POMORSKI UNIWERSYTET MEDYCZNY
W SZCZECINIE

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“Ostre uszkodzenie nerek związane z operacjami kardiochirurgicznymi – czynniki wpływające i strategie postępowania.”

Rozprawa doktorska w dziedzinie nauk medycznych i nauk o zdrowiu

Dyscyplina nauki medyczne

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Szczecin 2024 r.

SPIS TREŚCI

1. WYKAZ STOSOWANYCH SKRÓTÓW

AKI - ostre uszkodzenie nerek (ang. acute kidney injury)

Ang II - angiotensyna II (ang. angiotensin II)

CABG - pomostowanie aortalno-wieńcowe (ang. coronary artery by-passing graft)

CaO2 - pojemność tlenowa krwi (ang. oxygen-carrying capacity of the blood)

CPB - krążenie pozaustrojowe (ang. cardiopulmonary by-pass)

CSA-AKI - ostre uszkodzenie nerek związane z operacjami kardiochirurgicznymi (ang. cardiac surgery-associated acute kidney injury)

iDO2 - dostarczanie tlenu indeksowane do powierzchni ciała (ang. oxygen delivery indexed for body surface area)

eGFR - szacowany wskaźnik filtracji kłębuszkowej (ang. estimated glomerular filtration rate)

IL-6 - interleukina 6 (ang. interleukin 6)

IL-8 - interleukina 8 (ang. interleukin 8)

IL-18 - interleukina 18 (ang. interleukin 18)

KIM-1 - cząsteczka uszkodzenie nerek 1 (ang. kidney injury molecule 1)

MAP - średnie ciśnienie tętnicze (ang. mean arterial pressure)

MMP-9 - metaloproteinaza macierzy zewnątrzkomórkowej 9 (ang. matrix metalloproteinase 9)

NGAL - lipokalina związana z żelatynazą neutrofili (ang. neutrophil gelatinase-associated lipocalin)

RAA - renina-angiotensyna-aldosteron (ang. renin-angiotensin-aldosterone)

TIMP-1 - tkankowy inhibitor metaloproteinazy 1 (ang. tissue inhibitor of metalloproteinase 1)

TNF-α - czynnik martwicy nowotworów alfa (ang. tumor necrosis factor-alpha)

2. NOTA INFORMACYJNA

Rozprawę doktorską stanowi zbiór powiązanych tematycznie artykułów naukowych opublikowanych w czasopismach naukowych zgodnie z Art. 13.2 Ustawy o stopniach naukowych i tytule naukowym oraz o stopniach i tytule w zakresie sztuki, Dz. U. z dnia 27 września 2017 r. Poz. 1789:

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   Impact Factor: 5.168, **punktacja MNiSW:** 100

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   Impact Factor: 4.000, **punktacja MNiSW:** 100

3. STRESZCZENIE W JĘZYKU POLSKIM

3.1. Wstęp

Ostre uszkodzenie nerek związane z operacjami kardiochirurgicznymi (ang. cardiac surgery-associated acute kidney injury - CSA-AKI) jest jednym z najczęstszych powikłań operacji kardiochirurgicznych. Krążenie pozaustrojowe (ang. cardiopulmonary by-pass - CPB) istotnie zmienia fizjologiczne warunki funkcjonowania organizmu człowieka i naraża nerki na wieloczynnikowe uszkodzenie. Poznanie i zrozumienie mechanizmów prowadzących do uszkodzenia nerek jest kluczowe pod kątem wprowadzenia odpowiednich strategii nefroprotekcji. Istotnym czynnikiem jest także odpowiednio wczesne wykrywanie ostrego uszkodzenia nerek w okresie pooperacyjnym, co pozwala na szybsze wdrożenie leczenia. Poniższy cykl prac naukowych ma na celu opisanie i lepsze zrozumienie czynników wpływających na występowanie CSA-AKI, a także ocenę przydatności specyficznych biomarkerów uszkodzenia nerek we wczesnej diagnostyce tego powikłania.

3.2. Materiał i metodyka

Poniższy cykl składa się z czterech prac naukowych, w tym jednego randomizowanego badania prospektywnego z interwencją eksperymentalną, dwóch prospektywnych badań obserwacyjnych oraz jednego przeglądu literatury. Łącznie w badaniach naukowych ujętych w tym cyklu wzięło udział 128 pacjentów Kliniki Kardiochirurgii PUM w Szczecinie, zakwalifikowanych do planowych operacji kardiochirurgicznych z wykorzystaniem CPB. U pacjentów tych analizowano stężenia specyficznych biomarkerów uszkodzenia nerek w surowicy i moczu w okresie pooperacyjnym. Stężenia biomarkerów u pacjentów w tej populacji porównywano pod kątem wystąpienia CSA-AKI oraz pod kątem zastosowania śródoperacyjnej hemofiltracji. Ponadto 80 pacjentów z tej populacji włączono do randomizowaego badania prospektywnego, w którym interwencję stanowiło zwiększanie rzutu pompy perfuzyjnej w celu uzyskania MAP >90 mmHg. Grupę

kontrolną stanowili pacjenci, u których zastosowano standardowy rzut pompy perfuzyjnej (2.4 l/min/m2).

3.3. Wyniki

CSA-AKI wystąpiło u blisko 1/3 populacji pacjentów, którzy wzięli udział w badaniach naukowych objętych poniższym cyklem. Czynnikami zwiększającymi ryzyko wystąpienia tego powikłania były: starszy wiek, niższy przedoperacyjny eGFR, przewlekła choroba nerek w wywiadzie oraz niski hematokryt. Do rozwoju przewlekłej choroby nerek po operacji predysponowały: niższy przedoperacyjny eGFR, większa objętość hemofiltracji, większy odsetek wody odebranej z objętości wewnątrznaczyniowej oraz wystąpienie CSA-AKI. W 6. godzinie po zakończeniu CPB pacjenci z CSA-AKI mieli istotnie wyższe stężenia IL-8 i TNF-α w surowicy oraz wyższe stężenie NGAL w moczu, normalizowane do wydalania kreatyniny. Indeks Youden'a dla powyższych biomarkerów wyniósł odpowiednio 0.34, 0.41 i 0.34. Utrzymywanie MAP > 90 mmHg podczas CPB nie zmniejszyło częstości występowania CSA-AKI; wiązało się natomiast z mniejszym wyrzutem reniny oraz zwiększeniem śródoperacyjnej diurezy w porównaniu do MAP < 70 mmHg. Zwiększenie rzutu pompy perfuzyjnej nie wiązało się ze zwiększoną częstością powikłań neurologicznych. Bazując na danych z literatury do strategii nefroprotekcji w trakcie operacji kardiochirurgicznych należy zaliczyć: utrzymywanie iDO2 nie mniejszego niż 260-300 ml/min/m2 podczas CPB, utrzymywanie MAP nie mniejszego niż 70-90 mmHg w trakcie całej operacji, stosowanie noradrenaliny w celu przeciwdziałania wazoplegii związanej ze znieczuleniem ogólnym i CPB (preferencyjnie w dawkach < 0.1 μg/kg/min) oraz śródoperacyjne nawadnianie pacjenta w celu uzyskania diurezy nie mniejszej niż 4 ml/kg/godz w trakcie CPB.

3.4. Wnioski

Wystąpienie ostrego uszkodzenia nerek związanego z operacjami kardiochirurgicznymi zwiększa chorobowość i śmiertelność pacjentów w okresie

pooperacyjnym, a także jest czynnikiem ryzyka wystąpienia przewlekłej choroby nerek. Zwiększanie rzutu pompy perfuzyjnej w celu podniesienia MAP w trakcie CPB jest obiecującą strategią nefroprotekcji, która zmniejsza hipoperfuzję nerek oraz poprawia ich śródoperacyjną funkcję. Specyficzne biomarkery uszkodzenia nerek są obiecującą alternatywą we wczesnej diagnostyce CSA-AKI; istnieje jednak potrzeba odpowiedniego wystandaryzowania tego narzędzia diagnostycznego zanim będzie ono mogło być wprowadzone do rutynowej praktyki klinicznej.

3.5. Słowa kluczowe

ostre uszkodzenie nerek; kardiochirurgia; krążenie pozaustrojowe; biomarkery uszkodzenia nerek; nefroprotekcja

4. STRESZCZENIE W JĘZYKU ANGIELSKIM

4.1. Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) is one of the most common complications of cardiac surgery. Cardiopulmonary by-pass (CPB) significantly changes the physiological conditions of the human body and exposes the kidneys to multifactorial damage. Knowing and understanding the mechanisms leading to kidney damage is crucial in order to introduce appropriate nephroprotection strategies. An important factor is also early detection of acute kidney injury in the postoperative period, which allows for faster implementation of treatment. The following series of scientific papers aims to describe and better understand the factors influencing the occurrence of CSA-AKI, as well as to assess the usefulness of novel kidney injury biomarkers in the early diagnosis of this complication.

4.2. Materials and methods

The following series consists of four scientific papers, including one randomized prospective study with an experimental intervention, two prospective observational studies and one literature review. A total of 128 patients of the Cardiac Surgery Clinic of the Pomeranian Medical University in Szczecin participated in the scientific research included in this series. They were all qualified for elective cardiac surgeries with the use of CPB. These patients took part in an observational study involving the analysis of the novel kidney injury biomarkers' concentration in the postoperative period. Biomarker levels in patients in this population were compared regarding the occurrence of CSA-AKI and the use of intraoperative hemofiltration. Moreover, 80 patients from this population participated in a randomized prospective study in which the intervention was to increase the CPB pump flow to achieve MAP >90 mmHg. The control group consisted of patients who received a standard CPB pump flow (2.4 l/min/m2).

4.3. Results

CSA-AKI occurred in nearly 1/3 of the patient population who participated in the research studies included in the series below. Factors increasing the risk of this complication were: older age, lower preoperative eGFR, history of chronic kidney disease and low hematocrit. The following factors predisposed to the development of chronic kidney disease after surgery: lower preoperative eGFR, higher hemofiltration volume, higher percentage of water removed from the intravascular volume, and the occurrence of CSA-AKI. At 6 hours after weaning from CPB, CSA-AKI patients had significantly higher serum IL-8 and TNF-α concentrations and higher urinary NGAL concentrations (normalized to creatinine secretion). Youden's index for the above biomarkers was 0.34, 0.41 and 0.34, respectively. Maintaining MAP > 90 mmHg during CPB did not reduce the incidence of CSA-AKI; however, it was associated with lower renin release and increased intraoperative diuresis compared to MAP < 70 mmHg. Increasing perfusion pump flow was not associated with an increased incidence of neurological complications. Based on the data from the literature, nephroprotection strategies during cardiac surgery include: maintaining iDO2 no lower than 260-300 ml/min/m2 during CPB, maintaining MAP no lower than 70-90 mmHg during the entire operation, using norepinephrine to counteract vasoplegia associated with general anesthesia and CPB (preferably at doses < 0.1 μg/kg/min) and intraoperative hydration of the patient to achieve a diuresis of no less than 4 ml/kg/h during CPB.

4.4. Conclusions

Cardiac surgery associated acute kidney injury increases patient morbidity and mortality in the postoperative period and is also a risk factor for the development of chronic kidney disease. Increasing MAP during the CBP by augmenting the CPB pump flow is a promising nephroprotective strategy that reduces kidney hypoperfusion and improves intraoperative renal function. Novel kidney injury biomarkers are a promising alternative in the early diagnosis of CSA-AKI; however, they need to be appropriately standardized before they can be introduced into routine clinical practice.

4.5. Keywords

acute kidney injury; cardiac surgery; cardiopulmonary by-pass; novel kidney injury biomarkers; nephroprotection

5. WSTĘP

5.1. Problematyka ostrego uszkodzenia nerek w kardiochirurgii

Ostatnie badania wykazały, że rocznie około miliona pacjentów poddawanych jest operacjom kardiochirurgicznym [1]. Według niektórych autorów u 20 do nawet 50% z nich wystąpi ostre uszkodzenie nerek związane z operacjami kardiochirurgicznymi (ang. cardiac surgery-associated acute kidney injury - CSA-AKI) [2,3]. Powikłanie to, poza dużą częstością występowania, niesie ze sobą poważne konsekwencje dla zdrowia pacjentów. Zwiększa chorobowość i śmiertelność pooperacyjną [2,4] i może skutkować rozwojem przewlekłej choroby nerek [5,6]. Patogeneza CSA-AKI nadal nie jest w pełni poznana i dlatego nie ma jasnych wytycznych jak unikać tego powikłania. Kolejną kwestią jest wczesne wykrycie uszkodzenia nerek w okresie pooperacyjnym, co umożliwia wdrożenie odpowiedniego leczenia.

5.2. Rola krążenia pozaustrojowego w ostrym uszkodzeniu nerek

Zastosowanie krążenia pozaustrojowego (ang. cardiopulmonary by-pass - CPB) jest czynnikiem, który najprawdopodobniej przyczynia się do pooperacyjnego upośledzenia funkcji nerek, jednak jego rola w rozwoju CSA-AKI jest nadal niejasna [7]. Istnieje kilka czynników związanych z CPB, które mogą przyczyniać się do uszkodzenia nerek: obniżone ciśnienie perfuzji i zmniejszenie przepływu krwi, zmniejszona zdolność krwi do przenoszenia tlenu (CaO2), ogólnoustrojowa reakcja zapalna oraz zwiększony stres oksydacyjny [8].

Nerki posiadają mechanizmy autoregulacyjne, które pozwalają na utrzymanie stabilnego przepływu krwi i szybkości filtracji w szerokim zakresie MAP. Według większości autorów dolna granica zakresu tej autoregulacji wynosi 70–80 mmHg [9,10]. Poniżej tego progu przepływ krwi przez nerki ulega zmniejszeniu, a komórki aparatu przykłębuszkowego tętniczki doprowadzającej zaczynają uwalniać reninę [11]. Renina jest pierwszym enzymem osi renina-angiotensyna-aldosteron (ang. renin-angiotensin-aldosterone - RAA), a jej uwalnianie ma na celu podniesienie systemowego ciśnienia krwi. Układ RAA ma również szczególny wpływ na krążenie nerkowe. Zwiększony poziom reniny prowadzi do wzrostu stężenia angiotensyny II (ang. angiotensin II - Ang II), silnego wazopresora. Ang II

obkurcza zarówno tętniczkę doprowadzającą, jak i odprowadzającą w kłębuszkach nerkowych, ale jej działanie na tętniczkę odprowadzającą jest silniejsze. Powoduje to wzrost efektywnego ciśnienia filtracji, ale także zmniejsza ilość krwi docierającej do rdzenia nerki. Jeśli MAP utrzymuje się poniżej progu autoregulacji nerek podczas CPB, zmniejsza się nerkowy przepływ krwi i drastycznie maleje przepływ krwi w rdzeniu nerek (zwężenie tętniczki odprowadzającej przez Ang II). Jeżeli dostarczanie tlenu indeksowane do powierzchni ciała (ang. oxygen delivery indexed for body surface area - iDO2) również się zmniejszy (niewystarczający rzut pompy, aby skompensować obniżony CaO2), nerki będą narażone na dodatkowe uszkodzenie niedokrwienne, co może wywołać CSA-AKI.

CPB jest również związane z odpowiedzią układu immunologicznego. Głównymi przyczynami są uraz chirurgiczny i kontakt krwi ze sztuczną powierzchnią drenów układu CPB. W odpowiedź immunologiczną zaangażowane są zarówno mechanizmy komórkowe, jak i humoralne. Leukocyty toczą się po sztucznej powierzchni układu CPB, co prowadzi do ich aktywacji [12]. Podobnie kontakt sztucznej powierzchni z cytokinami C5a i C3d powoduje aktywację dopełniacza, co nasila humoralną odpowiedź zapalną [13]. Zwiększona aktywacja układu odpornościowego wiąże się z gorszymi wynikami klinicznymi po operacjach kardiochirurgicznych [14,15], w tym z większą częstością występowania AKI.

Zaburzenia równowagi płynowej i wzrost osmolalności osocza to kolejne wyzwania stojące przed nerkami podczas operacji kardiochirurgicznej. Rozpoczęcie CPB wiąże się ze znaczącą transfuzją hiperosmotycznych płynów – primingu wypełniającego obwód CPB oraz roztworu kardioplegicznego służącego do zatrzymania akcji serca. Po rozpoczęciu CPB osmolalność osocza wzrasta do około 322 mOsm/l i pozostaje podwyższona (>300 mOsm/l) przez kolejne 24 godziny [16]. Hiperosmolalność osocza powoduje odwodnienie komórek (w tym komórek nerek), a także obciąża nerki znacznym ładunkiem osmotycznym, zwiększając ryzyko AKI [17]. Otwarcie klatki piersiowej skutkuje powstaniem dużej powierzchni parowania z błon śluzowych. Nieodczuwalna utrata wody na skutek parowania może sięgać nawet 1000 ml podczas rutynowego zabiegu pomostowania aortalno-wieńcowego (ang. coronary artery by-passing graft - CABG) [18]. Zaniedbanie przez pacjenta spożycia odpowiedniej ilości płynów w

okresie przedoperacyjnym może pogłębić odwodnienie hipertoniczne w trakcie zabiegu.

5.3. Wczesne wykrywanie ostrego uszkodzenia nerek

W dalszym ciągu złotym standardem w diagnostyce CSA-AKI pozostaje wzrost kreatyniny lub spadek diurezy godzinowej zgodnie z kryteriami KDIGO. Niestety specyfika operacji kardiochirurgicznych z wykorzystaniem CPB obniża czułość tej metody diagnostycznej i zmusza badaczy do poszukiwania alternatywnych rozwiązań. Podczas krążenia pozaustrojowego dochodzi do masywnej transfuzji płynów w objętości przynajmniej 2000 ml w krótkim czasie (objętość priming'u oraz przynajmniej jedna dawka kardiopleginy). Powoduje to istotne rozcieńczenie kreatyniny zawartej w osoczu i nieadekwatność jej stężenia do pooperacyjnej funkcji nerek; śródoperacyjna hemofiltracja usuwa część kreatyniny z osocza, nasilając to zjawisko.

Kolejny problem stanowi czas potrzebny na akumulację odpowiedniej ilości kreatyniny w ustroju, aby jej stężenie spełniło kryteria rozpoznania AKI. Literatura wskazuje, że znakomita większość CSA-AKI jest diagnozowana po 24 godzinach od operacji [19,20]. Badania przeprowadzone w ostatnich latach dowodzą, że możliwe jest wykrycie CSA-AKI już po 6 godzinach od zakończenia CPB przy użyciu specyficznych biomarkerów uszkodzenia nerek w moczu, takich jak lipokalina związana z żelatynazą neutrofilów (ang. neutrophil gelatinase-associated lipocalin - NGAL), cząsteczka uszkodzenia nerek 1 (ang. kidney injury molecule 1 - KIM-1), metaloproteinaza macierzy zewnątrzkomórkowej 9 (ang. matrix metalloproteinase 9 - MMP-9) i interleukina 18 (ang. interleukin 18 - IL-18) [21-25]. Dodatkowo obecne w surowicy cząsteczki, takie jak interleukina 6 (ang. interleukin 6 - IL-6), interleukina 8 (ang. interleukin 8 - IL-8) i czynnik martwicy nowotworów alfa (ang. tumor necrosis factor-alpha - TNF-α), są obiecującym narzędziem diagnostycznym w tym zakresie [26-28]. Odpowiednie wystandaryzowanie stężenia tych biomarkerów skróciłoby czas potrzebny do rozpoznania CSA-AKI i pozwoliło na wcześniejsze włączenie leczenia.

5.4. Strategie nefroprotekcji

Wobec braku jednolitych standardów nefroprotekcji podczas operacji kardiochirurgicznych, najlepszą strategią wydaje się być dążenie do przywrócenia fizjologicznych warunków funkcjonowania ustroju w trakcie CPB. Należy przez to rozumieć przede wszystkim utrzymywanie adekwatnego przepływu krwi, odpowiedniego iDO2 oraz zapewnienie fizjologicznego MAP. Nie należy także zapominać o kluczowym wpływie odpowiedniej podaży płynów na funkcję nerek.

5.5. Podsumowanie wstępu

Krążenie pozaustrojowe stanowi wyzwanie dla organizmu pacjenta, w tym także dla nerek. Wysoka częstość występowania CSA-AKI oraz jego udowodniony negatywny wpływ na rokowanie pacjentów i wyniki leczenia skłania do poszukiwania metod zapobiegania temu powikłaniu. Kolejnym istotnym problemem jest odpowiednio wczesna diagnostyka CSA-AKI, pozwalająca na wdrożenie odpowiedniego leczenia.

6. CELE PRAC

1. Ocena przydatności specyficznych biomarkerów uszkodzenia nerek (IL-6, IL-8, TNF-α, NGAL, KIM-1, IL-18, MMP-9 i TIMP-1) we wczesnej diagnostyce CSA-AKI oraz w rokowaniu co do długoterminowej czynności nerek po operacji kardiochirurgicznej.
2. Podkreślenie znaczenia opieki okołooperacyjnej w zapobieganiu CSA-AKI.
3. Zaproponowanie strategii nefroprotekcji w trakcie operacji kardiochirurgicznych.
4. Ocena wpływu MAP >90 mmHg (osiąganego poprzez zwiększenie rzutu pompy perfuzyjnej) na pooperacyjną czynność nerek oraz wybrane powikłania narządowe operacji kardiochirurgicznych.

7. MATERIAŁ I METODYKA

7.1. Materiał

Łącznie w badaniach naukowych ujętych w tym cyklu wzięło udział 128 pacjentów Kliniki Kardiochirurgii PUM w Szczecinie zakwalifikowanych do planowych operacji kardiochirurgicznych z wykorzystaniem CPB. U pacjentów tych analizowano stężenia specyficznych biomarkerów uszkodzenia nerek w surowicy i moczu w okresie pooperacyjnym. Stężenia biomarkerów u pacjentów w tej populacji porównywano pod kątem wystąpienia CSA-AKI oraz pod kątem zastosowania śródoperacyjnej hemofiltracji. Ponadto 80 pacjentów z tej populacji wzięło udział w randomizowanym badaniu prospektywnym, w którym interwencję stanowiło zwiększanie rzutu pompy perfuzyjnej w celu uzyskania MAP >90 mmHg. Grupę kontrolną stanowili pacjenci, u których zastosowano standardowy rzut pompy perfuzyjnej (2.4 l/min/m2). Główne kryteria wykluczenia wspólne dla wszystkich 3 badań z udziałem pacjentów obejmowały: przewlekłą chorobę nerek w stadium 5 wg KDIGO, aktywne procesy zapalne, aktywną chorobę nowotworową oraz zwężenie tętnic nerkowych w wywiadzie.

