirium after cardiac operations. Ann Thorac Surg. 2012;93(3):705–11.
8. Sauër AC, Veldhuijzen DS, Ottens TH, Slooter AJC, Kalkman CJ, Van Dijk D. Association between delirium and cognitive change after cardiac surgery. Br J Anaesth. 2017;119(2):308–15.
9. EDA and ADS. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer (European Delirium Association and American Delirium Society). BMC Med. 2014;12(1):141.
10. Organization WH. International statistical classification of diseases and related health problems. 10th rev. World Health Organization; 1994
11. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet. 2010;375(9716):773–5.
12. Cascella M, Muzio MR, Bimonte S, Cuomo A, Jakobsson JG. Postoperative delirium and postoperative cognitive dysfunction: Updates in pathophysiology, potential translational approaches to clinical practice and further research perspectives. Minerva Anestesiol. 2018;84(2):246–60.
13. Sapolsky RM. Stress, Glucocorticoids, and Damage to the Nervous System: The

Current State of Confusion. Stress. 1996 Jul;1(1):1–19.

14. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. Int J Geriatr Psychiatry. 2018;33(11):1428–57.
15. Harukuni I, Bhardwaj A. Mechanisms of brain injury after global cerebral ischemia. Neurol Clin. 2006 Feb;24(1):1–21.
16. Karlidag R, Unal S, Sezer OH, Bay Karabulut A, Battaloğlu B, But A, et al. The role of oxidative stress in postoperative delirium. Gen Hosp Psychiatry. 2006;28(5):418–23.
17. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: Pathophysiology and treatment. An update. Eur J Cardio-thoracic Surg. 2002;21(2):232–44.
18. Clementi A, Virzì GM, Muciño-Bermejo MJ, Nalesso F, Giavarina D, Carta M, et al. Presepsin and Procalcitonin Levels as Markers of Adverse Postoperative Complications and Mortality in Cardiac Surgery Patients. Blood Purif. 2019;47(1–3):140–8.
19. Klingele M, Bomberg H, Schuster S, Schäfers HJ, Groesdonk HV. Prognostic value of procalcitonin in patients after elective cardiac surgery: a prospective cohort study. Ann Intensive Care. 2016;6(1).
20. Keranov S, Kim WK, Arsalan M, Renker M, Keller T, Bauer T, et al. Predictive value of preprocedural procalcitonin for short- and long-term mortality after transfemoral transcatheter aortic valve implantation. Heart Vessels. 2019;34(12):1993–2001.
21. Liu Z, Pang X, Zhang X, Cao G, Fang C, Wu S. Incidence and Risk Factors of Delirium in Patients After Type-A Aortic Dissection Surgery. J Cardiothorac Vasc Anesth. 2017;31(6):1996–9.
22. Rice MR, Young HF, Bullock R, DI X, Doppenberg EMR, Woodward JJ. Increased Free Radical Production Due to Subdural Hematoma in the Rat: Effect of Increased Inspired Oxygen Fraction. J Neurotrauma. 2009;15(5):337–47.

9. OŚWIADCZENIA WSPÓŁAUTORÓW

Wrocław 10.01.2021

Lek. Katarzyna Forkasiewicz-Gardynik
Katedra i Klinika Anestezjologii i Intensywnej Terapii
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy: Kupiec A, Adamik B, Forkasiewicz-Gardynik K, Goździk W. Intra-operative hyperoxia and the risk of delirium in elderly patients after cardiac surgery. Aging (Albany NY). 2020 Apr 19;12(8):7006-7014, mój udział polegał na gromadzeniu i zestawianiu danych.

Podpis

Wrocław 11.01.2021

Lek. Natalia Kozera

Katedra i Klinika Anestezjologii i Intensywnej Terapii

Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy: Kupiec A, Adamik B, Kozera N, Gozdzik W. Elevated Procalcitonin as a Risk Factor for Postoperative Delirium in the Elderly after Cardiac Surgery-A Prospective Observational Study. J Clin Med. 2020 Nov 26;9(12):E3837, mój udział polegał na gromadzeniu i zestawianiu danych.

Podpis

Kozera Natalia

Wrocław 11.01.2021

Dr hab. n. med. Waldemar Goździk, prof. nadzw.
Katedra i Klinika Anestezjologii i Intensywnej Terapii
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy: Kupiec A, Adamik B, Forkasiewicz-Gardynik K, Goździk W. Intra-operative hyperoxia and the risk of delirium in elderly patients after cardiac surgery. Aging (Albany NY). 2020 Apr 19;12(8):7006-7014, mój udział polegał na kierowaniu projektem naukowym oraz przygotowaniu tekstu manuskryptu.

Podpis

Wrocław 11.01.2021

Dr hab. n. med. Waldemar Goździk, prof. nadzw.
Katedra i Klinika Anestezjologii i Intensywnej Terapii
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy: Kupiec A, Adamik B, Kozera N, Gozdzik W. Elevated Procalcitonin as a Risk Factor for Postoperative Delirium in the Elderly after Cardiac Surgery-A Prospective Observational Study. J Clin Med. 2020 Nov 26:9(12):E3837, mój udział polegał na kierowaniu projektem naukowym oraz przygotowaniu tekstu manuskryptu.

Podpis

Wrocław 11.01.2021

Dr hab. Barbara Adamik
Katedra i Klinika Anestezjologii i Intensywnej Terapii
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy: Kupiec A, Adamik B, Forkasiewicz-Gardynik K, Goździk W. Intra-operative hyperoxia and the risk of delirium in elderly patients after cardiac surgery. Aging (Albany NY). 2020 Apr 19;12(8):7006-7014, mój udział polegał na analizie statystycznej wyników oraz przygotowaniu tekstu manuskryptu.

Podpis

Barbara Adamik

Wrocław 11.01.2021

Dr hab. Barbara Adamik

Katedra i Klinika Anestezjologii i Intensywnej Terapii

Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy: Kupiec A, Adamik B, Kozera N, Gozdzik W. Elevated Procalcitonin as a Risk Factor for Postoperative Delirium in the Elderly after Cardiac Surgery-A Prospective Observational Study. J Clin Med. 2020 Nov 26;9(12):E3837, mój udział polegał na analizie statystycznej wyników oraz przygotowaniu tekstu manuskryptu.

Podpis

Barbara Adamik