7.2. Metodyka

Poniższy cykl składa się z czterech prac naukowych, w tym jednego randomizowanego badania prospektywnego z interwencją eksperymentalną, dwóch prospektywnych badań obserwacyjnych oraz jednego przeglądu literatury. Przed rozpoczęciem rekrutacji pacjentów projekty badań uzyskały pozytywną opinię Komisji Bioetycznej Pomorskiego Uniwersytetu Medycznego w Szczecinie (uchwały Komisji: KB-0012/165/19 oraz KB-0012/45/2021). Każdy uczestnik badania został poinformowany o przebiegu badania oraz potencjalnych korzyściach i zagrożeniach z niego wynikających, a następnie podpisał zgodę na udział w badaniu. W badaniu obserwacyjnym obejmującym 128 uczestników analizowano stężenia biomarkerów uszkodzenia nerek we krwi oraz w moczu, w 6. godzinie po zakończeniu CPB. W badaniu obserwacyjnym obejmującym 48 uczestników oraz w badaniu z interwencją eksperymentalną obejmującym 80 uczestników schemat pobrań materiału biologicznego był następujący: próbki krwi pobierano przed operacją oraz 6 godzin po zakończeniu CPB; próbki moczu pobierano przed operacją oraz w 6., 24. i 48. godzinie

po zakończeniu CPB, a także w 5. dniu po operacji. W osoczu oznaczano stężenie IL-6, IL-8 oraz TNF-α. W moczu oznaczano stężenie NGAL, KIM-1 oraz MMP-9. W badaniu obserwacyjnym obejmującym 48 uczestników oznaczano także stężenie tkankowego inhibitora metaloproteinazy 1 w moczu (ang. tissue inhibitor of metalloproteinase 1 - TIMP-1). W badaniu dotyczącym eksperymentalnej interwencji zwiększania rzutu pompy perfuzyjnej oznaczano dodatkowo stężenie reniny w osoczu przed operacją oraz 6 godzin po zakończeniu CPB. Krew pobierano z tętnicy promieniowej przy użyciu sterylnych pojemników S-Monovette 3,4 ml (K3 EDTA: 1,6 mg/1 ml krwi; SARSTEDT AG & Co. KG Sarstedtstrasse 1, 51588 Numbrecht, Niemcy). Mocz pobierano bezpośrednio z cewnika Foley'a przy użyciu standardowych niesterylnych pojemników na mocz. Po pobraniu próbki krwi i moczu przechowywano w temperaturze 5°C nie dłużej niż 4 godziny, a następnie odwirowano (4°C, 10 min, 4000 obr/min). Po odwirowaniu pobrano 1 ml supernatantu i przechowywano w temperaturze -70°C nie dłużej niż sześć miesięcy. Ilościową ocenę stężeń IL-6, IL-8 i TNF-α (w osoczu) oraz NGAL, KIM-1, IL-18 i MMP-9 (w moczu) u pacjentów włączonych do badania przeprowadzono przy użyciu preparatu Luminex Technologia xMAP (Luminex Corporation, Austin, Teksas, USA). Stężenie reniny w osoczu mierzono za pomocą standardowych zestawów ELISA (Demeditec Diagnostics GmbH, 24145 Kiel – Niemcy).

7.3. Analiza statystyczna

Analizę statystyczną wykonano przy pomocy programu Statistica 13 (StatSoft, Tulsa, OK, USA). Do porównania zmiennych jakościowych pomiędzy grupami wykorzystano dokładny test Fishera. Zastosowano następujące testy nieparametryczne: test Manna–Whitneya dla różnic między grupami oraz współczynnik korelacji rang Spearmana dla korelacji między parametrami. Do znalezienia niezależnych czynników predykcyjnych AKI z normalizującą transformacją logarytmiczną stężeń biomarkerów wykorzystano wielowymiarową regresję logistyczną. W celu oszacowania wartości diagnostycznej biomarkerów w odniesieniu do rokowania w AKI przeprowadzono analizę krzywej ROC. Sugerowane punkty odcięcia oparto na maksymalizacji wskaźnika Youdena. Za istotne statystycznie uznano powiązania z $p < 0.05$.

8. WYNIKI

(1) Częstość występowania CSA-AKI w badanej populacji wyniosła 32%. Bazując na kryteriach KDIGO, większość przypadków CSA-AKI (63%) rozpoznano 24 godziny po operacji.

(2) Odsetek pacjentów z CSA-AKI był wyższy wśród pacjentów starszych (M = 70 (67–79) lat vs 66 (61–70) lat w grupie kontrolnej, p = 0.013), z niższym przedoperacyjnym eGFR (M = 62 (53–75) ml/min/1.73 m2 vs 85 (78–93) ml/min/1.73 m2 w grupie kontrolnej, p < 0.001), obciążonych przewlekłą chorobą nerek (40% vs. 6.06% w grupie kontrolnej, p = 0.008) oraz u pacjentów z niższym przedoperacyjnym hematokrytem (M = 37.8 (35.5–40.6)% vs 40.9 (38.6–44.1)% w grupie kontrolnej, p = 0.002). Zaobserwowano także częstsze występowanie CSA-AKI wśród pacjentów poddanych śródoperacyjnej hemofiltracji (60 vs 27.3% w grupie kontrolnej); wynik nie był istotny statystycznie (p = 0.052).

(3) Pacjenci, u których po operacji doszło do rozwoju przewlekłej choroby nerek mieli niższy przedoperacyjny eGFR (M = 61 (55–68.5) ml/min/1.73 m2 vs 82 (68.5–91) ml/min/1.73 m2 w grupie kontrolnej, p = 0.035), większą średnią objętość hemofiltracji (M = 1500 (750–1750) ml vs 0 (0–900) ml w grupie kontrolnej, p = 0.039) oraz większy odsetek wody odebranej z objętości wewnątrznaczyniowej (M = 40.56 (17.05–51.92)% vs. 0 (0–16.62)% w grupie kontrolnej, p = 0.028).

(4) Wartość eGFR po 3 miesiącach od operacji wykazywała silną dodatnią korelację z przedoperacyjnym eGFR (R = 0.733, p < 0.001), a także z wartościami eGFR we wczesnym okresie pooperacyjnym (R: 0.737 - 0.820, p < 0.001). Podobną korelację zaobserwowano pomiędzy objętością diurezy śródoperacyjnej a eGFR po 3 miesiącach od operacji (R = 0.449, p = 0.002).

(5) Zaobserwowano istotną różnicę w stężeniu biomarkerów w 6. godzinie po zakończeniu CPB pomiędzy pacjentami z CSA-AKI oraz pacjentami bez CSA-AKI: IL-8 w surowicy (34.2 pg/ml vs 21.1 pg/ml w grupie bez CSA-AKI, p < 0.001), TNF-α w surowicy (8.7 pg/ml vs 6.0 pg/ml w grupie bez CSA-AKI, p < 0.001) oraz NGAL w moczu normalizowanego do wydalania kreatyniny (56.6 ng/mg vs 23.4 ng/mg w grupie bez CSA-AKI, p < 0.001). Indeks Youden'a: IL-8 (0.34), TNF-α (0.41), NGAL normalizowane do wydalania kreatyniny (0.34).

(6) Wystąpienie CSA-AKI zwiększało ryzyko wystąpienia lub progresji przewlekłej choroby nerek w okresie pooperacyjnym (17% pacjentów w grupie CSA-AKI vs 0% pacjentów w grupie bez CSA-AKI, p = 0.008).

(7) Utrzymywanie MAP > 90 mmHg w trakcie CPB nie wpłynęło na występowanie CSA-AKI po operacji kardiochirurgicznej (p = 0.929), natomiast wiązało się ze znacznie mniejszym wzrostem stężenia reniny w porównaniu do MAP < 70 mmHg (166.9% vs 364.3% w grupie MAP < 70 mmHg, p = 0.008) oraz uzyskaniem większej diurezy podczas CPB (4.97 ± 2.89 ml/kg/godz. vs 2.9 ± 1.78 ml/kg/godz. w grupie MAP < 70 mmHg, p = 0.006).

(8) Nie zaobserwowano istotnych różnic w częstości występowania powikłań neurologicznych pomiędzy pacjentami u których utrzymywano MAP > 90 mmHg w porównaniu do grupy MAP < 70 mmHg: pooperacyjny udar mózgu (0% vs 5% w grupie MAP < 70 mmHg, p = 0.171), pooperacyjny przemijający epizod niedokrwienny mózgu (0% vs 0% w grupie MAP < 70 mmHg, p = 1.000), delirium pooperacyjne (12% vs 32% w grupie MAP < 70 mmHg, p = 0.077).

(9) Bazując na danych z literatury do strategii nefroprotekcji w trakcie operacji kardiochirurgicznych należy zaliczyć: utrzymywanie iDO2 nie mniejszego niż 260-300 ml/min/m2 podczas CPB, utrzymywanie MAP nie mniejszego niż 70-90 mmHg w trakcie całej operacji, stosowanie noradrenaliny w celu przeciwdziałania wazoplegii związanej ze znieczuleniem ogólnym i CPB (preferencyjnie w dawkach < 0.1 μg/kg/min) oraz śródoperacyjne nawadnianie pacjenta w celu uzyskania diurezy nie mniejszej niż 4 ml/kg/godz w trakcie CPB.

9. WNIOSKI

Ostre uszkodzenie nerek związane z operacjami kardiochirurgicznymi stanowi istotny problem zdrowotny ze względu na znaczną (i wciąż rosnącą) populację pacjentów poddawanych tym operacjom. Wystąpienie tego powikłania zwiększa chorobowość i śmiertelność pacjentów w okresie pooperacyjnym, a także jest czynnikiem ryzyka wystąpienia przewlekłej choroby nerek. Zapobieganie występowaniu tego powikłania oraz jego wczesna diagnostyka i leczenie są niezbędne dla poprawy zdrowia pacjentów poddawanych operacjom kardiochirurgicznym.

Zwiększanie rzutu pompy perfuzyjnej w celu podniesienia MAP w trakcie CPB jest obiecującą strategią nefroprotekcji, która zmniejsza hipoperfuzję nerek oraz poprawia ich śródoperacyjną funkcję (zwiększona diureza). Poniższe badania wykazały, że strategia ta jest także bezpieczna dla centralnego układu nerwowego i nie zwiększa częstości występowania powikłań neurologicznych. Śródoperacyjna hemofiltracja powinna być prowadzona pod uważną kontrolą bilansu płynowego tak, aby zapobiec śródoperacyjnej hipowolemii, która może nasilać uszkodzenie nerek podczas operacji.

Specyficzne biomarkery uszkodzenia nerek są obiecującą alternatywą we wczesnej diagnostyce CSA-AKI. Ich kinetyka w ustroju jest korzystniejsza niż kinetyka kreatyniny, a czas potrzeby na osiągnięcie istotnego wzrostu stężenia dużo krótszy. Możliwość oznaczania niektórych z tych biomarkerów w moczu jest ich kolejną zaletą, która zmniejsza inwazyjność diagnostyki. Istnieje jednak potrzeba odpowiedniego wystandaryzowania tego narzędzia diagnostycznego zanim będzie ono mogło być wprowadzone do praktyki klinicznej.

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11. PUBLIKACJE STANOWIĄCE ROZPRAWĘ DOKTORSKĄ

Załącznik 1 - Assessment and Prognosis in CSA-AKI Using Novel Kidney Injury Biomarkers: A Prospective Observational Study. *Biology* 2021, *10*, 823.

biology

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Article

Assessment and Prognosis in CSA-AKI Using Novel Kidney Injury Biomarkers: A Prospective Observational Study

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Simple Summary: Cardiac surgery associated acute kidney injury is a common complication of cardiac surgeries that worsens postoperative outcomes and the patient's prognosis. One of the main problems concerning this complication is its early diagnostics. In this study, the authors attempt to provide new data regarding the usage of novel kidney injury biomarkers in early detection of acute kidney injury and in the prognosis of the long-term postoperative kidney function. Perioperative factors that may influence kidney function were also analysed. It was concluded that biomarkers such as IL-6, IL-8, TNF-α, MMP-9 and NGAL are reliable acute kidney injury indicators. It was also demonstrated that intraoperative hypoperfusion secondary to hypovolemia is a main factor that damages the kidneys during cardiac surgeries. The authors hope that these findings will contribute to the development of new diagnostic protocols for acute kidney injury, which would involve novel renal biomarkers, thus enabling quicker diagnosis and more effective treatment of acute kidney injury.

Abstract: Background: There is a need for early diagnostic solutions for cardiac surgery associated acute kidney injury (CSA-AKI) as serum creatinine changes do not occur dynamically enough. Moreover, new approaches are needed for kidney protective strategy in patients undergoing cardiac surgery procedures; Methods: Samples of serum and urine were taken from the selected group of patients undergoing elective cardiac surgery procedures. The aim of this study was to assess the utility of specific inflammation and kidney injury biomarkers in the early diagnostic of CSA-AKI and in the prognosis of long-term postoperative kidney function; Results: At 6 h after weaning from cardiopulmonary bypass, there were significant differences in IL-6, IL-8, TNF-α, MMP-9 and NGAL concentrations in patients with CSA-AKI, compared to the control group. Serum IL-8 and urine NGAL 6 h after weaning from CPB proved to be independent acute kidney injury predictors. The TNF-α, MMP-9, IL-18, TIMP-1 and MMP-9/TIMP-1 ratio in the early postoperative period correlated with long-term kidney function impairment; Conclusions: Novel kidney injury biomarkers are an eligible tool for early diagnosis of CSA-AKI. They are also reliable indicators of long-term postoperative kidney function impairment risk after cardiac surgery procedures.

Keywords: CSA-AKI; novel kidney injury biomarkers; cardiac surgery; cardiopulmonary bypass; intraoperative hemofiltration

Citation: Udzik, J.; Waszczyk, A.; Safranow, K.; Biskupski, A.; Majer, K.; Kwiatkowski, S.; Kwiatkowska, E. Assessment and Prognosis in CSA-AKI Using Novel Kidney Injury Biomarkers: A Prospective Observational Study. *Biology* **2021**, *10*, 823. https://doi.org/10.3390/biology10090823

Academic Editors: Pasquale Pagliaro and Andrés Moya

Received: 14 July 2021
Accepted: 18 August 2021
Published: 24 August 2021

1. Introduction

Cardiac surgery procedures are related to a high incidence of nephrological complications. These complications concern 5–30% of patients who undergo heart surgery, increasing mortality in this group of patients even up to 80% [1]. The use of cardiopulmonary bypass (CPB) is a factor that most probably contributes to postoperative kidney function impairment, but its role in the development of cardiac surgery associated acute kidney injury (CSA-AKI) is still unclear [2]. CPB may cause kidney damage in three main mechanisms: microcirculation disruption, systemic inflammatory response and increased oxidative stress [3]. Proinflammatory cytokines play a considerable role in these mechanisms of kidney damage. Propagation of the immune response takes place while blood leukocytes make contact with the artificial surface of the CPB tubing system-role of interleukin 6 (IL-6), interleukin 8 (IL-8) and tumor necrosis factor alpha (TNF-α). Both enhanced immune response and increased oxidative stress (secondary to extracorporeal oxygenation) intensify microcirculation disruptions in the renal tubules arterioles, leading to ischemia within these structures.

eGFR, which derives from serum creatinine concentration (S_{Cr}), is a classical parameter used for kidney function monitoring. It is, however, an indirect indicator of kidney damage which demonstrates only the loss of function. AKI biomarkers such as kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and interleukin 18 (IL-18) are direct and far more specific indicators of kidney damage. Many scientific reports were published that state their usefulness in the diagnostic of AKI, including CSA-AKI [4–6].

Both NGAL and KIM-1 are highly specific kidney injury biomarkers, which are produced by the structures of the nephron in response to its damage [7,8]. NGAL appears in urine after 3 h from kidney injury, peaks at 6 h and maintains elevated for a longer time period stimulating tissue regeneration [6]. According to some authors, persistently elevated urine NGAL is an independent risk factor for chronic kidney disease (CKD) development [9]. KIM-1 appears in urine several h after a damage to the nephron structures, and in 2–6 h after weaning from CPB, it has 90% sensitivity in detecting CSA-AKI [10]. Urine KIM-1 peaks at 48–72 h after the injury [5], and it stays elevated until proximal tubules are completely regenerated. Similarly to NGAL, it has a protective effect on kidney cells by enhancing their regeneration. Persistent urine KIM-1 elevation is also a risk factor for CKD [11].

Urine IL-18 increases 4–6 h after a cardiac surgery procedure with the use of CPB, peaks at 12 h and normalizes in 48 h [12,13]. A meta-analysis of the previously conducted research showed that it has 58% sensitivity and 75% specifity in detecting CSA-AKI [14].

Moreover, cytokines such as IL-6, IL-8, TNF-α, matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of metalloproteinase 1 (TIMP-1) are used for inflammatory response and organ damage assessment, including AKI [15–18]. IL-6 and IL-8 are both sensitive biomarkers of inflammatory processes. Their serum concentrations elevate significantly in patients with CSA-AKI as early as 2–12 h after weaning from CPB. Monitoring the increase in serum IL-6 and IL-8 in critically ill patients with AKI is important, because it is related to higher mortality risk during hospitalization [19].

TNF-α plays a major role in the pathophysiology of ischemia-reperfusion injury—IRI, which is one of the basic mechanisms underlying AKI [20]. For this reason, it is used in scientific studies to diagnose CSA-AKI. Its serum concentration is significantly higher 6 h after the operation in patients with AKI compared to the control group [21].

MMP-9 and its tissue inhibitor TIMP-1 play a key role in extracellular matrix (ECM) remodeling, including remodeling secondary to injury. Of diagnostic significance are not only MMP-9 and TIMP-1 concentrations, but also their mutual relation—MMP-9/TIMP-1 ratio [16,18]. Elevated MMP-9 serum concentration can be observed as early as several h after the damaging factor appears, whereas TIMP-1 serum concentration peaks at 24–48 h after the injury [22]. Serum concentrations of MMP-9 and TIMP-1 correspond well with their urine concentration, even in case of impaired kidney function [23,24].

Intraoperative hemofiltration is a procedure mainly used to remove water from the vascular bed in case of excessive hemodilution associated with CPB. Some researchers have also found that intraoperative hemofiltration can reduce serum proinflammatory cytokines concentration [25,26]. In the current study, authors decided to investigate this lead further and see if the use of hemofiltration can result in lower postoperative cytokines concentration and better outcomes of the procedure.

AKI is a serious clinical condition, and the time to make a diagnosis is vital in terms of treatment results [27]. Three basic scales are used to diagnose AKI—Table 1.

Table 1. AKI diagnostic criteria according to KDIGO, AKIN and RIFLE scales.

	KDIGO	AKIN	RIFLE
S_{Cr}	$\uparrow S_{Cr} \geq 0.3$ mg/dL in 48 h or $\uparrow S_{Cr} \geq 50\%$ in 7 days	$\uparrow S_{Cr} \geq 0.3$ mg/dL or $\uparrow S_{Cr} \geq 50\%$ in 48 h	$\uparrow S_{Cr} \geq 50\%$ in 7 days
Diuresis	<0.5 mL/kg/h for at least 6 h		

Legend: AKIN—AKIN kidney injury scale, KDIGO—KDIGO kidney injury scale, RIFLE—RIFLE kidney injury scale, S_{Cr}—serum creatinine concentration; ↑—increase.

Demonstrated criteria of AKI diagnosis are based on a serum creatinine increase and diuresis, which are both indirect kidney damage indicators. Serum creatinine concentration after a cardiac surgery procedure with the use of CPB may be inadequately low due to high fluids administration or intraoperative hemofiltration. Decreased diuresis may also result from intraoperative hemofiltration or from prerenal causes such as low cardiac output syndrome (LCOS) which is a frequent complication of heart surgeries [28], but does not necessarily lead to AKI.

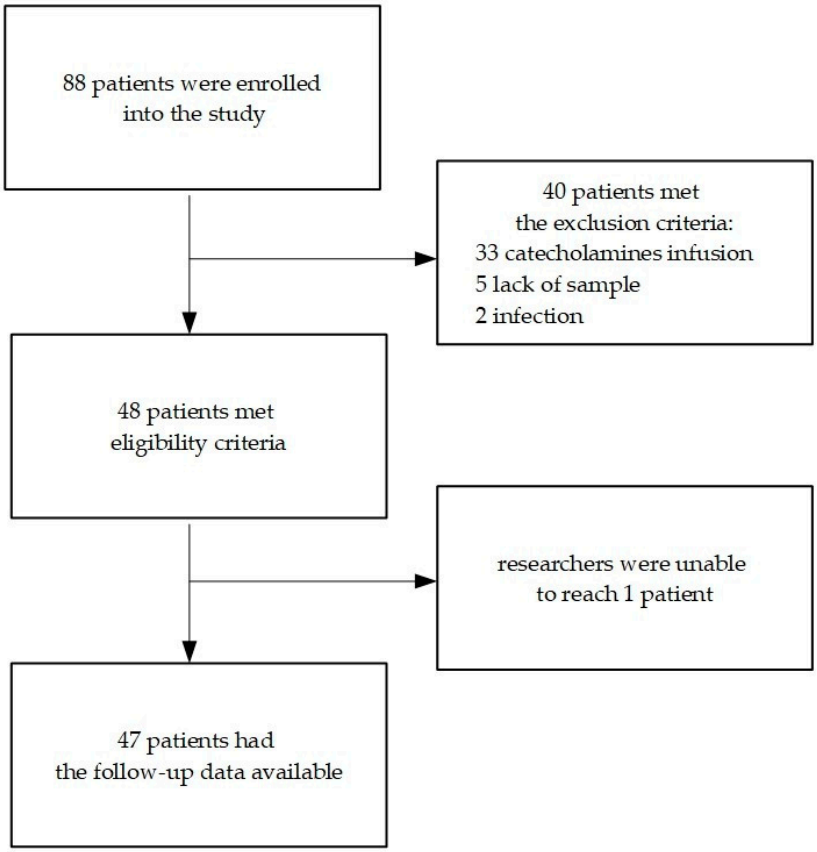
Regarding the above, using serum creatinine concentration and diuresis for detecting CSA-AKI may extend the time to make this diagnosis and apply suitable treatment. CSA-AKI is a specific type of AKI, as the physician knows exactly when it may occur. The problem lies in early identification of patients in whom the surgery was complicated by AKI. For this reason, the aim of this study was to assess the utility of specific inflammation and kidney injury biomarkers (IL-6, IL-8, TNF-α, NGAL, KIM-1, IL-18, MMP-9 and TIMP-1) in the early diagnostic of CSA-AKI and in the prognosis of long-term postoperative kidney function. The assessment also included perioperative factors that might influence postoperative kidney function.

2. Materials and Methods

A total of 88 patients in the cardiac surgery clinic (31 women and 57 men) who qualified for an elective cardiac surgery procedure with the use of CPB were initially enrolled into the study. Patients' medical history, laboratory results and postoperative outcomes were analysed. A total of 48 patients (18 women and 30 men) were eventually included in the study—Scheme 1.

The most frequent reason for a patient's exclusion proved to be prolonged catecholamines infusion (33 patients—82.5% of excluded group). Less frequent reasons included a lack of sample on the 5th day after the operation (5 patients—12.5% of excluded group) and early postoperative infection (2 patients—5% of the excluded group; one patient developed postoperative pneumonia, and the other had postoperative wound infection). Follow-up data were obtained from 47 patients (compliance rate was 97.92%).

Samples of blood and urine were taken at the designated time points (Table 2). Preoperative samples were collected in the operating room directly after the induction of general anesthesia. Should the patients require continuous renal replacement therapy (CRRT) after the operation, an additional blood sample was to be taken 6 h after the end of treatment (S2). Eventually, none of the patients from this study population required renal replacement therapy after the operation; thus, the "S2" blood sample was not taken from any patient.



Scheme 1. Patients enrollment into the study.

Table 2. Types of material collected from the patients and selected biomarkers of renal injury identified in them at the designated time points.

Collected Material	Time of Collection	Biomarkers Identified in the Material
serum	preoperatively(S0) 6 h after weaning from CPB (S1) 6 h after finishing CRRT (S2)	IL-6, IL-8, TNF-α
urine	preoperatively (U0)	KIM-1, NGAL, IL-18, MMP-9, TIMP-1
	6 h after weaning from CPB (U1)	KIM-1, NGAL, IL-18, MMP-9
	24 h after the operation (U2)	
	48 h after the operation (U3)	KIM-1, NGAL, IL-18, MMP-9, TIMP-1
	5 days after the operation (U4)	KIM-1, NGAL, IL-18, MMP-9

Legend: CPB—cardiopulmonary bypass, CRRT—continuous renal replacement therapy, IL-6—interleukin 6, IL-8-interleukin 8, IL—18-interleukin 18, KIM-1—kidney injury molecule 1, MMP-9—urine matrix metalloproteinase 9, NGAL—neutrophil gelatinase-associated lipocalin, TIMP-1—tissue inhibitor of metalloproteinase 1.

Blood was collected using S-Monovette 3.4 mL sterile containers (K3 EDTA: 1.6 mg/1 mL of blood; SARSTEDT AG & Co. KG Sarstedtstrasse 1, 51588 Nümbrecht, Germany). Urine was collected using standard non-sterile urine containers. After the collection, samples were stored at 5 °C for no longer than 4 h and subsequently centrifuged (4 °C, 10 min, 4000 RPM). After centrifugation, 1 mL of supernatant was taken and stored at −70 °C.

In patients eventually included in the study, long-term postoperative kidney function was assessed after no less than 3 months from the date of the operation, with accordance to KDIGO guidelines [29]. For this purpose, serum creatinine concentration was measured, and the estimated glomerular filtration rate (eGFR) was subsequently calculated using

both CKD-EPI and MDRD formulas for each patient. Preoperative eGFR and eGFR in the early postoperative period were calculated using the CKD-EPI formula.

Inclusion criteria:

- obtaining a written consent for study enrollment
- qualification for elective cardiac surgery procedure with the use of CPB, age > 18 years.

Exclusion criteria:

- CKD stage V according to KDIGO (eGFR < 15 mL/min/1.73 m^2)
- taking nephrotoxic medications before the operation (including loop diuretics)
- degenerative changes in renal arteries in medical history
- active neoplasm disease
- catecholamines administration longer than 3 h after the procedure or new catecholamines administration after more than 3 h after the procedure
- postoperative infection (up to 7 days after the procedure)
- cardiac arrest in the postoperative period
- early decease (up to 7 days after the procedure)
- lack of any of the samples from Table 2

In order to adjust the hemofiltration volume for patient's sex and body mass, a percentage of taken total body water (TBW) was calculated for each patient who underwent intraoperative hemofiltration (based on the publication by Chumlea et al. [30]). The percentage of water taken from the intravascular space was also calculated for these patients (based on the publication by Feldschuh et al. [31]). Formulas are depicted in Scheme 2.

Fraction of Taken TBW = $V_{HEMOFILTRATION}$ [mL]/Body Mass [kg] × % H_2O *			**Fraction of Taken Intravascular Volume = $V_{HEMOFILTRATION}$ [mL]/Body Mass [kg] × $V_{INTRAVASCULAR}$ [mL/kg]**	
Sex	**Age [Years]**	**% H_2O * [%]**	**Sex**	**$V_{INTRAVASCULAR}$ [mL/kg]**
Female	50–59	42.7	Female	55
	>60	43		
Male	50–59	51	Male	73
	>60	46		

Scheme 2. Formulas used to calculate fraction of taken TBW and intravascular volume. Legend: TBW—total body water [mL], $V_{HEMOFILTRATION}$—hemofiltration volume [mL], $V_{INTRAVASCULAR}$—intravascular volume [mL/kg].

Intraoperative hematocrit level was measured 10–15 min after the initiation of CPB ($Ht_{CPB}1$) and subsequently every 30 min during the whole CPB procedure ($Ht_{CPB}2$ etc.). Intraoperative hemofiltration was initiated basing on a decision of the operating team (cardiac surgeon, anesthesiologist, perfusionist) with regard to the patient's condition and CPB parameters. Main reasons for implementing this procedure were hematocrit level < 22% and intraoperative anuria.

Postoperative creatine kinase MB isoenzyme (CK-MB) was measured in the 6th, 9th and 12th h after the operation. Postoperative creatinine and C-reactive protein (CRP) concentrations were measured on the 1st day after the operation and subsequently every 48 h for the next 5 days (in some patients, measurements were also taken on the 7th day). During the first 24 h after the operation, diuresis was measured every 2 h.

Patients were monitored for AKI development for 5 consecutive days after the operation. The KDIGO scale was assumed as a referential scale for diagnosing AKI. The simultaneous assessment of kidney function was performed using RIFLE and AKIN criteria.

In patients included in the study, a total dose of catecholamines was noted, including both intraoperative and postoperative catecholamines administration. The dose was then adjusted for patient's body mass (mg/kg of body mass).

The study population was divided into study and control groups based on the following end points: AKI development during the first 5 days after the operation according to KDIGO criteria, long-term postoperative kidney function impairment (defined as eGFR decline after ≥3 months after the operation < 60 mL/min/1.73 m^2 in patients with preoperative eGFR > 60 mL/min/1.73 m^2 or eGFR decline in patients with preoperative eGFR < 60 mL/min/1.73 m^2 that qualifies them into the next CKD stage) and undergoing intraoperative hemofiltration.

Quantitative measurements of serum IL-6, IL-8 and TNF-α and urine NGAL, KIM-1, IL-18 and MMP-9 in patients included in the study were performed using the Luminex technology. The method involved magnetic microspheres with a solid phase for antibodies or antigens immobilized on their surface. A 2-fold dilution was applied to urine samples, whereas serum samples were not diluted. Commercial Luminex Human Discovery Assays (R&D Systems, Minneapolis, MN, USA) were used to measure IL-6, IL-8, TNF-α, NGAL, KIM-1, IL-18 and MMP-9 concentrations. The quantification procedure was performed according to manufacturer's instruction using Luminex 200 device (Luminex Corporation, Austin, TX, USA). Reagents' concentrations were calculated using a standard 6-points curve.

Total urine concentrations of TIMP-1 were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (Quantikene; R&D Systems, Inc., Minneapolis, MN, USA), performed according to manufacturer's instructions.

Most of the quantitative data in this study had distributions considerably different from the normal distribution (Shapiro–Wilk test). Hence, non-parametric tests were applied to analyze that data while median and quartiles were used for descriptive statistics: M, (Q1–Q3). The U Mann–Whitney test was used to compare data between the groups, and the assessment of changes' significance was performed using Friedman's ANOVA test and Wilcoxon signed-rank test. Correlations between the variables were analyzed using the Spearman rank correlation coefficient (Rs). Qualitative data were compared between the groups using a chi-square test or Fisher's exact test for 2 × 2 tables. In order to determine independent AKI predictors, multiple logistic regression analysis was performed. A statistical significance level of $p < 0.05$ was assumed. Statistical analysis was conducted using licensed Statistica 13.6.0 software (StatSoft, Inc., Tulsa, OK, USA).

The dataset generated for this study is available as Supplementary Material—Table S1.

3. Results

Mean time from the operation to the control creatinine measurement was 34 ± 14 weeks, and the median was 37 weeks; the shortest follow-up time was 13 weeks, and the longest was 66 weeks. Baseline characteristics and operation-related data of all patients initially enrolled into the study are presented in Table 3. Data of patients eventually included in the study and the excluded ones were compared. Aside from the presence of exclusion criteria, there were no significant differences between the groups.

Table 3. Baseline characteristics and operation-related data of all patients initially enrolled into the study (n = 88).

Quality	Included (n = 48)	Excluded (n = 40)	p-Value
Age M, (Q1–Q3) [years]	67.5, (63–71)	70, (65–73)	0.352
Sex (n,%)	Female–18, 37.5	Female–13, 32.5	0.66
	Male–30, 62.5	Male–27, 67.5	
BMI M, (Q1–Q3) [kg/m^2]	28.36, (26–31.10)	28.66, (24.95–31.63)	0.845
ESL M, (Q1–Q3) [%]	3.20, (2.16–5.1)	3.23, (2.71–6.01)	0.291

Table 3. *Cont.*

Quality		Included (*n* = 48)	Excluded (*n* = 40)	*p*-Value
CAD (*n*,%)		I–2, 5.13	I–1, 3.45	0.557
		II–19, 48.72	II–11, 37.93	
		III–15, 38.46	III–16, 55.17	
		IV–3, 7.7	IV–1, 3.45	
HA (*n*,%)		38, 79.2	28, 70	0.337
DM (*n*,%)		12, 25	11, 27.5	0.812
HbA1C M, (Q1–Q3) [%]		5.75 (5.5–6.3)	5.9 (5.7–6.2)	0.214
Dyslipidemia (*n*,%)		12, 25	9, 22.5	0.808
CKD (*n*,%)		3a stage–5, 10.42	3a stage–4, 10	0.965
		3b stage–3, 6.25	3b stage–2, 5	
S_{Cr} 0 M, (Q1–Q3) [mg/dL]		0.91, (0.80–1.03)	0.90, (0,77–1.07)	0.655
eGFR 0 M, (Q1–Q3) [mL/min/1.73 m^2]		80.5, (64.5–90.75)	82.5, (68–92)	0.643
Hematocrit 0 M, (Q1–Q3) [%]		40.3, (37.83–43.68)	41.4, (38.9–45)	0.144
CRP 0 M, (Q1–Q3) [mg/L]		1.15, (0.56–2.32)	1.35, (0.42–3.25)	0.783
CK-MB 0 M, (Q1–Q3) [IU/L]		17 (14.25–21)	16, (14–21)	0.478
IL-6 0 M, (Q1–Q3) [ng/mL]		1.66, (1.27–1.97)	X	X
IL-8 0 M, (Q1–Q3) [ng/mL]		4.39, (2.61–6.2)	X	X
TNF-α 0 M, (Q1–Q3) [ng/mL]		2.20, (1.73–3.26)	X	X
NGAL 0 M, (Q1–Q3) [ng/mL]		4512.06, (2875.93–9867.93)	X	X
KIM-1 0 M, (Q1–Q3) [ng/mL]		336.81, (122.49–992.37)	X	X
IL-18 0 M, (Q1–Q3) [ng/mL]		25.06, (18.09–36.48)	X	X
MMP-9 0 M, (Q1–Q3) [ng/mL]		135.28, (50.70–747.43)	X	X
TIMP-1 0 M, (Q1–Q3) [ng/mL]		1.01, (0.57–2.61)	X	X
MMP-9 / TIMP-1 ratio 0 M, (Q1–Q3)		150.73, (51.48–789.38)	X	X
CABG (*n*,%)		20, 41.67	23, 57.5	0.199
Valvular (*n*,%)		14, 29.17	8, 20	0.459
CABG + valvular (*n*,%)		6, 12.5	5, 12.5	1.0
Complex procedures (*n*,%)		8, 16.67	4, 10	0.535
CPB time M, (Q1–Q3) [min]		82, (67.5–105)	68, (54–110)	0.192
Aortic cross-clamp time M, (Q1–Q3) [min]		57.5, (34.75–78.75)	45, (31–65)	0.245
Exclusion criterion (*n*,%)	Catecholamines infusion	0, 0.0	33, 82.5	<0.001
	Lack of sample	0, 0.0	5, 12.5	0.024
	Infection	0, 0.0	2, 5	0.215
30-days mortality (*n*,%)		0, 0.0	1, 2.5	0.461

Legend: BMI—body mass index [kg/m^2], CABG—coronary artery bypassing graft, CAD—coronary artery disease, CKD—chronic kidney disease, CK-MB 0—initial serum creatine kinase MB isoenzyme concentration [IU/L]; CPB time—cardiopulmonary bypass time [min], CRP 0—initial serum C-reactive protein concentration [mg/L], DM—diabetes mellitus, eGFR 0—initial estimated glomerular filtration rate [mL/min/1.73 m^2], ESL—EuroSCORE Logistic [%], HA—hypertonia arterialis, HbA1C—glycated hemoglobin percentage [%], Hematocrit 0—initial hematocrit concentration [%], IL-6 0—initial serum interleukin 6 concentration [ng/mL], IL-8 0—initial serum interleukin 8 concentration [ng/mL], IL-18 0—initial urine interleukin 18 concentration [ng/mL], KIM-1 0—initial urine kidney injury molecule 1 concentration [ng/mL], M—median, MMP-9 0—initial urine matrix metalloproteinase 9 concentration [ng/mL], NGAL 0—initial urine neutrophil gelatinase-associated lipocalin concentration [ng/mL], S_{Cr} 0—initial serum creatinine concentration [mg/dL], TIMP-1 0—initial urine tissue inhibitor of metalloproteinase 1 concentration [ng/mL], TNF-α 0—initial serum tumor necrosis factor α concentration [ng/mL], X—given biomarker concentration/*p*-value were not available.

3.1. AKI vs. no-AKI

CSA-AKI developed in 15 patients (eight women and seven men), which accounts for 31.25% of the study population. AKI was most frequently diagnosed on the 1st day after the operation (66.67%), and the latest diagnosis was made on the 3rd postoperative day (13.33%). Patients who developed postoperative AKI were older (M = 70 (67–79) years vs. 66 (61–70) years in the control group, $p = 0.013$), had worse preoperative kidney function (creatinine concentration: M = 1.03 (0.9–1.28) mg/dL vs. 0.88 (0.78–0.99) mg/dL in the control group, $p = 0.012$; eGFR value: M = 62 (53–75) mL/min/1.73 m^2 vs. 85 (78–93) mL/min/1.73 m^2 in the control group, $p < 0.001$), higher preoperative CKD incidence (40% vs. 6.06% in the control group, $p = 0.008$) and lower preoperative hematocrit (M = 37.8 (35.5–40.6)% vs. 40.9 (38.6–44.1)% in the control group, $p = 0.002$). There were no significant differences in arterial hypertension, diabetes or dyslipidemia incidence between the groups.

Regarding intraoperative features: patients with AKI were administered a higher amount of intravenous fluids during the operation (M = 3500 (2800–3850) mL vs. 2800 (2400–3300) mL in the control group, $p = 0.016$), had lower intraoperative diuresis (M = 800 (300–1500) mL vs. 1600 (1200–1900) mL in the control group, $p = 0.006$), and as a result higher fluid balance from the time of the operation (M = 700 (300–1200) mL vs. −100 (–400–500) mL in the control group, $p < 0.001$). These patients also had a lower hematocrit level during CPB ($Ht_{CPB}1$: M = 20 (19–22)% vs. 23 (19–25)% in the control group, $p = 0.012$; $Ht_{CPB}2$: M = 23.5 (21–27)% vs. 27.5 (25.5–29.5)% in the control group, $p = 0.004$) and a higher percentage of patients undergoing coronary artery bypassing graft (CABG) combined with the valvular procedure (CABG + valvular: 33.33% vs. 3.03% in the control group, $p = 0.008$), although there were no significant differences in aortic cross-clamp time or CPB duration time ($p = 1.000$ in both cases).

Patients with AKI had lower diuresis during the first 2 h after the procedure (M = 300 (200–800) mL vs. 800 (400–1000) mL in the control group, $p = 0.040$).

Biomarkers' concentrations in the AKI group (Figure 1) were as follows: higher preoperative serum TNF-α (M = 2.7 (2.42–4.22) ng/mL vs. 2.13 (1.59–2.7) ng/mL in the control group, $p = 0.012$) and lower preoperative urine IL-18 (M = 19.93 (9.88–25.06) ng/mL vs. 31.05 (23.52–37.62) ng/mL in the control group, $p = 0.009$). At 6 h after weaning from CPB, patients with AKI had higher serum IL-6 (M = 128.58 (95.53–255.2) ng/mL vs. 86.62 (57.36–115.84) ng/mL in the control group, $p = 0.005$), IL-8 (M = 31.02 (17.89–41.66) ng/mL vs. 12.09 (8.74–22.27) ng/mL in the control group, $p = 0.016$) and TNF-α (M = 6.43 (4.5–7.08) ng/mL vs. 3.9 (2.7–4.52) ng/mL in the control group, $p = 0.002$). Urine concentrations of NGAL and MMP-9 were also significantly higher in these patients (NGAL: M = 13231.76 (4914.81–34148.3) ng/mL vs. 4261.32 (2868.19–9138.28) ng/mL in the control group, $p = 0.013$; MMP-9: M = 9661.94 (1485.62–14,451.8) ng/mL vs. 3499.39 (1274.58–8656) ng/mL in the control group, $p = 0.044$). Absolute urine IL-18 concentration 6 h after weaning from CPB did not differ significantly between the groups ($p = 0.597$), but in patients with AKI, there was a significant increase in urine IL-18 compared to the initial value (M = 122.02 (100–204.21)% vs. 89.8 (77.97–112.53)% in the control group, $p = 0.002$). Urine TIMP-1 concentration 48 h after the operation was significantly lower in patients with AKI, regarding both the absolute values (M = 1.61 (0.55–2.26) ng/mL vs. 3.3 (1.68–5.92) ng/mL in the control group, $p = 0.007$) and the percentage of increase from the initial value (M = 145.05 (64.91–211.91)% vs. 268.81 (111.43–733.73)% in the control group, $p = 0.030$).

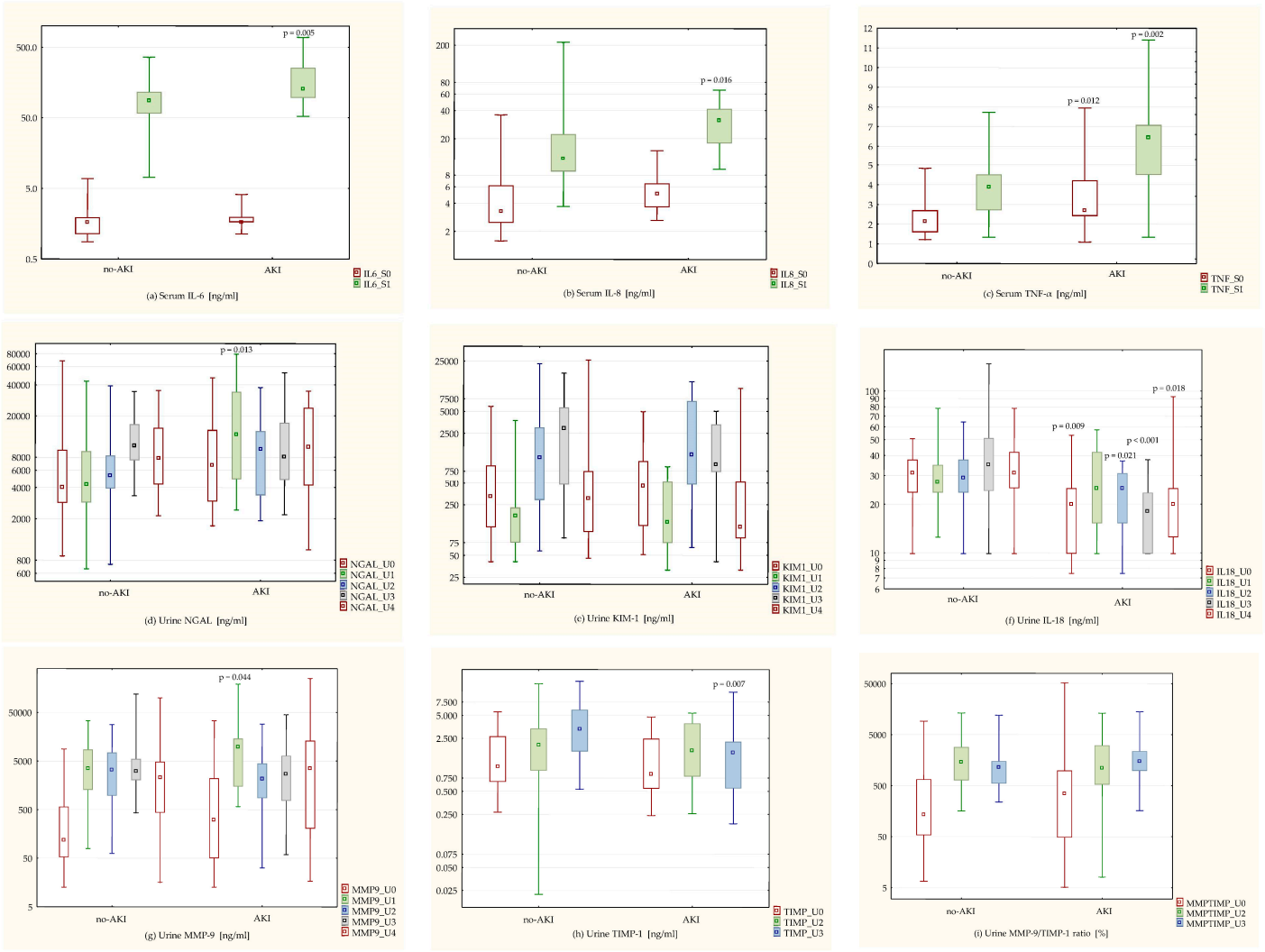


Figure 1. Biomarkers' concentrations (**a**–**i**) at the designated time points in patients without AKI vs. with AKI. Sampling time descriptors in the legend (S0, S1, U0–U4) are consistent with the time points mentioned in Table 2. Dots on the chart represent the median value; boxes represent values between the 1st and 3rd quartile (Q1–Q3), and whiskers represent the extreme values. For values that differed significantly between the study and control group ($p < 0.05$), p-values are written above the upper whisker in the AKI group.

Nine patients in the AKI group underwent intraoperative hemofiltration (60% of the AKI group) vs. nine patients who underwent intraoperative hemofiltration in the no-AKI group (27.27%). The difference, however, was not statistically significant ($p = 0.052$).

Comparing to KDIGO criteria, the RIFLE scale demonstrated 53.33% sensitivity and 100% specificity in diagnosing AKI. The AKIN scale had 100% sensitivity and 100% specificity in diagnosing AKI when compared to KDIGO criteria.

The diuresis criterion (<0.5 mL/kg/h for at least 6 h) allowed the diagnosis of AKI in one patient in the 22nd hour after the operation (6.67% of patients with CSA-AKI).

Multiple logistic regression analysis adjusted for patients' age proved that the best independent predictors of CSA-AKI are: intraoperative diuresis (OR = 0.047, CI: 0.005–0.451 over 1000 mL, $p = 0.006$), IL-8 6 h after weaning from CPB (OR = 11.991, CI: 1.549–92.830 over 1 ng/mL, $p = 0.014$) and NGAL 6 h after weaning from CPB (OR = 3.434, CI: 1.180–9.991 over 1 ng/mL, $p = 0.020$).

3.2. Long-Term Postoperative Kidney Function Impairment vs. Unchanged Long-Term Postoperative Kidney Function

In the long-term observation (≥3 months after the procedure), kidney function impairment was observed in four patients (three women and one man), which accounts for 8.33% of the study population. Three patients developed CKD (two patients in KDIGO stage 3a and one patient in KDIGO stage 3b) subsequently to developing postoperative AKI. In one patient who did not suffer from CSA-AKI, progression of a preoperative CKD was observed (from KDIGO 3a stage to KDIGO 3b stage).

Patients in whom long-term postoperative kidney function impairment was observed had lower preoperative eGFR (M = 61 (55–68.5) mL/min/1.73 m^2 vs. 82 (68.5–91) mL/min/1.73 m^2 in the control group, $p = 0.035$), higher mean hemofiltration volume (M = 1500 (750–1750) mL vs. 0 (0–900) mL in the control group, $p = 0.039$), higher percentage of taken TBW (M = 5.2 (3–6.64)% vs. 0 (0–2.71)% in the control group, $p = 0.028$), higher percentage of water taken from the intravascular volume (M = 40.56 (17.05–51.92)% vs. 0 (0–16.62)% in the control group, $p = 0.028$) and lower diuresis between 2nd and 4th hour after the procedure (M = 150 (75–200) mL vs. 400 (200–800) mL in the control group, $p = 0.009$).

Patients with long-term postoperative kidney function impairment did not differ significantly from the patients in a control group in terms of arterial hypertension, diabetes, dyslipidemia and preoperative CKD incidence. There was also no difference between the types of procedures performed in both groups.

Intraoperative hemofiltration was used in three patients with long-term postoperative kidney function impairment (75% of the group), compared to 15 patients in whom long-term postoperative kidney function did not change (34.09% of the group). The difference was not statistically significant ($p = 0.142$).

There was a strong correlation between preoperative kidney function and kidney function in a long-term observation. A similar correlation was observed between early postoperative kidney function and long-term kidney function—Table 4.

Table 4. Relationship between perioperative and long-term kidney function. Spearman rank correlation coefficients are presented together with statistical significance.

	S_{Cr} after 3 Months r (*p*–Value)	eGFR by CKD-EPI after 3 Months r (*p*–Value)	eGFR by MDRD after 3 Months r (*p*–Value)
S_{Cr} 0	0.694 *	−0.556 *	−0.569 *
eGFR 0	−0.480 *	0.773 *	0.718 *
S_{Cr} 1	0.652 *	−0.661 *	−0.686 *
eGFR 1	−0.499 *	0.745 *	0.714 *
S_{Cr} 2	0.633 *	−0.607 *	−0.586 *
eGFR 2	−0.478 *	0.737 *	0.652 *
S_{Cr} 3	0.673 *	−0.569 *	−0.546 *
eGFR 3	−0.505 *	0.745 *	0.653 *
S_{Cr} 4	0.742 *	−0.628 *	−0.631 *
eGFR 4	−0.669 *	0.820 *	0.724 *
Intraoperative diuresis	−0.393 ($p = 0.006$)	0.449 ($p = 0.002$)	0.423 ($p = 0.003$)

Legend: eGFR—estimated glomerular filtration rate [mL/min/1.73 m^2], r-Spearman rank correlation coefficient, S_{Cr}—serum creatinine concentration [mg/dL]; 0—initial level, 1—level from first 24 h after the operation, 2—level from the 3rd day after the operation, 3—level from the 5th day after the operation, 4—level from the 7th day after the operation; * *p*-value < 0.001.

There was a negative correlation between serum TNF-α concentration and eGFR value after ≥3 months from the operation (TNF-α & eGFR by CKD-EPI: r = −0.431, $p = 0.002$; TNF-α & eGFR by MDRD: r = −0.361, $p = 0.013$), whereas for serum TNF-α concentration

6 h after weaning from CPB, a significant correlation was only with eGFR by CKD-EPI after ≥3 months (r = −0.372, $p = 0.01$).

Urine IL-18 concentration 6 h after weaning from CPB correlated negatively with the eGFR value after ≥3 months from the operation (eGFR by CKD-EPI: r = −0.293, $p = 0.045$; eGFR by MDRD: r = −0.288, $p = 0.049$).

There was a negative correlation between urine MMP-9 concentration 6 h after weaning from CPB and postoperative kidney function after ≥3 months from the operation (MMP-9 & S_{Cr}: r = 0.418, $p = 0.003$; MMP-9 & eGFR by CKD-EPI: r = −0.371, $p = 0.010$; MMP-9 & eGFR by MDRD: r = −0.301, $p = 0.040$). There was a similar correlation between urine MMP-9 concentration on the 5th day after the operation and the eGFR value after ≥3 months from the operation (MMP-9 & eGFR by CKD-EPI: r = −0.368, $p = 0.011$; MMP-9 & eGFR by MDRD: r = −0.342, $p = 0.019$).

A positive correlation was observed between urine TIMP-1 concentration 48 h after the operation and the eGFR value after ≥3 months from the operation (TIMP-1 & eGFR by CKD-EPI: r = 0.296, $p = 0.043$; TIMP-1 & eGFR by MDRD: r = 0.320, $p = 0.028$). Analogically, there was a negative correlation between the MMP-9/TIMP-1 ratio 48 h after the operation and postoperative kidney function after ≥3 months from the operation (ratio & S_{Cr}: r = 0.372, $p = 0.010$; ratio & eGFR by CKD-EPI: r = −0.394, p =0.006; ratio & eGFR by MDRD: r = −0.365, $p = 0.012$).

3.3. Patients Who Developed CSA-AKI and Had Impaired Long-Term Kidney Function vs. Patients Who Developed CSA-AKI and Had Unchanged Long-Term Kidney Function

A total of 12 out of 15 patients (five women and seven men) who developed postoperative AKI made a complete recovery of kidney function after ≥3 months from the operation (follow-up eGFR > 60 mL/min/1.73 m^2). In three female patients, long-term postoperative kidney function impairment occurred, in the form of newly diagnosed CKD.

Patients with long-term postoperative kidney function impairment after ≥3 months from the operation had higher mean hemofiltration volume (M = 1500 (1500–2000) mL vs. 250 (0–800) mL in the control group, $p = 0.009$), higher percentage of taken TBW (M = 6.01 (4.39–7.27)% vs. 0.86 (0–2.31)% in the control group, $p = 0.009$) and higher percentage of water taken from the intravascular volume (M = 47.02 (34.09–56.82)% vs. 5.43 (0–18.01)% in the control group, $p = 0.009$). Fluid balance and intraoperative diuresis did not show significant differences between the groups (p-value 0.448 and 0.536, respectively).

Patients who suffered from CSA-AKI and experienced long-term postoperative kidney function impairment had a significantly lower hematocrit level in the 2nd measurement during CPB (approximately 45 min after the initiation of CPB; M = 18 (18–18)% vs. 25 (22–27)% in the control group, $p = 0.006$) and a higher preoperative serum IL-8 concentration (M = 7.89 (5.25–14.85) ng/mL vs. 4.73 (3.39–5.59) ng/mL in the control group, $p = 0.048$). A higher preoperative urine IL-18 concentration was also observed in these patients (M = 36.99 (19.93–53.28) ng/mL vs. 12.48 (9.88–25.06) ng/mL in the control group), although the result lacked statistical significance ($p = 0.070$).

3.4. Patients Who Underwent Intraoperative Hemofiltration vs. Patients Who Did Not Undergo Intraoperative Hemofiltration

A total of 18 patients in this study population (nine women and nine men) underwent intraoperative hemofiltration, which accounts for 37.5% of this population. These patients had a lower preoperative hematocrit level (M = 37.7 (35.5–40.7)% vs. 41 (39.3–44.9)% in the control group, $p < 0.001$), a higher initial serum TNF-α concentration (M = 2.7 (2.38–3.95) ng/mL vs. 2 (1.59–2.42) ng/mL in the control group, $p = 0.003$), lower intraoperative diuresis (M = 1100 (400–1500) mL vs. 1600 (1200–2000) mL in the control group, $p = 0.011$) and higher total noradrenaline demand (M = 0.006 (0–0.009) mg/kg vs. 0 (0–0.005) mg/kg in the control group, $p = 0.024$). A positive relation between undergoing intraoperative hemofiltration and the necessity of catecholamines administration was statistically significant (OR = 3.9, CI: 1.06–14.28, $p = 0.035$). Fluid balance from the operation did not show significant differences between the groups ($p = 0.240$). Serum

TNF-α concentration 6 h after weaning from CPB was higher in patients who underwent intraoperative hemofiltration (M = 5.1 (3.6–6.77) ng/mL vs. 3.98 (2.56–4.52) ng/mL in the control group, $p = 0.020$).

CSA-AKI developed in nine patients who underwent intraoperative hemofiltration (50%), compared to six patients in the control group (20%). The difference, however, did not obtain statistical significance ($p = 0.052$). The eGFR value after ≥3 months from the operation was lower in the hemofiltration group, compared to the control group (eGFR by CKD-EPI: M = 65 (58–86) mL/min/1.73 m^2 vs. 89.5 (74–93) mL/min/1.73 m^2 in the control group, $p = 0.014$; eGFR by MDRD: M = 67.3 (58.8–87.3) mL/min/1.73 m^2 vs. 85.95 (75.3–96.5) mL/min/1.73 m^2 in the control group, $p = 0.032$).

3.5. IL-6

Preoperative serum IL-6 concentration correlated positively with patients' age (r = 0.419, $p = 0.003$) and the ESL value (r = 0.397, $p = 0.005$). IL-6 serum concentration 6 h after weaning from CPB was higher in patients with CSA-AKI, both in terms of absolute values (M = 128.58 (95.53–255.2) ng/mL vs. 86.62 (57.36–115.84) ng/mL in the control group, $p = 0.005$) and a percentage increase from the initial value (M = 9230 (4453.19–19551.76)% vs. 4189.89 (3001.29–7174.96)% in the control group, $p = 0.044$)—Figure 1a. Serum IL-6 concentration 6 h after weaning from CPB correlated positively with fluid balance from the operation (r = 0.473, $p < 0.001$) as well as early postoperative kidney function impairment—Table 5.

Table 5. Relationship between selected parameters and early postoperative kidney function. Spearman rank correlation coefficients are presented together with statistical significance ("r" for *p*-value < 0.05 are put in bold).

	Serum IL-6 6 h after Weaning from CPB (IL6_S1) r, (*p*)	**Serum IL-8 6 h after Weaning from CPB (IL8_S1) r, (*p*)**	**Preoperative Serum TNF-α (TNF_S0) r, (*p*)**	**Serum TNF-α 6 h after Weaning from CPB (TNF_S1) r, (*p*)**	**Urine NGAL 6 h after Weaning from CPB (NGAL_U1) r, (*p*)**	**Urine MMP-9 6 h after Weaning from CPB (MMP9_U1) r, (*p*)**	**Intraoperative Diuresis r, (*p*)**
S_{Cr} 1	**0.358** ($p = 0.013$)	0.193 ($p = 0.189$)	0.247 ($p = 0.090$)	**0.373** ($p = 0.009$)	**0.343** ($p = 0.017$)	**0.380** ($p = 0.008$)	**−0.431** ($p = 0.002$)
eGFR 1	**−0.348** ($p = 0.015$)	**−0.295** ($p = 0.042$)	**−0.354** ($p = 0.014$)	**−0.455** ($p = 0.001$)	**−0.337** ($p = 0.019$)	**−0.307** ($p = 0.034$)	**0.415** ($p = 0.003$)
S_{Cr} 2	0.258 ($p = 0.077$)	0.132 ($p = 0.369$).	0.254 ($p = 0.081$)	**0.295** ($p = 0.041$)	0.262 ($p = 0.072$)	**0.470** ($p < 0.001$)	**−0.471** ($p < 0.001$)
eGFR 2	**−0.311** ($p = 0.032$)	**−0.285** ($p = 0.050$)	**−0.401** ($p = 0.005$)	**−0.418** ($p = 0.003$)	**−0.331** ($p = 0.021$)	**−0.447** ($p = 0.001$)	**0.446** ($p = 0.001$)
S_{Cr} 3	**0.304** ($p = 0.044$)	0.067 ($p = 0.666$)	0.263 ($p = 0.085$)	0.284 ($p = 0.062$)	0.209 ($p = 0.174$)	**0.461** ($p = 0.002$)	**−0.534** ($p < 0.001$)
eGFR 3	**−0.355** ($p = 0.018$)	−0.245 ($p = 0.110$)	**−0.427** ($p = 0.004$)	**−0.443** ($p = 0.003$)	**−0.327** ($p = 0.030$)	**−0.453** ($p = 0.002$)	**0.496** ($p < 0.001$)
S_{Cr} 4	0.220 ($p = 0.219$)	−0.104 ($p = 0.564$)	0.211 ($p = 0.239$)	0.202 ($p = 0.259$)	0.136 ($p = 0.452$)	**0.378** ($p = 0.030$)	**−0.471** ($p = 0.006$)
eGFR 4	−0.298 ($p = 0.092$)	0.130 ($p = 0.472$)	**−0.454** ($p = 0.008$)	**−0.420** ($p = 0.015$)	−0.244 ($p = 0.172$)	**−0.407** ($p = 0.019$)	**0.486** ($p = 0.004$)

Legend: eGFR—estimated glomerular filtration rate [mL/min/1.73 m^2], *p*—*p*-value, r—Spearman rank correlation coefficient, S_{Cr}—serum creatinine concentration [mg/dL]; 0—initial level, 1—level from first 24 h after the operation, 2—level from the 3rd day after the operation, 3—level from the 5th day after the operation, 4—level from the 7th day after the operation.

3.6. IL-8

Serum IL-8 concentration 6 h after weaning from CPB was higher in patients with AKI (M = 7.89 (5.25–14.85) ng/mL vs. 4.73 (3.39–5.59) ng/mL in the control group, $p = 0.016$)—Figure 1b. Moreover, preoperative serum IL-8 concentration was higher in patients with

AKI in whom long-term postoperative kidney function impairment occurred, compared to patients with AKI and unchanged long-term postoperative kidney function (M = 7.89 (5.25–14.85) ng/mL vs. 4.73 (3.39–5.59) ng/mL in the control group, $p = 0.048$). Serum IL-8 concentration 6 h after weaning from CPB correlated negatively with the eGFR value during the first 72 h after the operation—Table 5.

3.7. TNF-α

Higher preoperative serum TNF-α concentration was observed in patients who later developed CSA-AKI (M = 2.7 (2.42–4.22) ng/mL vs. 2.13 (1.59–2.7) ng/mL in the control group, $p = 0.012$) and patients who underwent intraoperative hemofiltration (M = 2.7 (2.38–3.95) ng/mL vs. 2 (1.59–2.42) ng/mL in the control group, $p = 0.003$)—Figure 1c. There was also a correlation between preoperative serum TNF-α concentration and patients' age (r = 0.326, $p = 0.024$), preoperative kidney function (TNF-α & S_{Cr}: r = 0.290, $p = 0.046$; TNF-α & eGFR: r = −0.513, $p < 0.001$) and eGFR decline in the early postoperative period—Table 5.

Higher serum TNF-α concentration 6 h after weaning from CPB was observed in patients who developed CSA-AKI (M = 6.43 (4.5–7.08) ng/mL vs. 3.9 (2.7–4.52) ng/mL in the control group, $p = 0.002$) and in patients who underwent intraoperative hemofiltration (M = 5.1 (3.6–6.77) ng/mL vs. 3.98 (2.56–4.52) ng/mL in the control group, $p = 0.020$).

Serum TNF-α concentration 6 h after weaning from CPB correlated with patients' age (r = 0.451, $p = 0.001$), percentage of taken TBW (r = 0.293, $p = 0.043$), percentage of water taken from the intravascular volume (r = 0.310, $p = 0.032$), mean partial oxygen pressure during CPB (r = 0.291, $p = 0.044$), serum creatinine concentration on the 1st and the 3rd postoperative day (TNF-α & S_{Cr} on the 1st day: r = 0.373, $p = 0.009$; TNF-α & S_{Cr} on the 3rd day: r = 0.295, $p = 0.415$), the preoperative eGFR value (r = −0.464, $p < 0.001$) and the eGFR value in the early postoperative period—Table 5.

3.8. NGAL

Urine NGAL concentration 6 h after weaning from CPB was higher in patients with CSA-AKI (M = 13231.76 (4914.81–34148.3) ng/mL vs. 4261.32 (2868.19–9138.28) ng/mL in the control group, $p = 0.013$)—Figure 1d. Urine NGAL concentration 6 h after weaning from CPB correlated with the preoperative eGFR value (r = −0.349, $p = 0.015$), diuresis from the first 24 h after the operation (r = −0.349, $p = 0.015$) and early postoperative kidney function—Table 5. The urine NGAL concentration increase 6 h after weaning from CPB correlated positively with patients' BMI (r = 0.349, $p = 0.015$). There was a negative correlation between diuresis from the first 24 h after the operation and urine NGAL concentrations 24 h and 5 days after the operation (r = −0.323, $p = 0.025$; r = −0.319, $p = 0.027$, respectively). Persistently increased NGAL on the 5th day after the operation correlated positively with preoperative HbA1C concentration (r = 0.355, $p = 0.015$).

3.9. KIM-1

There were no significant differences in urine KIM-1 concentration in patients with CSA-AKI, compared to the control group—Figure 1e. There were also no differences found in urine KIM-1 concentration in patients who underwent intraoperative hemofiltration as well as patients who developed long-term postoperative kidney function impairment. Urine KIM-1 concentration, however, correlated with CPB parameters. Longer CPB time correlated positively with the percentage of KIM-1 increase at 24 and 48 h after the operation, compared to the initial value (r = 0.328, $p = 0.023$; r = 0.306, $p = 0.035$, respectively). A similar correlation was found for the aortic cross-clamp time (clamping time & percentage of KIM-1 increase at 24 h: r = 0.365, $p = 0.011$; clamping time & percentage of KIM-1 increase at 48 h: r = 0.396, $p = 0.005$).

3.10. IL-18

Preoperative urine IL-18 concentration was higher in patients who did not develop CSA-AKI (M = 31.05 (23.53–37.62) ng/mL vs. M = 19.93 (9.88–25.06) ng/mL in the AKI group, $p = 0.009$)—Figure 1f. Urine IL-18 concentration was higher in these patients during the whole early postoperative period (up to the 5th day after the surgery), with the exception of the 6th hour after the operation where there was no significant difference between IL-18 concentrations in both groups ($p = 0.597$). Analyzing the percentage of IL-18 increase from the initial value in the consecutive time points, it was noted that in patients with AKI, there was a significantly higher increase in IL-18 urine concentration 6 h after weaning from CPB (M = 122.02 (100–204.21)% vs. 89.80 (77.97–112.53)% in the control group, $p = 0.002$). The significance of IL-18 concentrations' change was assessed using Friedman's ANOVA test ($p < 0.023$) and subsequently with the Wilcoxon signed-rank test ($p < 0.023$). Friedman's ANOVA test did not reveal any significant differences in consecutive IL-18 concentrations in the no-AKI group ($p < 0.076$). The urine IL-18 concentration in patients with AKI normalized within 48 h.

3.11. MMP-9

The urine MMP-9 concentration 6 h after weaning from CPB was higher in patients with CSA-AKI (M = 9661.94 (1485.62–14,451.8) ng/mL vs. 3499.39 (1274.58–8656) ng/mL in the control group, $p = 0.044$). A higher urine MMP-9 concentration correlated positively with worse preoperative kidney function (MMP-9 & S_{Cr}: r = 0.430, $p = 0.002$; MMP-9 & eGFR: r = −0.368, $p = 0.010$), kidney function in the early postoperative period (Table 5) and also with kidney function after ≥3 months from the operation (MMP-9 & S_{Cr}: r = 0.418, $p = 0.003$; MMP-9 & eGFR by CKD-EPI: r = −0.371, $p = 0.010$; MMP-9 & eGFR by MDRD: r = −0.301, $p = 0.040$).

Urine MMP-9 concentrations at 24 and 48 h after the operation correlated negatively with mean partial oxygen pressure during CPB (r = −0.408, $p = 0.004$; r = −0.368, $p = 0.010$, respectively). Persistently elevated MMP-9 on the 5th day after the operation correlated with the preoperative HbA1C concentration (r = 0.308, $p = 0.037$), preoperative eGFR value (r = −0.296, $p = 0.041$) and eGFR value after ≥3 months from the operation (MMP-9 & eGFR by CKD-EPI: r = −0.368, $p = 0.011$; MMP-9 & eGFR by MDRD: r = −0.342, $p = 0.019$).

3.12. TIMP-1

The percentage of urine TIMP-1 increase 24 h after the operation correlated positively with total CPB time and aortic cross-clamp time (r = 0.362, $p = 0.012$; r = 0.365, $p = 0.011$, respectively) as well as with intraoperative diuresis (r = 0.309, $p = 0.032$) and CRP concentrations on the 1st and the 3rd postoperative day (r = 0.298, $p = 0.040$; r = 0.419, $p = 0.003$, respectively). The urine TIMP-1 concentration 48 h after the operation was lower in patients with CSA-AKI, regarding both the absolute values (M = 1.61 (0.55–2.26) ng/mL vs. 3.3 (1.68–5.92) ng/mL in the control group, $p = 0.007$) and percentage of increase from the initial value (M = 145.05 (64.91–211.91)% vs. 268.81 (111.43–733.73)% in the control group, $p = 0.030$).

In both groups of patients (AKI and no-AKI), there was a significant increase in urine TIMP-1 concentration 24 h after the operation (AKI group: $p = 0.003$; no-AKI group: $p = 0.037$). In the AKI group, no further increase in TIMP-1 concentration was observed 48 h after the operation, unlike in the no-AKI group where there was a significant urine TIMP-1 increase ($p < 0.001$).

The urine TIMP-1 concentration 48 h after the operation correlated with the ESL value (r = −0.297, $p = 0.040$), preoperative eGFR value (r = 0.380, $p = 0.008$) and eGFR value after ≥3 months from the operation (TIMP-1 & eGFR by CKD-EPI: r = 0.296, $p = 0.043$; TIMP-1 & eGFR by MDRD: r = 0.320, $p = 0.028$). The percentage of TIMP-1 increase 48 h after the operation correlated with patients' age (r = −0.321, $p = 0.026$) and with intraoperative diuresis (r = 0.327, $p = 0.023$).

3.13. MMP-9/TIMP-1 Ratio

There was no statistically significant difference between MMP-9/TIMP-1 ratio values in patients with CSA-AKI compared to the control group, at any moment of the observation. Mean partial oxygen pressure correlated negatively with MMP-9/TIMP-1 ratio values at 24 and 48 h after the operation (r = −0.472, $p < 0.001$; r = −0.318, $p = 0.028$, respectively). The MMP-9/TIMP-1 ratio value correlated positively with long-term kidney function impairment after ≥3 months from the operation (ratio & S_{Cr}: r = 0.372, $p = 0.010$; ratio & eGFR by CKD-EPI: r = −0.394, $p = 0.006$; ratio & eGFR by MDRD: r = −0.365, $p = 0.012$).

3.14. Diuresis

It was found that intraoperative diuresis correlated with preoperative kidney function (diuresis & S_{Cr}: r = −0.384, $p = 0.007$; diuresis & eGFR: r = 0.395, $p = 0.005$) and also early postoperative kidney function—Table 5. Diuresis from the operation was also significantly lower in patients who developed postoperative AKI (M = 800 (300–1500) mL vs. 1600 (1200–1900) mL in the control group, $p = 0.006$) as well as diuresis from the first 2 h after the operation (M = 300 (200–800) mL vs. 800 (400–1000) mL in the control group, $p = 0.040$). Intraoperative diuresis (adjusted for patients age) was found to be an independent predictor of CSA-AKI (OR = 0.047, CI: 0.005–0.451 over 1000 mL, $p = 0.006$). Patients who underwent intraoperative hemofiltration had lower intraoperative diuresis (M = 1100 (400–1500) mL vs. 1600 (1200–2000) mL in the control group, $p = 0.011$). Patients with long-term postoperative kidney function impairment had lower diuresis between the 2nd and 4th hour after the operation (M = 150 (75–200) mL vs. 400 (200–800) mL in the control group, $p = 0.009$).

4. Discussion

The main objective of this study was to assess the utility of novel kidney biomarkers in early CSA-AKI diagnostics and in the prognosis of long-term kidney function in patients after cardiac surgery procedures. The serum creatinine concentration and its derivative—eGFR are well-known and standardized kidney function indicators, validated for diagnosing AKI. Nevertheless, a long time period needed for the change of these indicators is their substantial disadvantage. A serum creatinine increase/eGFR decline happens only at the moment of advanced kidney damage [32], according to some authors even up to 48 h after CSA-AKI occurs [33].

It is consistent with the results of this study, in which most cases of CSA-AKI were diagnosed 24 h after the operation, and in some patients, a creatinine increase occurred even after 72 h. Such a delay in diagnostics and implementing the proper treatment seriously influences a patient's prognosis [34].

It was demonstrated during the course of this study that between patients with and without CSA-AKI, significant differences exist in kidney injury biomarkers' concentrations, as soon as 6 h after weaning from CPB. These differences mostly concern serum IL-6, IL-8 and TNF-α, urine NGAL and MMP-9 as well as the percentage of urine IL-18 increase. Among the above, independent AKI predictors proved to be IL-8 and NGAL. It is consistent with the results obtained by other authors [6,13,15,18,21,34]. Another advantage of NGAL, MMP-9 and IL-18 usage in this instant is that they are marked in urine; therefore, the test is non-invasive.

Another quality of IL-6, IL-8, TNF-α, NGAL and MMP-9, aside from indicating AKI, is that their concentrations after the operation correlate with early postoperative kidney function. For TNF-α, this correlation exists also for its preoperative value. This opens a possibility of using these biomarkers to optimize postoperative care in patients after cardiac surgery procedures.

Preoperative factors that contribute to increased risk of CSA-AKI were older age, worse initial kidney function and lower hematocrit, which is consistent with the present state of medical knowledge. Another factor that favors CSA-AKI occurrence proved to be lower intraoperative diuresis [35] and also lower diuresis during the first 2 h after the operation. Intraoperative diuresis was an independent AKI predictor, which also

correlated with early postoperative kidney function. Diuresis in the early postoperative period correlated with long-term kidney function impairment. Considering that hourly diuresis assessment is non-invasive, easy-to-perform and generates very low costs, it is justified to state that intra- and postoperative diuresis measurement is a very good tool for postoperative kidney function evaluation.

Patients who developed CSA-AKI had a higher preoperative serum TNF-α concentration and a lower preoperative urine IL-18 concentration. Other authors reported that there is no connection between preoperative serum TNF-α concentration and AKI development [36,37]. Nevertheless, it was proven that serum TNF-α increases in response to prolonged inflammation related to arterial hypertension and diabetes [38] (which were present in the vast majority of patients included in this study). Another well-documented fact is that TNF-α induces inflammation in kidneys and favors their damage [39]. Considering the above, it seems logical to conclude that elevated preoperative serum TNF-α concentration reflects the subclinical proinflammatory state, which increases the risk of postoperative kidney damage.

It would be misguided to hypothesize that a higher IL-18 concentration has a protective effect on the kidneys. In patients who did not develop CSA-AKI, the postoperative IL-18 concentration maintains at a relatively unchanged level, while in patients with CSA-AKI, it rises considerably 6 h after weaning from CPB and normalizes 48 h after the operation. Similar results were obtained by other researchers [12,13]. Presumably, a relative change in IL-18 concentration compared to the initial value could be a more reliable AKI indicator than its absolute value.

Patients who did not develop CSA-AKI were statistically younger than patients with AKI, which means that they earlier developed an advanced form of heart disease that required surgical intervention. Some authors reported that patients with a genetic predisposition to a higher IL-18 concentration have a higher risk of arterial hypertension, ischemic heart disease and its complications [40–43]. This may explain the higher IL-18 phenomenon is these younger patients.

A postoperative increase in urine TIMP-1 concentration was observed in the entire study population, but it was significantly greater in patients who did not develop CSA-AKI. A considerably lower urine TIMP-1 concentration 48 h after the operation in the AKI group may reflect an imbalance between MMP-9 and TIMP-1 activities. The MMP-9/TIMP-1 imbalance is associated with multiple disorders such as autoimmune diseases, chronic obstructive pulmonary disease exacerbations and blood-brain barrier disruption [44–46]. Considering the above, it is justified to assume that the MMP-9/TIMP-1 imbalance may play a role in the development of CSA-AKI. Such a hypothesis is supported by a positive correlation between the MMP-9/TIMP-1 ratio value 48 h after the operation and long-term postoperative kidney function impairment observed in this study follow-up. Undermining this hypothesis, however, is the fact that there was no statistically significant difference between MMP-9/TIMP-1 ratio values 48 h after the operation in patients with AKI vs. no-AKI. Further investigation is required in this regard.

One of the factors favoring AKI progression to CKD was a higher preoperative serum IL-8 concentration. It is consistent with the findings of other authors, who proved the role of IL-8 within the kidneys in the progression of acute inflammatory disorders to the chronic form [47].

The relationship between intraoperative hemofiltration volume and long-term postoperative kidney function impairment seems to undermine the role of hemofiltration as a nephroprotective agent during CPB. The theory of protecting the kidneys by removing proinflammatory cytokines through the filtering membrane did not find any support in the results of this study. The percentage of patients with AKI was considerably greater in the hemofiltration group (borderline significance result), and the eGFR value after $\geq$3 months was significantly lower in these patients (though an unequivocal relationship with CKD was not proved).

There is a noticeable connection between the percentage of taken TBW and water taken from the intravascular volume and long-term postoperative kidney function impairment. It suggests that a prerenal mechanism of kidney damage secondary to hypovolemia outweighs the potential benefits coming from proinflammatory cytokines' removal. Higher postoperative TNF-α and a higher demand for noradrenaline in the hemofiltration group both support this conclusion. It seems that a zero-balance hemofiltration could bring more benefits to the patients in this regard [48]. In light of the results of this study, intraoperative hemofiltration is a method of increasing the hematocrit level during CPB burdened with a high risk of nephrological complications.

Identification of patients endangered with long-term postoperative kidney function impairment and early implementation of the proper treatment are essential in terms of reducing morbidity and mortality among patients who had AKI [49,50]. Novel kidney injury biomarkers' concentrations in the early postoperative period correlate significantly with serum creatinine and/or with the eGFR value ≥3 months after cardiac surgery procedure. The correlation mainly exists 6 h after weaning from CPB for TNF-α [51], MMP-9 and IL-18 [52,53], but preoperative TNF-α, TIMP-1 at 48 h, MMP-9 on the 5th day and the MMP-9/TIMP-1 ratio [54] at 48 h are also of importance here. This proves that novel kidney injury biomarkers are also an eligible tool for the assessment of CKD risk after cardiac surgery procedures.

A positive correlation between the preoperative HbA1C level and persistently elevated NGAL and MMP-9 5 days after the operation may reflect a relationship between inadequate glycemia control and prolonged inflammation after the surgery [55].

5. Conclusions

In conclusion, novel kidney injury biomarkers such as IL-6, IL-8, TNF-α, MMP-9 and NGAL are reliable AKI indicators, which enable early postoperative identification of patients who suffer from CSA-AKI. Serum IL-8 and urine NGAL 6 h after weaning from CPB proved to be independent AKI predictors. Another AKI predictor was intraoperative diuresis, which also strongly correlates with early postoperative kidney function. In light of the results of this study, also the preoperative serum TNF-α concentration should be considered as a possible indicator of higher AKI risk. Older age, impaired preoperative kidney function and lower perioperative hematocrit level are the most relevant factors that contribute to the occurrence of CSA-AKI. Factors favoring long-term kidney function impairment proved to be a higher preoperative serum IL-8 concentration and intraoperative hypovolemia. TNF-α, MMP-9, IL-18, TIMP-1 and the MMP-9/TIMP-1 ratio in the early postoperative period also correlated with long-term kidney function impairment. Non-zero-balanced hemofiltration did not bring any benefits in terms of protecting kidneys from CPB-related damage in this study population.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/biology10090823/s1, Table S1: CSA-AKI data.

Author Contributions: Conceptualization, J.U. and E.K.; methodology, J.U. and E.K.; investigation, J.U. and A.W.; resources, E.K. and S.K.; data curation, K.S.; writing—original draft preparation, J.U. and A.W.; writing—review and editing, E.K., A.B., K.M. and S.K.; visualization, K.S.; supervision, A.B., K.M.; project administration, J.U. and E.K.; funding acquisition, E.K. All authors have read and agreed to the published version of the manuscript.

Funding: The project was financed from the program of the Minister of Science and Higher Education under the name "Regional Initiative of Excellence" in years 2019–2022. Project number: 002/RID/2018/19.

Institutional Review Board Statement: The project was approved by the Bioethical Committee of the Pomeranian Medical University in Szczecin (referential number: KB-0012/165/19).

Informed Consent Statement: Patients enrolled into the study were informed about the purpose of the study, the extent of gathered data, study protocol and any potential risks and benefits result-

ing from participating in this investigation. Every contestant gave his or her written consent for enrollment into the study.

Data Availability Statement: The dataset generated for this study is available as Supplementary Materials.

Acknowledgments: The authors want to thank members of the anesthesia team: Marzena Zajdel, Iwona Sell and Dariusz Cerzniewski for their invaluable help in sample collection, as well as members of the perfusionists team: Ryszard Biskup, Marek Nowak and Krzysztof Znaczko for their meritorical contribution to this study.

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

Limitations: The greatest limitation of this study was a low sample size, due to strict exclusion criteria and a significant decrease in the number of patients admitted for elective procedures caused by the COVID-19 pandemic. Another limitation was the lack of precise criteria for implementing intraoperative hemofiltration, which forced the authors to rely on a subjective assessment of the operating team.

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Załącznik 2 - The Utility of Novel Kidney Injury Biomarkers in Early Detection of CSA-AKI. Int. J. Mol. Sci. 2022, 23, 15864.

International Journal of
Molecular Sciences

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The Utility of Novel Kidney Injury Biomarkers in Early Detection of CSA-AKI

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Citation: Udzik, J.; Waszczyk, A.; Wojciechowska-Koszko, I.; Kwiatkowski, P.; Roszkowska, P.; Rogulska, K.; Safranow, K.; Biskupski, A.; Kwiatkowski, S.; Kwiatkowska, E. The Utility of Novel Kidney Injury Biomarkers in Early Detection of CSA-AKI. *Int. J. Mol. Sci.* **2022**, *23*, 15864. https://doi.org/10.3390/ijms232415864

Academic Editors: Giovana S. Di Marco and Marcus Brand

Received: 23 November 2022
Accepted: 12 December 2022
Published: 14 December 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Cardiac surgery-associated acute kidney injury (CSA-AKI) is one of the most common complications of cardiac surgery procedures. In this study, the authors attempt to provide new data regarding the application of novel kidney injury biomarkers in the early diagnostics of CSA-AKI. 128 adult patients undergoing elective cardiac surgery procedures with the use of cardiopulmonary by-pass (CPB) were enrolled in this study. Novel kidney injury biomarkers were marked in the plasma and urine 6 h after weaning from the CPB. A significant difference in the postoperative biomarkers' concentration between the AKI and no-AKI group was found, regarding plasma IL-8, plasma TNF-α and urine NGAL, normalized for creatinine excretion (NGAL/Cr). These were also independent predictors of CSA-AKI. An independent risk factor for CSA-AKI proved to be preoperative CKD. Plasma IL-8 and TNF-α, as well as urine NGAL/Cr, are independent early indicators of CSA-AKI and pose a promising alternative for creatinine measurements. The cut-off points for these biomarkers proposed in this investigation should be confronted with more data and revised to achieve a suitable diagnostic value.

Keywords: CSA-AKI; kidney injury biomarkers; cardiac surgery; cardiopulmonary by-pass

1. Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) is one of the most common complications of cardiac surgery procedures, affecting approximately 25–30% of patients [1,2]. The KDIGO guidelines for diagnostics of acute kidney injury (AKI) published in the 2012 [3,4] are still up to date, as they are based on a highly standardized and repetitive measurement—serum creatinine. Up to this day, in routine clinical practice, physicians rely on serum creatinine in the diagnostics of CSA-AKI as well due to the lack of a superior alternative. There are constant attempts, however, to find such an alternative. Many researchers aim to find more specific markers of kidney injury with more favorable serum kinetics and those unaffected by cardiac surgery's specific features [5–8].

The main issue concerning CSA-AKI diagnostics with serum creatinine is the massive fluid transfusion, mainly during cardiopulmonary by-pass. This involves a priming fluid of approximately 1500 mL, at least 500 mL of cardioplegic solution (assuming the use of lower

volume blood cardioplegia) and intravenous fluids from anesthesia, which rarely account for less than 500 mL. This sums to at least 2500 mL of fluids administered to the patient during the operation. Additionally, there are fluids administered in the postoperative period. As a result of this considerable fluid intake, serum metabolites (including creatinine) become diluted. For this reason, it usually takes about 24 h for the serum creatinine to accumulate and meet the AKI criteria [9,10]. Studies conducted in recent years prove it is possible to detect CSA-AKI as soon as 6 h after weaning from cardiopulmonary bypass (CPB) using urine kidney injury biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), matrix metalloproteinase 9 (MMP-9) and interleukin 18 (IL-18) [6,8,11–14]. Additionally, the molecules present in the serum, such as interleukin 6 (IL-6), interleukin 8 (IL-8) and tumor necrosis factor-alpha (TNF-α), are a promising diagnostic tool in this regard [8,15–17].

IL-6 is produced by myeloid cells together with interleukin 1 beta (IL-1 β) and TNF-α, which leads to an increase in IL-6 production through a positive feedback mechanism. This mechanism is so potent that the IL-6 level can increase as much as six orders of magnitude. This makes IL-6 a sensitive indicator of inflammation, infection and neoplasia growth [18–20].

IL-8 is another proinflammatory cytokine produced by mononuclear macrophages in systemic infections. Its increase is associated with higher mortality in patients with sepsis [21]. It is also known to play a role in the progression of acute inflammatory changes within the kidney to the chronic form [22].

One of the main pathophysiological mechanisms underlying AKI is renal ischemia followed by reperfusion (ischemia–reperfusion injury—IRI). The most important cytokine in this process is TNF-α, which acts by activating cyclooxygenase 2 (COX-2) [23]. The major role of TNF-α was proved by studies that demonstrated a kidney protective influence of anti-TNF-α therapy in ischemic AKI [24].

NGAL is secreted by the cells of the proximal kidney tubule, the ascending limb of the Henle loop and the collecting duct. NGAL, present in urine, is produced in the lungs, liver and leukocytes (including leukocytes that infiltrate kidneys) as a response to the inflammation process [25], which is a disadvantage of this biomarker. Nevertheless, combined with other specific renal biomarkers (such as KIM-1), urine NGAL concentrations may provide additional information about the extent of kidney tissue damage. After kidney injury, NGAL reaches its maximal urine concentration in 6 h, and its prolonged presence is linked to tissue regeneration processes within the kidney [11].

KIM-1 is an orphan transmembrane receptor produced in substantial amounts in the proximal tubule subsequent to an injury [26]. It can be detected in urine a few hours after kidney injury, and it is proven to have a high sensitivity in detecting AKI. After reaching its maximal urine concentration within 72 h from injury, it maintains elevated, stimulating proximal tubule cell regeneration [12,27].

MMP-9 is dynamically expressed and activated in inflamed tissues, degrading the extracellular matrix proteins and taking part in tissue remodeling secondary to injury [28,29]. MMP-9 is also related to urine KIM-1 elevation, as it mediates the shedding of the extracellular domain of this receptor [30].

IL-18 is produced as an inactive precursor by macrophages, dendritic cells, epithelial cells, keratinocytes, chondrocytes and fibroblasts. In the kidneys, its primary sources are tubule epithelial cells [31–33]. An IL-18 increase resulting from AKI was demonstrated in numerous clinical studies, including studies on patients after kidney transplant who developed acute tubular necrosis [34,35]. Urine IL-18 concentration is reported to increase 4–6 h after cardiac surgery [13].

The above-described biomarkers were incorporated into this investigation, as they have dynamic serum kinetics (IL-6, IL-8 and TNF-α) or are secreted with urine (NGAL, KIM-1, MMP-9 and IL-18), which makes them a noninvasive alternative to serum creatinine measurements. All of them were also proved to be reliable kidney injury indicators. An early diagnosis is vital for the rapid treatment of CSA-AKI and, as a consequence, for

reducing morbidity and mortality due to postoperative renal failure [4,27,36–40]. In this study, the authors attempt to provide new data regarding the application of novel kidney injury biomarkers in the diagnostics of CSA-AKI.

2. Results

The overall prevalence of CSA-AKI in this study population was 32%. Most AKI cases were diagnosed 24 h after the operation (63.41%). After the 24th postoperative hour, the number of newly diagnosed AKI gradually decreased: 17.07% on the 2nd postoperative day, 12.2% on the 3rd and 7.32% in the next 48 h.

The preoperative characteristics of the study population with regard to AKI occurrence are included in Table 1.

Table 1. Preoperative characteristics of the study population.

	AKI (n = 41)	no-AKI (n = 87)	p-Value
Age M (Q1–Q3) (years)	70 (67–75)	67 (61–72)	**0.013**
Male n (%)	25 (60.98)	65 (74.71)	0.147
Female n (%)	16 (39.02)	22 (25.29)	
BMI M (Q1–Q3)	27.85 (25.91–30.70)	28.09 (25.53–31.10)	0.815
ES II M (Q1–Q3)	3.81 (2.10–5.42)	2.92 (1.70–4.77)	0.267
Hypertension n (%)	35 (85.37)	67 (77.01)	0.349
Diabetes n (%)	15 (36.59)	27 (31.03)	0.550
Dyslipidemia n (%)	19 (46.34)	38 (43.68)	0.850
CKD n (%)	15 (36.59)	7 (8.05)	**<0.001**
Preoperative hematocrit (Q1–Q3) (%)	39.50 (37.35–42.80)	41.40 (39.30–43.20)	**0.045**
Hb_{A1C} M (Q1–Q3) [%]	5.90 (5.70–6.70)	5.90 (5.50–6.30)	0.344
Preoperative creatinine (Q1–Q3) (mg/dl)	1.02 (0.89–1.26)	0.89 (0.76–1.01)	**0.002**
Preoperative eGFR Q1–Q3) (mL/min/1.73 m^2)	65 (55–81)	82 (71–93)	**<0.001**

Legend: BMI—body mass index, CKD—chronic kidney disease, eGFR—estimated glomerular filtration rate, ES II—EuroSCORE II, Hb_{A1C}—glycated hemoglobin and M—median.

The overall preoperative incidence of chronic kidney disease (CKD) in this study population was 17.19%, out of which 68.18% was KDIGO 3a stage, and the remaining 31.82% was KDIGO 3b stage.

In the AKI group, there was a higher percentage of patients who underwent complex procedures (coronary artery by-pass grafting combined with valvular surgery): 26.83% (vs. 10.34% in the control group, p = 0.034). The percentage of patients who underwent isolated coronary artery by-pass grafting and isolated valvular surgeries did not differ significantly between the groups (p-value 0.259 and 0.349, respectively). There was no difference between the total CPB time and aortic cross-clamp time between the AKI and no-AKI group (p-value 0.267 and 0.308, respectively).

A significant difference in the postoperative biomarkers' concentration between the AKI and no-AKI group was found regarding plasma IL-8, plasma TNF-α and urine NGAL normalized for creatinine excretion (NGAL/Cr); p-value was <0.001 in all cases—Figure 1.

A positive correlation was observed between the patients' age and some biomarker concentrations. Additionally, a negative correlation existed between some of the biomarkers and preoperative kidney function, as well as the mean hematocrit value during CPB—Table 2.

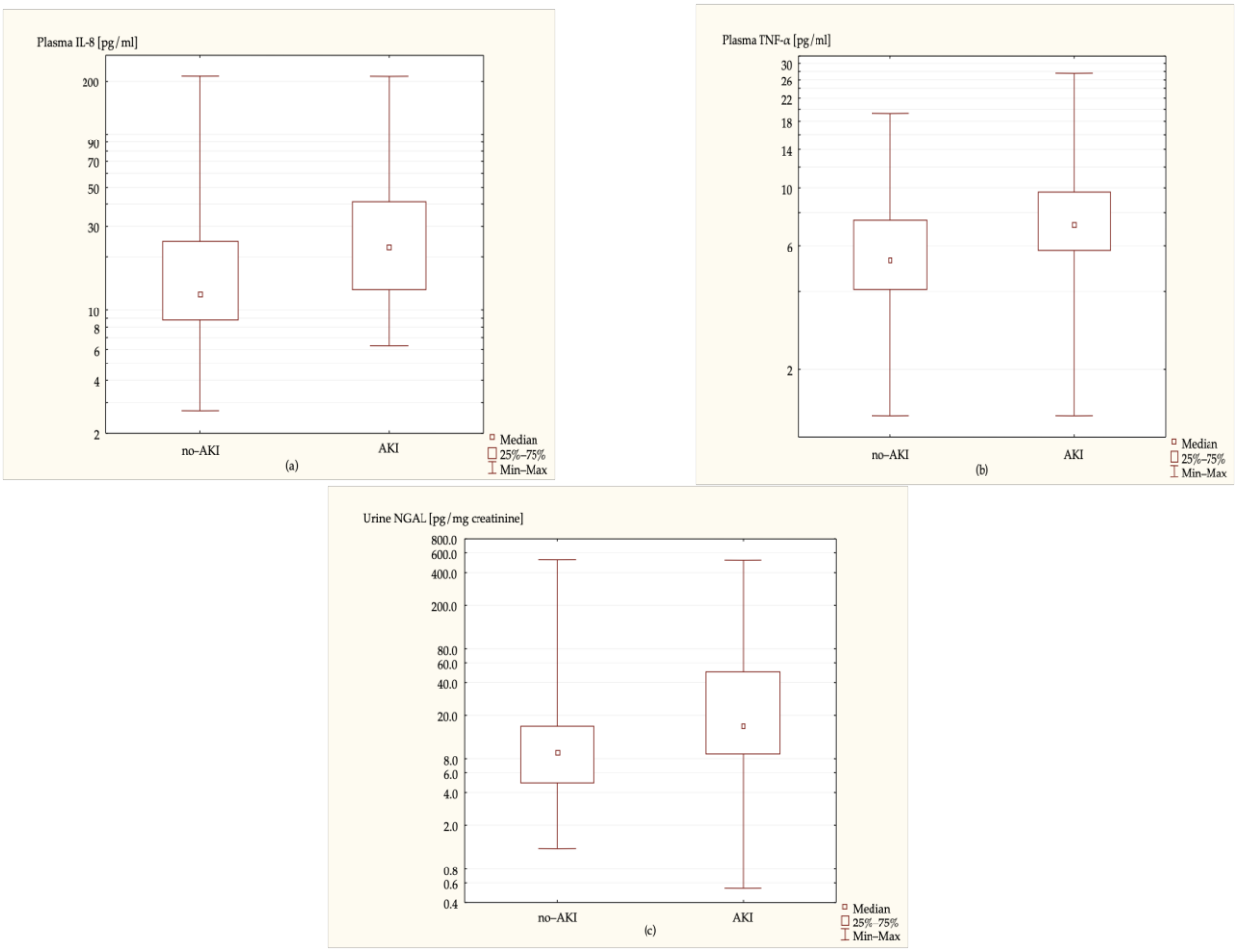

Figure 1. Postoperative biomarker concentrations in the control group and the AKI group (p-value < 0.001 in all cases). The Y-axis was logarithmized for improved data clarity. (**a**) Plasma IL-8 (pg/mL), (**b**) plasma TNF-α (pg/mL), (**c**) urine NGAL normalized for creatinine excretion (ng/mg).

Table 2. Spearman's correlation coefficient analysis.

	R	p-Value
Age and TNF-α	0.234	**0.008**
Age and NGAL/Cr	0.238	**0.007**
Preoperative eGFR and IL-8	−0.190	**0.031**
Preoperative eGFR and TNF-α	−0.373	**<0.001**
Preoperative eGFR and NGAL/Cr	−0.226	**0.010**
Mean HtCPB and IL-8	−0.251	**0.004**

Legend: eGFR—estimated glomerular filtration rate, HtCPB—hematocrit value during CPB, IL-8—plasma IL-8 concentration 6 h after weaning from CPB, NGAL/Cr—urine NGAL concentration 6 h after weaning from CPB normalized for creatinine excretion and TNF-α—plasma TNF-α concentration 6 h after weaning from CPB.

3. Discussion

Multivariable logistic regression was applied to adjust the analysis for potentially confounding factors (age, sex and the incidence of preoperative CKD). According to this analysis, the independent predictors of CSA-AKI were high plasma TNF-α, high plasma IL-8 and high urine NGAL/Cr. An independent risk factor for CSA-AKI proved to be preoperative CKD. There was a positive correlation between plasma IL-8 and plasma TNF-α, hence the loss of statistical significance for these biomarkers when incorporating them into one logistic regression model. For this reason, two different logistic regression models were calculated, as presented in Table 3.

Table 3. Logistic regression models for independent CSA-AKI predictors and risk factors.

(a) Logistic Regression Model Involving Age, Sex, Preoperative CKD, Plasma TNF-α and Urine NGAL/Cr			
	OR	**CI**	***p*-Value**
Age	1.03	0.97–1.09	0.377
Sex	0.94	0.34–2.59	0.910
Preoperative CKD	3.64	1.19–11.16	**0.022**
Log TNF-α	3.19	1.20–8.49	**0.019**
Log NGAL/Cr	1.68	1.15–2.47	**0.007**
(b) Logistic Regression Model Involving Age, Sex, Preoperative CKD, Plasma IL-8 and Urine NGAL/Cr			
	OR	**CI**	***p*-Value**
Age	1.04	0.98–1.10	0.230
Sex	1.16	0.42–3.23	0.774
Preoperative CKD	5.03	1.71–14.78	**0.003**
Log IL-8	1.88	1.07–3.30	**0.026**
Log NGAL/Cr	1.57	1.08–2.29	**0.018**

Legend: CI—95% confidence interval, CKD—chronic kidney disease, Log NGAL/Cr—log-transformed urine NGAL concentration 6 h after weaning from CPB normalized for creatinine excretion, Log TNF-α—log-transformed plasma TNF-α concentration 6 h after weaning from CPB and OR—odds ratio, Log IL-8—log-transformed plasma IL-8 concentration 6 h after weaning from CPB and OR—odds ratio.

Receiver operating characteristic (ROC) analysis was conducted to assess the biomarkers' potential to serve as a diagnostic tool. Plasma IL-8, plasma TNF-α and urine NGAL/Cr proved to be the most suitable AKI indicators (AUC > 0.5, p-value < 0.001). The results of the analysis are presented in Figure 2.

Cardiac surgery procedures are burdened with considerable perioperative risk (2.2% overall mortality rate vs. 1.1% for non-cardiac surgeries in Europe and the USA) [41,42]. Considering the high incidence of CSA-AKI and its impact on patient survival, there is a need for an improved diagnostic strategy regarding this complication.

Numerous studies report elevated levels of novel kidney injury biomarkers in patients with postoperative AKI [6,12,16,28,43–46]. The data, however, are incoherent as different diagnostic criteria were used and different methods were applied in various studies. For instance, Wagener et al. [47], as well as Che et al. [48], assumed the RIFLE criteria for CSA-AKI diagnostics, while the golden standard nowadays is the KDIGO criteria. Wagener et al. also did not adjust the urine NGAL concentration to urine creatinine excretion, the same as Heise et al. [49], which is also not up to the current norms. Meta-analysis of the urinary NGAL performance in CSA-AKI diagnostics conducted by Zhou et al. [50] is naturally more comprehensive than this investigation, and yet, it merges data obtained from adult and child populations. This may influence the cut-off values given in that article as there are distinctive differences in the kidney injury biomarkers' origin in the pediatric population [51]. A recent systematic review by Pan et al. [52] on the biomarkers' accuracy in a hospital-acquired AKI prediction was not limited to cardiac surgery patients, which may influence the result's usefulness in the field of cardiac surgery.

In this study, the authors wanted to provide transparent, up-to-date data concerning adult post-cardiac surgery patients, and so, all the current standards in this field of investigation were kept (available in the "Materials and Methods" section).

Despite a modest sample size, the authors provided cut-off points for the most promising biomarkers as a step toward the clinical application of this research. The Luminex® technology used in this investigation was proven to have high reliability in the field of kidney injury research [53]. It is, therefore, reasonable to assume that researchers conducting similar investigations will also rely on this technology. The results of such investigations should be comparable to the results of this study, thus, providing an opportunity to merge these data.

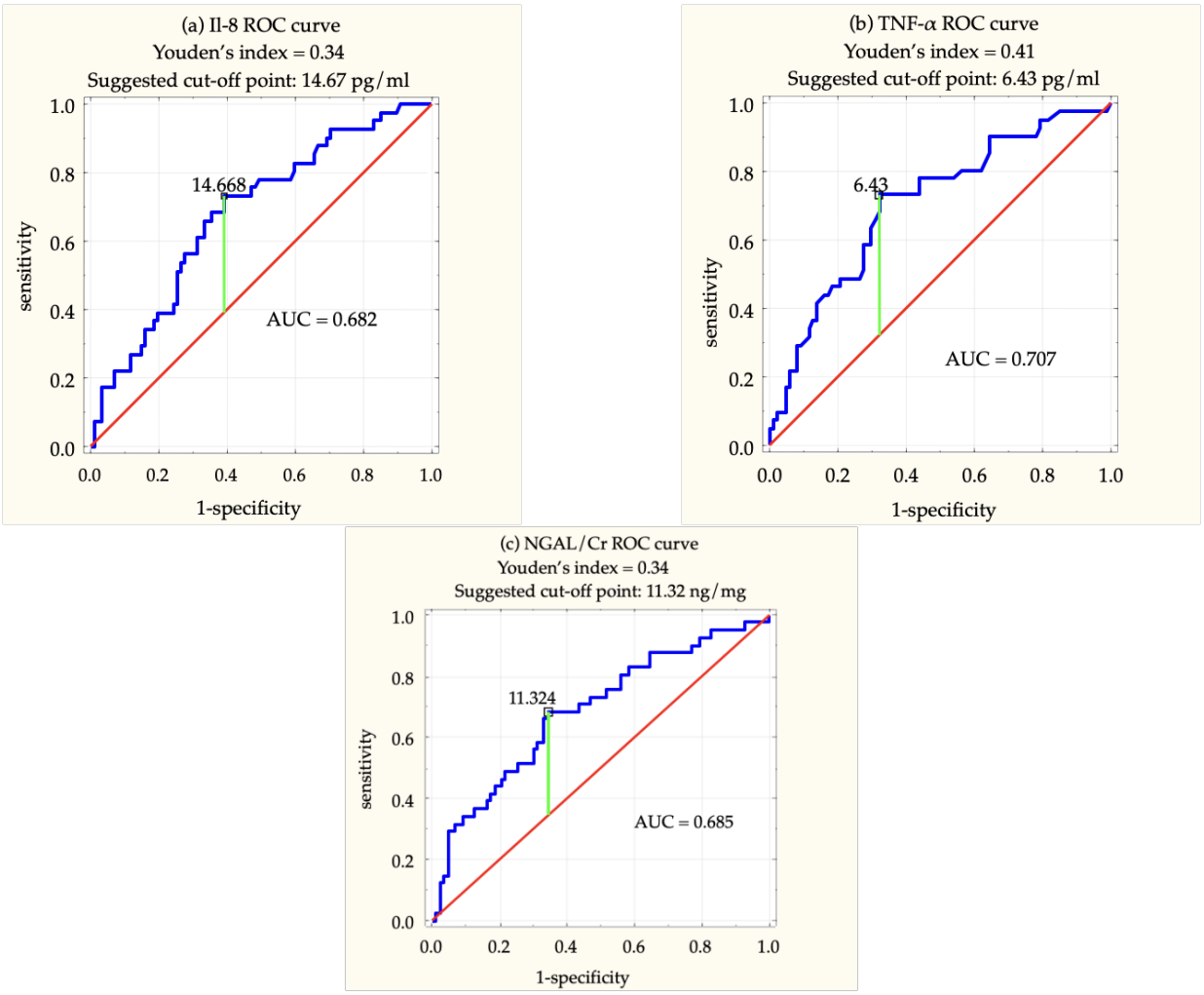

Figure 2. ROC analysis of the selected AKI indicators: (**a**) plasma IL-8, (**b**) plasma TNF-α and (**c**) urine NGAL normalized for creatinine excretion—NGAL/Cr. AUC—area under a curve.

As demonstrated by Youden's index (<0.5 in all cases), the results of this study cannot be yet introduced to clinical practice. A larger patient cohort is required to improve the sensitivity and specificity of these tests. However, considering the favorable kinetics of these biomarkers and less invasive testing methods compared to serum creatinine (regarding NGAL), further endeavors in this field are highly recommended. In more than half of this study population, AKI could have been diagnosed up to four times faster if biomarkers were used instead of creatinine measurements. In the rest of the patients, the diagnosis could have been made even so much as days earlier. This lost time is a severe handicap for the kidneys striving to regenerate from injury, as it delays introducing a proper treatment.

Two essential issues concerning introducing novel biomarkers to routine diagnostics are poor testing standardization and high cost. Nonetheless, these obstacles can be overcome if sufficient data are gathered and the testing becomes more widespread.

While the main objective of this study was to provide new data regarding novel kidney injury biomarkers, other observations were made during this research. Older age, lower intraoperative hematocrit value and poorer preoperative kidney function are all known risk factors for CSA-AKI. In this study the authors demonstrated that they also directly correlate with the postoperative biomarkers' concentrations. This suggests that these factors enhance kidney damage during cardiac surgery and should not be underestimated even in the absence of clinically evident AKI.

4. Materials and Methods

A cohort of 128 adult patients undergoing elective cardiac surgery procedures with the use of CPB were enrolled in this study over a 24-month period. Regional Bioethical Committee approved the study protocol and conditions (document's signature: KB-0012/45/2021). Informed consent was obtained from each patient prior to the enrollment.

Inclusion criteria:

- Qualification for an elective cardiac surgery procedure with the use of CPB;
- Written consent for study enrolment.

Exclusion criteria:

- End-stage renal disease (eGFR < 15 mL/min/1.73 m^2);
- Kidney artery stenosis in medical history;
- Active inflammatory disease;
- Active neoplasm;
- Mayor intraoperative complications causing hypotension;
- Mayor postoperative complications causing hypotension;
- Need for continuous renal replacement therapy (CRRT) within 6 h after the procedure.

Blood and urine samples were collected from the patients 6 h after weaning from CPB. Blood was collected from the radial artery using S-Monovette 3.4 mL sterile containers (K3 EDTA: 1.6 mg/1 mL of blood; SARSTEDT AG & Co. KG Sarstedtstrasse 1, 51588 Numbrecht, Germany). Urine was collected directly from the Foley catheter using standard non-sterile urine containers. After the collection, blood and urine samples were stored at 5 °C for no longer than 4 h and subsequently centrifuged (4 °C, 10 min, 4000 RPM). After centrifugation, 1 mL of supernatant was taken and stored at −70 °C for no longer than six months.

Quantitative assessment of IL-6, IL-8 and TNF-α (in plasma), as well as NGAL, KIM-1, IL-18 and MMP-9 (in urine) levels in patients enrolled in this study was performed using Luminex xMAP technology (Luminex Corporation, Austin, TX, USA). The first measurements using urine samples were carried out on the native urine form, and the results obtained exceeded the upper detection limit for this assay. Due to that, an optimization process was conducted in order to determine the optimal dilution for all samples. The following dilutions were selected as optimal: 1:2 (for NGAL and KIM-1) and 1:10 (for IL-18 and MMP-9). Plasma samples were tested in their native form. Thawed samples were centrifuged (4 °C, 4 min, 16,000 RPM) immediately before use. The analysis was conducted according to manuals provided with the multiplex reagent kit (Human Magnetic Luminex Assay, R&D Systems, Minneapolis, MN, USA) using the Luminex 100 analyzer and Xponent 4.2 Build software. On a microplate, 50 µL of samples were incubated in each well with a 50 µL diluted microparticle cocktail for 2 h at room temperature on a horizontal orbital microplate shaker (0.12″ orbit) set at 800 ± 50 RPM. A magnetic Manual MagPlex® Bead Washing device was used to wash the samples. The microplates were placed on the separator for 1 min, after which the remains not attached to the magnet were removed. Subsequently, 100 µL of the wash buffer was added to each well and incubated for 1 min, after which the remains not attached to the magnet were once again removed. This last step was repeated three times.

In this step, 50 µL of a diluted Biotin-Antibody Cocktail were then added to the wells and incubated for 1 h at room temperature on the shaker (800 ± 50 RPM). Microplates were washed again. In this step, 50 µL of diluted Streptavidin-PE were added and incubated for 30 min at room temperature on the shaker (800 ± 50 RPM). Microplates were washed again. The microparticles were then resuspended by adding 100 µL of the wash buffer and incubated for 2 min on the shaker (800 ± 50 RPM). The microplates were read within 90 min using the Luminex® standards. Concentrations of the analyzed biomarkers were calculated based on a standard 6-point curve.

Creatinine concentration was also determined in the urine samples to normalize the urinary biomarkers' concentrations to creatinine excretion. Creatinine was measured in

the defrosted urine samples after 12 h of storage in a dark and cooled compartment (5 °C). A kinetic colorimetric test based on Jaffe's method was used to measure the creatinine concentration in urine (Cobas Pro c503 module, Roche, Basel, Switzerland).

A quantitative assessment of the protein level in the urine samples was not conducted as there was, at most, a trace amount of protein present in the samples. Such an amount of protein was deemed insignificant as it does not interfere with the biomarker's level measurement. Postoperative AKI was diagnosed according to the KDIGO criteria ($\geq$0.3 mg or 50% increase in serum creatinine within 48 h or diuresis < 0.5 mL/kg/h for at least 6 h) until the 5th postoperative day. Serum creatinine was measured on the day preceding the operation, on the 1st postoperative day and, subsequently, every 48 h.

Fisher's exact test was used to compare qualitative variables between the groups. Since most quantitative variables were non-normally distributed, they were presented as median (M) and interquartile range (Q1–Q3). Following, non-parametric tests were used: Mann–Whitney test for differences between the groups and Spearman's rank correlation coefficient for correlations between the parameters. Multivariable logistic regression was used to find independent predictors of AKI with normalizing logarithmic transformation of biomarker concentrations. Receiver operating characteristic (ROC) analysis was conducted to estimate the diagnostic value of the biomarkers in relation to AKI prognosis. The suggested cut-off points were based on the maximization of Youden's index. Associations with $p < 0.05$ were considered statistically significant. Calculations were performed with Statistica 13 program.

The objective of this study was to assess the utility of novel kidney injury biomarkers in the early diagnostics of CSA-AKI.

5. Conclusions

Plasma IL-8 and TNF-α, as well as urine NGAL/Cr, are independent early indicators of CSA-AKI and pose a promising alternative for creatinine measurements. Cut-off points for these biomarkers proposed in this investigation should be confronted with more data and revised to achieve a suitable diagnostic value. Future investigations in this area should focus on providing specific data to improve these biomarkers' clinical performance.

Author Contributions: Conceptualization, J.U. and E.K.; methodology, A.B.; validation, I.W.-K., P.K., P.R. and K.R.; formal analysis, K.S.; investigation, I.W.-K., P.K., P.R. and K.R.; resources, S.K.; data curation, A.W.; writing—original draft preparation, J.U.; writing—review and editing, E.K. and A.W.; visualization, K.S.; supervision, E.K.; project administration, A.B.; funding acquisition, S.K. All authors have read and agreed to the published version of the manuscript.

Funding: The project was financed by the Minister of Science and Higher Education program under the name "Regional Initiative of Excellence" in 2019–2022. Project number: 002/RID/2021/22.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee (document's signature: KB-0012/45/2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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

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Journal of
Clinical Medicine

MDPI

Review

Alterations to Kidney Physiology during Cardiopulmonary Bypass—A Narrative Review of the Literature and Practical Remarks

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Abstract: Introduction: According to different authors, cardiac surgery-associated acute kidney injury (CSA-AKI) incidence can be as high as 20–50%. This complication increases postoperative morbidity and mortality and impairs long-term kidney function in some patients. This review aims to summarize current knowledge regarding alterations to renal physiology during cardiopulmonary bypass (CPB) and to discuss possible nephroprotective strategies for cardiac surgeries. Relevant sections: Systemic and renal circulation, Vasoactive drugs, Fluid balance and Osmotic regulation and Inflammatory response. Conclusions: Considering the available scientific evidence, it is concluded that adequate kidney perfusion and fluid balance are the most critical factors determining postoperative kidney function. By adequate perfusion, one should understand perfusion with proper oxygen delivery and sufficient perfusion pressure. Maintaining the fluid balance is imperative for a normal kidney filtration process, which is essential for preserving the intra- and postoperative kidney function. Future directions: The review of the available literature regarding kidney function during cardiac surgery revealed a need for a more holistic approach to this subject.

Keywords: cardiac surgery; clinical physiology; cardiopulmonary bypass; acute kidney injury

Citation: Udzik, J.; Pacholewicz, J.; Biskupski, A.; Walerowicz, P.; Januszkiewicz, K.; Kwiatkowska, E. Alterations to Kidney Physiology during Cardiopulmonary Bypass—A Narrative Review of the Literature and Practical Remarks. *J. Clin. Med.* **2023**, *12*, 6894. https://doi.org/10.3390/jcm12216894

Academic Editor: Bernhard Rauch

Received: 8 October 2023
Accepted: 31 October 2023
Published: 1 November 2023

1. Introduction

Recent data estimate that about a million patients undergo cardiac surgery every year [1]. Of these, 20 to even 50%, according to some authors, will suffer from cardiac surgery associated acute kidney injury (CSA-AKI) [2–4]. Apart from its high incidence, this complication bears severe consequences for the patient's health. It increases postoperative morbidity and mortality [2,5,6], and can result in the development of chronic kidney disease (CKD) [4,7].

Cardiopulmonary bypass (CPB) is a technique that allows one to conduct most valvular procedures and coronary surgeries while having the heart in diastole. It preserves systemic blood circulation and provides very effective blood oxygenation. However, it is also the reason for many complications associated with heart surgery, such as excessive blood loss, systemic inflammatory response syndrome (SIRS), cerebral stroke, and AKI [8]. If not for the use of the CPB, cardiac surgery might have a complication rate similar to prolonged non-cardiac surgeries. Moreover, the off-pump cardiac surgeries have the advantage of shorter operation time (no time spent on cannulation, decannulation, and reperfusion) and no need for great vessels' cannulation, which reduces the surgical trauma. Nonetheless, CPB enables the surgeon to perform operations involving the opening of the aorta and/or chambers of the heart (e.g., valvular surgery, correction of the septal defects

within the heart). The most common cardiac surgery—coronary artery bypass grafting (CABG) [9]—can be performed without the use of CPB, but it renders the operation technically difficult and is not preferred by most surgeons [10]. All things considered, CPB has its disadvantages and related complications but is otherwise indispensable to cardiac surgery.

In order to understand how the kidneys are being damaged during cardiac surgery, one has to realize all the alterations to the functioning of the human body once extracorporeal circulation is initiated. Cardiac output (CO) is replaced with the CPB pump flow; therefore, the perfusionist controls the blood flow through the entire body, as well as the pressure within the arterial system. Priming solution filling the CPB circuit fuses with the patient's blood, causing hemodilution and decreasing the oxygen-carrying capacity of the blood (CaO_2). Both priming and cardioplegic solutions used to stop and protect the heart are highly osmotic fluids which increase the osmolality of the intravascular and interstitial fluid. Leukocytes in the blood come in contact with the artificial surface of the CPB tubing system, which causes their activation and leads to the induction of the inflammatory response [11]. Should any organ or tissue become ischemic during the CPB, it will suffer from ischemia-reperfusion injury (IRI) after weaning from it.

Three major factors can cause AKI: prerenal, renal, and postrenal. The prerenal causes dominate during cardiac surgery, followed by the renal factors. In this review, the authors discuss the alterations to renal physiology during the CPB and address the key factors influencing kidney function during and after cardiac surgery. This review aims to highlight the importance of perioperative care in the prevention of CSA-AKI and to provide practical suggestions on nephroprotective strategies during cardiac surgery.

2. Relevant Sections

2.1. Systemic and Renal Circulation

Before the beginning of CPB, the tubing system needs to be connected to the patient's circulatory system. The venous cannula (or cannulas) is placed in the vena cava and usually passes through the right atrium. This compromises the blood's return to the heart and decreases CO before CPB begins. Together, with a decrease in CO, there is a decrease in the mean arterial pressure (MAP). Though the time when the heart and the great vessels are cannulated but the CPB is not yet started is usually short, it is essential to maintain an adequate CO and MAP at all times. Even a period of hypotension (defined as MAP < 65 mmHg) as short as 10 min increases the risk of kidney injury [12]. Possible interventions at this stage of surgery involve raising the patient's legs (to increase preload) or starting a low-dose adrenaline infusion ($\leq$0.05 µg/kg/min).

There are three components of effective circulation: blood flow, CaO_2, and perfusion pressure. Without the first two, the oxygen delivery (DO_2) to the tissues will be compromised. Most standard CPB protocols include the pump flow rate of 2.4–2.8 L/min/m^2 for normothermic CPB [13]. There is, however, an increasing number of scientific evidence that perfusion during the CPB should be goal-directed (goal directed perfusion—GDP) [14–16]. The CaO_2 decrease associated with hemodilution varies between the patients, so the pump flow should be adjusted for each patient to maintain an adequate DO_2. This is the essence of the GDP approach—adjusting blood flow (CPB pump performance) to reduced CaO_2 to maintain desired DO_2. Some researchers advocate that the DO_2 indexed for the body surface area (iDO_2) should be kept above a critical threshold in order to prevent AKI. De Somer et al. [16] determined it to be 262 mL/min/m^2, and Mukaida et al. [15] set it at 300 mL/min/m^2. Ranucci et al. [17] also proved that maintaining an $iDO_2 \geq 280$ mL/min/m^2 during the CPB reduces CSA-AKI incidence. Srey et al. [18] applied the idea of Ranucci and his team but simplified the method. Continuous iDO_2 monitors used by Ranucci are an expensive tool. For this reason, Srey and his team devised a formula that allows for easy calculation of the safe minimal flow rate, knowing the patient's body surface area (BSA) and current hemoglobin level. The method assumes the nadir iDO_2 of 280 mL/min/m^2 and is an easy and affordable solution that can improve the postoperative outcome regarding kidney function.

Perfusion pressure is a derivative of blood flow and systemic vascular resistance (SVR) [19]. The latter usually decreases during the CPB [20] due to loss of the pulsatile blood flow [21], and also some biochemical and immunological alterations known as the vasoplegic syndrome [22,23]. The pulse wave is initiated by the left ventricular stroke volume stretching the elastic wall of the aorta [24]. This wave of recurring expansion and contraction of the arterial wall travels down to the smallest arterioles thanks to the elastic fibers of the tunica media. The force exerted on the intravascular fluid by these fibers is an essential component of the SVR. Thus, when a continuous flow of the CPB pump is applied, the SVR decreases. A full description of the pathogenesis of vasoplegic syndrome exceeds the scope of this article. It will suffice to say that it involves, among other factors, leukocyte activation, cytokine release (such as IL-6 or TNF-α), and an increase in nitric oxide production in the epithelium [22]. All these factors promote vasodilation, which in such cases can be resistant to vasopressor agents. Another factor that exacerbates vasoplegia during cardiac surgery is the influence of general anesthesia [25,26]. This factor is not unique to cardiac surgery but is especially pronounced here as high doses of fentanyl are used during this type of procedure, which may enhance vasodilation [27–29].

If the CPB pump flow is not high enough to compensate for decreased SVR, the pressure within the arterial tree will also decrease. In some medical professionals, there is a notion that systemic pressure during the CPB is of secondary importance as the CPB pump provides an adequate blood flow, and there is a very effective gas exchange in the oxygenator. This notion is not true. Certain areas of the circulatory system are highly dependent on blood flow pressure. Such areas involve cerebral [30] and renal arteries [31]. The anatomy of the renal arterial system differs from the other organs in the human body. The final branches of the renal artery—the afferent arterioles—divide and form the capillary net of the kidney glomerulus [32]. Subsequently, they reassemble into the efferent arteriole instead of forming the postcapillary veins. The efferent arterioles then follow the ascending limb of the Henle's loop and divide again into capillaries surrounding the tubules. The capillaries then reassemble into veins, which arise alongside the descending limb of the Henle's loop and confluence into greater vessels. Only a small percentage of arterial blood bypasses the glomerulus and is shunted directly into the postglomerular arteries [33]. This unique structure of the kidney vessels (capillaries reassembling into arteries) enables the creation of an outwardly directed pressure gradient within the kidney glomerulus—the effective filtration pressure (EFP). The efferent arterioles' diameter, which is smaller than the afferent arterioles, facilitates this process. This anatomical dependency between the glomerular and peritubular vessels results in the blood flow through the peritubular vessels being almost entirely dependent on the outflow from the efferent arterioles.

The afferent and efferent arterioles are the guardians of the EFP. The afferent arteriole is equipped with a pressure sensor known as the juxtaglomerular cells [34]. Should the blood pressure within the afferent arteriole decrease, these cells will release renin, the first enzyme of the renin-angiotensin-aldosterone (RAA) axis. The RAA system is activated by low systemic pressure and is set on raising it to normal values. The threshold pressure value that activates the juxtaglomerular cells is 70–90 mmHg, according to different authors [31,35,36]. Brzozowski et al. [36] state that renin-release increases when the blood pressure falls below 90 mmHg, and that serum renin concentration doubles with every 5 mmHg of the pressure drop. Renin is an enzyme that converts Angiotensinogen to Angiotensin I (Ang I), which is later converted to Angiotensin II (Ang II) [37]. Ang II is a powerful systemic vasopressor, but it also has a particular effect on the kidneys. It constricts both the afferent and efferent arterioles. However, there is a more significant increase in the efferent arteriole resistance [38] due to its smaller resting diameter [39] and greater angiotensin receptors' density in the efferent arteriole [40]. The net effect of this action is a rise in the EFP and a decrease in blood flow to the postglomerular vessels. The experimental mammalian studies show that a steady state response of the efferent arteriole to the Ang II is a 30% diameter reduction [41]. This means an over 4-fold increase in vascular resistance.

Combined with reduced in-flow (due to afferent arteriole constriction), the blood flow to the postglomerular vessels becomes markedly decreased.

In their study, Küllmar et al. [42] demonstrated that increased plasma renin concentration was associated with cardiovascular instability and a higher incidence of CSA-AKI after cardiac surgeries. Lannemyr et al. [43] conducted a study involving renal vessel catheterization and concluded that renal perfusion decreases during the CPB due to renal vasoconstriction. The reason for this result is most probably the MAP value of 60–80 mmHg that was maintained in this study, which was probably below the kidneys' autoregulatory threshold and provoked renin release.

The tubules are a very metabolically active region of the kidney, as numerous ATP-dependent ion transporters are located within their walls [44]. The cortical tubules can meet this high energy demand thanks to the high blood flow in this area of the kidney [45]. The medullary tubules, however, have a considerably lower blood supply—they receive 10–15% of the total renal blood flow (RBF). The efferent arterioles originating from juxtamedullary nephrons (15% of the total nephrons' count [46]) penetrate the medulla as descending vasa recta (DVR). They divide into the capillaries and reassemble into the ascending vasa recta (AVR), which confluence with the cortical veins. The blood flow through the medulla is restricted [47] in order to allow for an effective substance exchange between the intratubular fluid and the intravascular fluid and also to prevent the washing out of the medullary osmotic gradient [45]. The parallel arrangement of the DVR and AVR necessary for countercurrent substance exchange is also the reason for oxygen shunting from the DVR to AVR, as some of the oxygen that diffuses from the DVR is not absorbed by the tubular cells but returns to the AVR [33].

There is one other important reason for maintaining sufficient perfusion pressure during the CPB. Most patients undergoing cardiac surgery are elderly, and coronary artery disease is still the most common reason for surgical intervention [9]. Suppose the patient has highly advanced atherosclerosis within the coronary arteries. In that case, it is justified to assume that he or she probably has atherosclerotic lesions in other regions of the arterial tree [48]. Renal artery stenosis more significant than 50–60% can significantly impair RBF [49], which would only worsen during the CPB. Atherosclerotic lesions cause a local increase in vascular resistance; sufficient flow pressure is required to overcome this resistance. Because of the loss of pulsation in the vascular bed during the CPB, the peak pressures achieved within the arterial system are lower than normal at the same MAP values. This is yet another argument in favor of keeping high perfusion pressure during the CPB, especially if the patient has a history of disseminated atherosclerosis. A patient's MAP before the induction of general anesthesia can be a helpful indicator of what MAP value the patient requires.

To summarize this section, during the CPB, the kidneys need both the adequate iDO_2 and blood pressure for proper functioning. According to recent studies, the iDO_2 of 260–300 $mL/min/m^2$ seems to be the lower threshold value necessary to maintain normal kidney oxygenation. The lower MAP threshold appears to be 70–90 mmHg. Below this MAP value, the kidneys start to release renin to raise the systemic blood pressure and maintain the EFP. This significantly reduces blood flow to the peritubular vessels and increases the risk of renal ischemia. This risk is especially high within the kidney medulla, as it is a highly metabolically active region and blood flow in this area is already limited under normal conditions. Adjusting the CPB pump flow is the simplest and most efficient method to obtain an adequate iDO_2 and perfusion pressure. It brings an instant effect, can be easily modified if needed, and mimics a physiological response of the organism to decreased CaO_2.

2.2. Vasoactive Drugs

2.2.1. Norepinephrine

Norepinephrine is an agonist of alpha-1 and beta-1 adrenergic receptors [50]. Apart from small doses (<0.03 μg/kg/min), norepinephrine's alpha agonism predominates and

it acts as a potent vasopressor, not an inotrope. Norepinephrine increases the SVR and afterload, but it also influences the venous portion of the vascular system. Constricting the small veins decreases the volume of blood stored within the venous system and increases the preload. This action of norepinephrine is most pronounced in states of pathological vasodilation, such as sepsis [51]. Because CPB provokes vasoplegia, norepinephrine can restore physiological vascular resistance. On the other hand, vasoconstriction caused by norepinephrine may lead to ischemia in certain body areas (such as skeletal muscles, skin, and intestines) [52]. This could increase lactate production [53] and cause subsequent systemic acidosis, but the literature on this subject is equivocal [54]. Concerning kidney function, there are numerous studies that report the detrimental effect of norepinephrine on kidney function [55–58]. However, in some of these studies, there were high doses of norepinephrine administered, e.g., Azau et al. [56] administered doses as high as 0.37 μg/kg/min, and Vedel et al. [57] administered doses as high as 0.4 μg/kg/min. Bellomo et al. [59], in their review, argue that norepinephrine can be beneficial for kidney function if used properly. Norepinephrine should only be used to restore normal vascular resistance. It should not be used to artificially raise the systemic blood pressure if the pathology underlying hypotension is hypovolemia or inadequately low CO. In such instances, norepinephrine is likely to cause tissue hypoperfusion and exacerbate organ damage. Therefore, norepinephrine should be perceived as an adjuvant to intraoperative care and administered only after the patient is provided with an adequate CO and properly hydrated. Considering the results of previous studies [56,57], lower norepinephrine doses are encouraged ($\leq$0.1 μg/kg/min).

2.2.2. Epinephrine

Epinephrine is a catecholamine exerting a sympathomimetic effect on both alpha- and beta-adrenergic receptors [60]. Its pharmacodynamic properties comprise increase in heart rate, greater heart muscle contractility, increase in SVR (including renal vessels vasoconstriction), and bronchodilatation. In small doses, epinephrine has greater affinity to beta receptors, and in large doses it becomes selective to alpha receptors. As the heart muscle is excluded from circulation during the CPB, epinephrine has limited use during the procedure itself [61,62]. However, some authors found it beneficial for weaning from the CPB [63].

2.2.3. Dopamine

Dopamine is a vasoactive agent which action is highly dependent on the dosage. In low doses (0.5–2 μg/kg/min), it dilates the visceral vessels, including the renal arteries. Moderate doses (2–10 μg/kg/min) increase cardiac output through augmented contractility and conductivity within the heart muscle. High doses (>10 μg/kg/min) increase SVR through action on the alpha- and beta-adrenergic receptors [64]. Theoretically, the vasodilatory effect on renal arteries improves the renal blood flow [65] and increases diuresis [66]. Nevertheless, the benefits of low-dose dopamine infusion during the CPB remain questionable [67]. As it would require high doses of dopamine to achieve its vasoconstrictive action, this catecholamine is not a first-choice drug in cardiac surgery.

2.2.4. Fenoldopam

Fenoldopam is a dopamine receptor agonist that dilatates the peripheral arteries and lowers blood pressure [68]. Its action is most pronounced in renal arteries. Increased renal blood flow increases diuresis and natriuresis, thus augmenting the hypotensive action of this drug. Lee et al. [69] developed a simulation model proving that fenoldopam infusion is the most effective strategy for maintaining optimal renal perfusion during cardiac surgery. As vascular resistance usually decreases during the CPB, fenoldopam's use in this setting is limited. However, if perfusion pressure remains high after the initiation of CPB, fenoldopam infusion can benefit both systemic circulation and renal blood flow.

2.2.5. Nitroglycerine

Nitroglycerine is a vasodilatory drug that acts by donating a nitric group (NO), which relaxes the vascular smooth muscles [70]. Nitroglycerine dilatates small venous vessels (decreasing the preload) as well as resistant arteries (decreasing the afterload and systemic pressure). Venous vasculature dilatation has one more effect: increasing the volume of blood stored within this part of the circulatory system. The vascular resistance during the CPB usually decreases, partially due to endogenous nitric oxide release. For this reason, nitroglycerine is reserved for patients with increased vascular tone and perfusion pressure during the CPB. Nitroglycerine is also beneficial for kidney perfusion and increases diuresis [71].

2.2.6. Nesiritide

Nesiritide is a recombinant human B-type natriuretic peptide (BNP), that causes vasodilation (including renal arteries), natriuresis, and RAA system inhibition [72]. Such mechanisms of action make it especially feasible for application in cardiac surgery. A meta-analysis conducted by Mitaka et al. [73] demonstrated that intraoperative BNP infusion increases the urine output and glomerular filtration rate, as well as reduces the postoperative serum creatinine levels. Also, a decreased time of ICU stay and hospital stay in patients treated with nesiritide was demonstrated in this study. Chen et al. [74] proved that patients with preoperative renal dysfunction also benefit from nesiritide infusion during cardiac surgery. Patients with preoperative left ventricular dysfunction had better kidney function and shorter hospital stay after intraoperative nesiritide infusion [75].

2.2.7. Methylene Blue

Methylene blue is used during the CPB because of its potential to counteract the vasoplegic syndrome through the inhibition of nitric oxide synthase [76]. Kofler et al. [77] demonstrated an additive effect of methylene blue and other vasopressors in patients unresponsive to norepinephrine and vasopressin infusion. Similar conclusions were reached by other authors [78,79]. This proves that methylene blue is an effective agent against vasopressor-resistant vasoplegia during cardiac surgery. However, the impact of methylene blue on kidney function is debatable. In the study by Kofler et al., there was a significant rise in the postoperative serum creatinine concentration in patients receiving methylene blue compared to the control group. On the other hand, in the study by Mehaffey et al. [79], early administration of methylene blue reduced the incidence of postoperative renal failure. Considering the deleterious impact of vasoplegic syndrome and severe hypotension on kidney function, the use of methylene blue is a promising solution, but further investigation is needed to confirm its safety in terms of kidney function.

2.3. Fluid Balance and Osmotic Regulation

Water homeostasis is of vital importance to human health under any circumstances. Cardiac surgery, however, poses an exceptional challenge for maintaining fluid balance. Several factors can impact this balance: preoperative fasting, intraoperative evaporation from internal organs, high osmolality fluids infusion, and altered capillary fluid filtration.

Normal total water intake ranges from 2000–2700 mL/day for women and 2500–3700 mL/day for men, according to different health organizations worldwide [80]. When a patient reports to a hospital for scheduled admission, he or she usually comes in on an empty stomach for the purpose of laboratory tests. After admission, the patient is allowed to eat and drink according to his or her needs until the evening. Preoperative anxiety, however, causes some patients to reduce their food and fluid intake. The above factors considered, and after all night fasting, a significant percentage of the patients enter the operating theatre with various degrees of dehydration [81,82]. This type of dehydration can be classified as hypertonic dehydration, as it is caused by insufficient fluid intake with none to minimal solutes loss [83]. It results in intracellular fluid (ICF) movement to the extracellular compartment [84]. This allows for maintaining normal extracellular fluid

(ECF) and plasma volume. Experimental studies indicate that in this kind of dehydration, the ICF deficits can persist even after three hours of ad libitum rehydration [85].

During cardiac surgery, two major factors exacerbate the patient's hypertonic dehydration. First, the evaporation from mucosal membranes of the mediastinum and intrathoracic organs can account for 1000 mL of insensible water loss during routine CABG procedure [86]. The second factor is hypertonic fluids administration: the priming fluid of the CPB circuit and cardioplegic solution, which cause water to shift from the intracellular space to the extracellular space. The priming solution is highly hypertonic, reaching between 379 mOsm/l [87] and even 580 mOsm/l [88], according to data presented by different authors. The main reason for the high osmolality of this solution is the addition of mannitol. Intravenous mannitol is restricted to the extracellular compartment; it does not enter the cells [89]. After administration, a steady state is reached between the intravascular and extravascular mannitol concentration, shifting towards the vessels as mannitol is secreted with urine. It binds the water molecules that move freely between the intracellular and extracellular compartments, causing cells' dehydration and osmotic diuresis. For these reasons, mannitol is known as a nephrotoxic agent. The effect of cardioplegia is similar, as standard cardioplegic solutions are also hypertonic (300–375 mOsm/l) [90]. Cardioplegia is administered to the ostia of the coronary arteries, but eventually, it reaches systemic circulation through the cardiac veins and venous cannula of the CPB circuit. The standard priming volume is 1400–1800 mL [91], and cardioplegia is 1100 mL for a single dose of Del Nido cardioplegia [92]. Gunnar et al. [93] demonstrated a significant increase in plasma osmolality after the commencement of CPB (322 $\pm$ 17 mOsm/kg). Hyperosmolality persists throughout the procedure (309 mOsm/kg in Gunnar's population) and normalizes only on the first postoperative day. Hyperosmotic environment causes a water shift from the cells to the extracellular compartment, which may damage organs such as the kidneys or the brain and disrupt the immune system's function [94]. Plasma osmolality of 320 mOsm/kg is reported to increase the risk of AKI. Dąbrowski et al. [94] also mention that hyperosmolality is especially detrimental to the kidneys as it forces osmotic diuresis within the glomerulus, thus reducing medullary blood flow.

One of the possible solutions to the problem of a high-volume priming fluid is using a miniaturized CPB circuit (mini-CPB). It is widely applied in the field of cardiac surgery [95,96], and apart from reducing the priming volume, it also reduces the need for blood transfusion, decreases the incidence of postoperative arrhythmias, and improves the overall treatment outcomes [97].

Another approach that can make the CPB more physiological and decrease the priming-related osmotic load is using albumins in the priming solution [98,99]. The need for a highly osmotic priming fluid is derived from the fact that this extra volume needs to be kept within the intravascular compartment. As discussed above, the priming fluid is also distributed within the interstitial space, but eventually, it returns to the vessels due to the osmotic gradient. Albumin exerts vessel-directed oncotic pressure [100] (as its concentration is higher in the serum than in the interstitial fluid) and could keep the extra volume within the vessels during the CPB. Russell et al. [99] demonstrated in their meta-analysis that using albumins in the priming solution improves the fluid balance and augments platelet preservation during the CPB. The same conclusion was reached by the expert consensus of Xiang et al. [101] One of the major issues with albumin usage is its high cost, and there are no randomized controlled trials demonstrating albumin's superiority regarding postoperative outcomes such as mortality, ICU stay time, or organ dysfunction. All in all, albumin addition to the priming solution appears to be a promising perspective, but further scientific evidence is needed to confirm its suitability.

Another untrue notion amongst some medical professionals regarding hydration is that the patient does not need rehydration before cardiac surgery, as he or she will receive a lot of intravenous fluids during the procedure. As demonstrated above, the cardiac surgery patient is administered a significant amount of hyperosmolar fluids, which may cause cell damage and exacerbate hypertonic dehydration. Moreover, colloids (such as mannitol)

may cause damage to the endothelial glycocalyx [102]. Therefore, to maintain normal fluid homeostasis, the patient must be intensively hydrated the day before the surgery to allow proper water distribution between the fluid compartments and sufficient cells hydration. It is safe to assume that on the day before the operation, the patients may reduce their fluid intake by half, so 1000 mL of fluids for women and 1500 mL for men appears to be a reasonable regimen based on their daily demand [80]. Needless to say, this concerns patients with no severe renal function impairment or congestive heart failure. In patients with normal kidney function and no relevant fluid congestion, the risk of fluid overload is very low, so the approach to fluid therapy in this instant can be liberal. There is no physiological advantage of intravenous rehydration over oral rehydration [103], but the patient's compliance is obviously better with intravenous fluids administration. On the day of the operation, the sleep-related water deficit should be corrected before the patient is admitted to the operating theater. Intravenous-balanced crystalloids may be applied here, as well as special oral rehydration solutions [104,105]. Following the recommended 25–35 mL/kg/day maintenance fluid volume [106] and assuming an eight-hour sleep, an average 80 kg patient should be given around 800 mL of fluids. Another advantage of liberal fluid therapy in this setting is the increased clearance of metabolites eliminated through the kidneys (e.g., creatinine, urea). This is beneficial as it renders the filtration process easier for the kidneys during the challenging time of surgery and CPB.

The clinical significance of altered capillary fluid filtration is hard to estimate as it changes significantly with systemic and interstitial fluid pressure, according to Starling's equation [107]. A decrease in the transcapillary filtration rate can be expected in patients with low MAP during the CPB. Increased interstitial fluid pressure (e.g., in congestive heart failure) may exacerbate this effect. On the other hand, an inflammatory response associated with CPB is believed by some authors to create a "capillary leakage", which increases fluid extravasation during and after cardiac surgery [108]. However, the data on this subject is inconsistent, and some authors deny the existence of such a phenomenon [109]. Infusing hypertonic solutions increases the osmolality of the intravascular fluid, but it also decreases the intravascular oncotic pressure due to a greater dilution of albumin. In time, the ions and mannitol diffuse through the capillary barrier, changing the driving forces of filtration yet again. The net effect of these changes is hard to estimate. Disruption in the interstitial fluid production and absorption can lead to inadequate substance exchange between the vessels and the cells, as well as impaired metabolite clearance. Maintaining physiological MAP during the CPB and proper hydration seems reasonable to optimize the capillary filtration during cardiac surgery.

A fundamental issue concerning water balance during the CPB is intraoperative fluids administration. As mentioned above, priming fluid and cardioplegic solution are hyperosmotic and do not provide proper hydration. Moreover, they exacerbate hypertonic dehydration of the cells and pose a significant challenge for the kidneys. Therefore, a reasonable intraoperative fluid administration regimen is needed using balanced crystalloids. Needless to say, fluid infusion comes at the cost of decreasing the CaO_2. Balance must always be kept between proper hydration and adequate iDO_2. Where does the compromise lie, then? Considering the vast literature describing the detrimental effects of inadequate iDO214–18, it is not advised to prioritize hydration over maintaining an acceptable CaO_2. A balanced crystalloid solution should be administered continuously during the procedure (large fluid boluses should be avoided), and provided a satisfying CaO_2, the infusion rate should be guided by urine output. Hori et al. [110] defined oliguria during the CPB as diuresis < 1.5 mL/kg/h. Song et al. [111] found that diuresis < 4 mL/kg/h during the CPB is an independent AKI predictor. Considering a tremendous osmotic load associated with CPB commencement, the threshold of 4 mL/kg/h of urine output does not appear steep. Currently, closed-loop systems (e.g., Renal Guard®) adjust the intravenous fluids' infusion rate to urine output in real time, which allows for a significant AKI incidence reduction [112].

Intraoperative hemofiltration is another procedure that significantly influences fluid balance during cardiac surgery. It allows for removing intravascular fluid, ions, and metabolites [8]. There are also strategies of using hemofiltration as a mean to remove proinflammatory cytokines during the CPB [113]. Unfortunately, there are no set indications for applying hemofiltration during the CPB. It is most commonly used in cases of severe hemodilution after the initiation of CPB or in severe hyperkaliemia. The therapeutic potential of hemofiltration is based on excessive intravascular fluid and metabolite removal. In normal settings, fluid overload and congestion cause increased venous pressure and interstitial oedema within the kidneys [114]. This impairs kidney function and makes removing excessive fluid through renal filtration impossible. However, when the CPB is initiated, there can be no intravascular fluid excess or congestion as the venous reservoir stores the excessive volume (assuming proper venous return). Therefore, fluid removal in this instance should be directed to achieve adequate hemoglobin concentration. Another factor is that the patient will eventually wean from the CPB, and most of the CPB circuit volume will be returned to circulation. In the case of fluid excess, hemofiltration should also be targeted to provide an adequate fluid balance in the post-CPB period. Intraoperative hypovolemia should be avoided though, as it has a proven detrimental impact on kidney function [115,116]. A further significant benefit of hemofiltration during the CPB is osmotic load and metabolite removal. This can facilitate kidney function after weaning from CPB. The literature reports no difference [117] or positive outcomes [118] of applying intraoperative hemofiltration regarding kidney function. This discrepancy may be due to the application of zero balance ultrafiltration in the study by Matata et al. [118] and the lack of data regarding fluid balance in the study by Kandil et al. [117]. All in all, the available data suggest that intraoperative hemofiltration can be beneficial for kidney function, especially in patients with decreased preoperative filtration rate. It should be applied to counteract excessive hemodilution and to remove osmotic load (e.g., when repeated cardioplegia infusions are needed). Hypovolemia must be avoided, and proper fluid balance must be maintained.

Furosemide is a loop diuretic agent, which can be utilized during cardiac surgery to promote diuresis and increase renal exertion of potassium, sodium, and chlorine ions [119]. The net effect of furosemide administration is similar to the use of hemofiltration: it decreases the intravascular volume and enhances ion removal. The vital difference is that furosemide does not improve creatinine and urea clearance, and furosemide-induced diuresis is not a sign of proper kidney function after cardiac surgery [120,121]. There are reports of furosemide's positive impact on kidney function after cardiac surgery [112,122], which is probably related to maintaining a proper fluid balance. Other authors found no benefit of furosemide use in the perioperative period, including no difference in the need for renal replacement therapy after the surgery [123–125]. Zheng et al. [126] found that preoperative use of furosemide was associated with higher CSA-AKI risk.

2.4. Inflammatory Response

CPB is associated with a response of the immune system [11,127]. The main reasons for this are surgical trauma and blood exposure to large foreign surfaces (the CPB tubing system). Both cellular and humoral mechanisms are involved. Leukocytes roll along the CPB circuit's artificial surface, eventually leading to their activation [128]. Similarly, contact between the artificial surface and C5a and C3d cytokines triggers the complement activation, which induces humoral inflammatory response [127]. Increased immune system activation decreases the total vascular resistance [22] and may change capillary permeability [108]. It is associated with worse clinical outcomes after cardiac surgery [129,130], including a higher incidence of AKI [131,132].

The ischemia-reperfusion injury is a particular form of inflammatory response that occurs after the blood flow is restored to previously ischemic tissues [133–136]. During ischemia, the ATP shortage results in a failure of the ATP-dependent ionic pumps and consequent intracellular sodium increase followed by an osmotic cells' swelling. Calcium-

related protease activation leads to the degradation of the cellular membrane. Gene expression is also disrupted in ischemic conditions. A plethora of genes are activated during hypoxia, leading to the increased translation of cytokines and proinflammatory mediators. During reperfusion, the influx of oxygen catalyzes the synthesis of reactive oxygen species (ROS). ROS are involved in a degradation of the lipid structures of the cellular membrane and subsequent eicosanoid synthesis, endothelial cells' activation, and adhesion molecules expression. Neutrophils activated by the proinflammatory cytokines are a further source of ROS and proteases that augment tissue destruction.

Some strategies have been developed to decrease the immune response associated with cardiac surgery and CPB. These involve the use of heparin-coated CPB circuits [137], pharmacological interventions (e.g., polyethylene glycol, infliximab, sildenafil, nitro-linoleate, resveratrol, trimetazidine, and others) [135], and also aerobic exercise-induced preconditioning [138]. However, currently, there is no universal and widely accepted solution to this problem [130,139,140]. In light of this, it appears that the best strategy so far is to avoid organ ischemia during cardiac surgery to eliminate the IRI component of the generalized surgery-associated inflammatory response.

3. Conclusions

As demonstrated in this review, there are numerous alterations to kidney physiology during cardiac surgery. Considering the available scientific evidence, it is concluded that adequate kidney perfusion and fluid balance are the most critical factors determining postoperative kidney function. By adequate perfusion, one should understand perfusion with proper oxygen delivery and sufficient perfusion pressure. Maintaining the fluid balance is imperative for a normal kidney filtration process, which is essential for preserving the intra and postoperative kidney function. Vasopressors are an ally in maintaining normal kidney perfusion during cardiac surgery, provided they are used to correct the surgery-associated vasoplegia, not abnormalities of a different origin.

KEY POINTS:

- Provide an iDO_2 no lower than 260–300 mL/min/m^2 during the CPB
- Maintain MAP no lower than 70–90 mmHg during the whole procedure
- Use small doses of norepinephrine (preferably < 0.1 µg/kg/min) to correct the vasoplegia associated with general anesthesia and CPB
- Start hydrating the patient on the day preceding the surgery and continue hydration during the perioperative period
- During the CPB, keep the fluid balance that allows for a diuresis of ≥4 mL/kg/h (do not abuse furosemide!)

4. Future Directions

The review of the available literature regarding kidney function during cardiac surgery revealed that there is a need for a more holistic approach to this subject. As described above, there are several factors crucial for preserving kidney function during the CPB: adequate iDO_2, high MAP, and a proper fluid balance. There is no evidence of the superiority of any of these factors over the others, hence the need to address them simultaneously in future studies in this area. Likewise, some other nephroprotective strategies could be implemented together to test their combined performance, e.g., mini-CPB with a heparin-coated tubing system and the addition of a nephroprotective pharmacological agent.

Author Contributions: Conceptualization, J.U. and E.K.; methodology, A.B.; investigation, J.U. and P.W.; writing—original draft preparation, J.U., A.B. and P.W.; writing—review and editing, J.P. and K.J.; supervision, J.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: There is no additional data for this study.

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

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Załącznik 4 - Higher perfusion pressure and pump flow during cardiopulmonary bypass are beneficial for kidney function–a single-centre prospective study. Front. Physiol. 2024, 15:1257631.

frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 14 February 2024
DOI 10.3389/fphys.2024.1257631

OPEN ACCESS

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RECEIVED 12 July 2023
ACCEPTED 29 January 2024
PUBLISHED 14 February 2024

CITATION
Udzik J, Pacholewicz J, Biskupski A, Safranow K, Wojciechowska-Koszko I, Kwiatkowski P, Roszkowska P, Rogulska K, Dziedziejko V, Marcinowska Z, Kwiatkowski S and Kwiatkowska E (2024), Higher perfusion pressure and pump flow during cardiopulmonary bypass are beneficial for kidney function–a single-centre prospective study.
Front. Physiol. 15:1257631.
doi: 10.3389/fphys.2024.1257631

Higher perfusion pressure and pump flow during cardiopulmonary bypass are beneficial for kidney function–a single-centre prospective study

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Background: Kidneys play an essential role in the circulatory system, regulating blood pressure and intravascular volume. They are also set on maintaining an adequate filtration pressure in the glomerulus. During the CPB, a decrease in systemic blood pressure and hemoglobin concentration may lead to renal ischemia and subsequent acute kidney injury.

Methods: One hundred nine adult patients were prospectively enrolled in this study. The intervention in this study was increasing the flow of the CPB pump to reach the target MAP of > 90 mmHg during the procedure. The control group had a standard pump flow of 2.4 L/min/m^2.

Results: Standard pump flow of 2.4 L/min/m^2 resulted in mean MAP < 90 mmHg during the CPB in most patients in the control group. Maintaining a higher MAP during CPB in this study population did not affect CSA-AKI incidence. However, it increased the intraoperative and postoperative diuresis and decreased renin release associated with CPB. Higher MAP during the CPB did not increase the incidence of cerebrovascular complications after the operation; patients in the highest MAP group had the lowest incidence of postoperative delirium, but the result did not obtain statistical significance.

Conclusion: Maintaining MAP > 90 mmHg during the CPB positively impacts intraoperative and postoperative kidney function. It significantly reduces renal hypoperfusion during the procedure compared to MAP < 70 mmHg. MAP > 90 mmHg is safe for the central nervous system, and preliminary results suggest that it may have a beneficial impact on the incidence of postoperative delirium.

KEYWORDS

cardiac surgery, cardiac anesthesia, cardiopulmonary bypass, acute kidney injury, mean arterial pressure

Introduction

Since the introduction of the cardiopulmonary bypass (CPB) technique in 1952, there has been an ongoing debate on the optimal conditions for this procedure. The plethora of functions of the circulatory system is not easily replaced, and many factors need to be considered. In this investigation, the authors focused on the Mean Arterial Pressure (MAP) and its impact on postoperative kidney function. Despite its vital importance to the procedure, this parameter is still widely discussed, and no unequivocal conclusion has been reached regarding its optimal range during CPB (Kunst et al., 2019; Kotani et al., 2022).

Kidneys play an important role in the circulatory system as they regulate the intravascular volume and initiate the Renin-Angiotensin-Aldosterone (RAA) axis response. The kidneys are also set on maintaining an adequate filtration pressure in the glomerulus, even at the cost of subsequent ischemia within the medulla. This dependency is due to the unique anatomy of renal vasculature (Navar et al., 2008). The ultimate branches of renal arteries–the afferent arterioles divide into a number of capillaries, forming the glomerulus' vascular net. The capillaries then reassemble to create the efferent arterioles. Efferent arterioles have smaller diameters than the afferent arterioles, creating an outwardly directed pressure gradient that is a driving force of the filtration process. After leaving the glomerulus, the efferent arterioles divide again into peritubular capillaries to enable water and ions exchange with the intratubular filtrate. Only a small fraction of the efferent arterioles descends into the renal medulla as vasa recta, providing blood flow to this area.

The renal medulla is a very metabolically active region, as numerous ion pumps in the ascending limb of the Henle loop move the ions in an ATP-dependent manner. However, the blood flow in the medulla is low (Kennedy-et al., 2013) to preserve the osmotic gradient and allow ions and water absorption into the vasa recta. The balance between oxygen demand and supply in the medulla is a fragile one; for the reasons mentioned above, it greatly depends on the blood flow from the glomerulus.

Kidneys have autoregulatory mechanisms that allow for maintaining a stable blood flow and filtration rate in a wide range of MAP. The lower range limit for this autoregulation is 70–80 mmHg, according to most authors (Jefferson et al., 2010; Burke et al., 2014). Below that threshold, the renal blood flow is decreased, and the juxtaglomerular cells of the afferent arteriole begin to release renin (Lappin). Renin is the first enzyme of the RAA axis, and its release aims to raise systemic blood pressure. The RAA system also has a particular effect on renal circulation. Increased renin level leads to a rise in Angiotensin II (Ang II), a potent vasopressor. Ang II constricts both the afferent and the efferent arteriole within the kidney glomerulus, but its effect is always greater on the efferent arteriole. This results in a rise in the effective filtration pressure but also decreases the amount of blood going to the medulla.

There are a few key changes to the circulation's conditions during the CPB. First, the loss of pulsatile blood flow (both in non-pulsatile and pulsatile CPB pumps (Elbers et al., 2011; Elvevoll et al., 2016)) decreases the vascular resistance via loss of the myogenic autoregulation (Clifford, 2011) and lowers the pressure achieved within the circulatory system. Secondly, hemodilution associated with CPB decreases the Oxygen-Carrying Capacity of the Blood (CaO2), thus reducing the Delivery of Oxygen (DO2) to the tissues (DO2 is standardly indexed for body surface area–iDO2). Realizing this, it stands to reason that to prevent these adverse changes to the circulatory system, it is necessary to maintain adequate perfusion pressure and iDO2 at the same time. The obvious way to achieve this is to increase the flow of the CPB pump (Jufar et al., 2022), as it both raises the perfusion pressure and increases the iDO2 (iDO2 is a derivative of CaO2 and cardiac output, which in this case is replaced by the CPB pump flow).

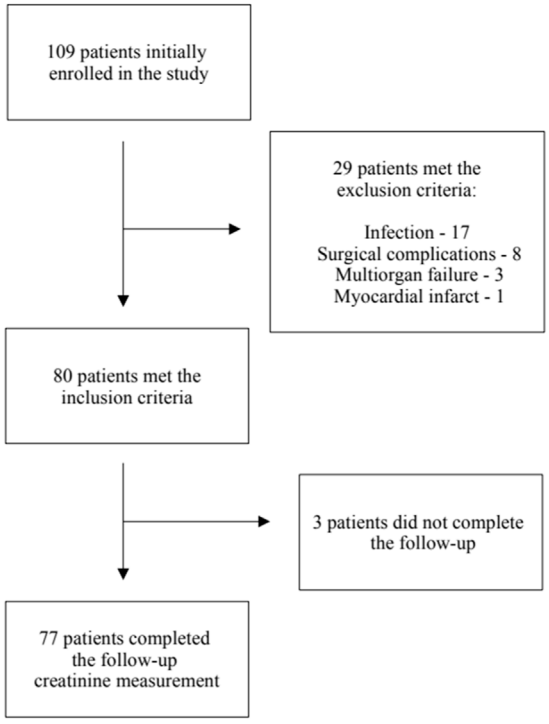
To summarize, if MAP is maintained below the minimal kidney's autoregulatory threshold during the CPB, it decreases the renal blood flow and drastically decreases medullary blood flow (efferent arteriole constriction with Ang II). Should iDO2 decrease as well (insufficient pump flow to compensate for a decreased CaO2), the kidneys will suffer additional ischemic damage, which can result in Cardiac Surgery Associated Acute Kidney Injury (CSA-AKI).

The main objective of this investigation was to assess the impact of increased MAP (achieved by increasing the CPB pump flow) on postoperative kidney function. Selected postoperative complications were also monitored to evaluate the impact of higher pressure on other organs.

Materials and methods

One hundred nine adult patients were prospectively enrolled in this study. After receiving complete information regarding this investigation's potential risks and benefits, each patient gave written consent to participate in the project. The investigation was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The local Bioethical Committee's approval was obtained prior to the patient's recruitment (document's signature: KB-0012/45/2021).

The intervention in this study was increasing the flow of the CPB pump to reach the target MAP of > 90 mmHg during the procedure. The control group had a standard pump flow of 2.4 L/min/m^2. The pump flow in the study group was increased maximally to 150% of the standard flow rate. Catecholamines (adrenaline and noradrenaline) infusion was not a part of the intervention protocol in this study. Vasopressors were administered prior to CPB to maintain MAP > 70 mmHg. During the CPB, vasopressors were usually ceased, and their continuation depended on the decision of the doctor who provided the anesthesia (not an investigative team member). After the study enrolment, every patient was randomized into the study or control group. In order to prevent discrepancies between the groups, the randomization protocol included the patient's gender and age. In the last year, the mean age of patients operated on in the facility where the study occurred was 69 years. The randomization scheme included two groups (<69 years of age and ≥ 69 years of age). Each group had two sub-groups of different gender. A series of letters, "A" or "B" (in equal amounts), was randomly generated for each of the four sub-groups using a computed signs generator. Consecutive patients enrolled in the study were randomly assigned to the study group (A) or the control group (B) within each sub-group based on age and gender.



SCHEME 1
Patient enrolment in the study.

As MAP does not maintain a constant value during the CPB, four MAP ranges were set for the whole study population. After the procedure, each patient was assigned to the MAP range that was dominant during his or her CPB. The ranges were as follows: < 55 mmHg, 56–70 mmHg, 71–90 mmHg, and ≥ 90 mmHg. As only one patient had the dominant CPB MAP of < 55 mmHg, this range was merged with the next one, leaving three MAP ranges in the ultimate result's analysis: < 70 mmHg, 71–90 mmHg, and > 90 mmHg.

Blood and urine samples were taken from each patient at the following time points:

- Blood: before the operation, 6 h after weaning for the CPB
- Urine: before the operation, 6 h after weaning for the CPB, 24 h after the operation, 48 h after the operation, and 5 days after the operation

Blood was collected using S-Monovette 3.4 mL sterile containers (K3 EDTA: 1.6 mg/1 mL of blood; SARSTEDT AG & Co. KG Sarstedtstrasse 1, 51588 Nümbrecht, Germany). Urine was collected using standard non-sterile urine containers. After the collection, samples were stored at 5 C for no longer than 4 h and centrifuged (4°C, 10 min, 4000 RPM). After centrifugation, 1 mL of supernatant was taken and stored at −70°C.

The following kidney injury biomarkers' concentration was measured in the samples:

- Blood: interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor-alpha (TNF-α)
- Urine: neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), matrix metalloproteinase 9 (MMP-9), and interleukin 18 (IL-18)

Quantitative assessment of IL-6, IL-8, and TNF-α (in plasma), as well as NGAL, KIM-1, IL-18, and MMP-9 (in urine) levels in patients enrolled in this study was performed using Luminex xMAP technology (Luminex Corporation, Austin, TX, United States). The concentrations of urine biomarkers were adjusted to creatinine excretion and presented in ng/mg of creatinine (NGAL/Cr, KIM-1/Cr, MMP-9/Cr, IL-18/Cr).

Plasma renin concentration was measured in the preoperative and 6 h after CPB blood samples, using standard ELISA kits (Demeditec Diagnostics GmbH, 24145 Kiel–Germany).

A preoperative creatinine clearance was measured using serum creatinine concentration and CKD-EPI formula. Early postoperative creatinine clearance (6 h after weaning from CPB) was calculated directly from serum and urine creatinine concentrations and urine volume. Urine output was monitored during the whole operation, and diuresis during the CPB was recorded separately.

Study inclusion criteria:

- Written consent to study enrolment
- Undergoing elective cardiac surgery procedure with the use of CPB
- Age at the time of enrolment ≥ 18 years

Study exclusion criteria:

- Postoperative complications involving increased inflammatory response (wound infection, pneumonia, sepsis) or possibly compromising cardiac output and CaO_2 (myocardial infarct, severe blood loss, multi-organ failure)
- Kidney artery stenosis
- Active neoplasm
- Active inflammatory diseases
- KDIGO stage 5 kidney disease
- Postoperative hypotension (MAP < 70 mmHg)

All patients included in the study were monitored for AKI and other postoperative complications for 5 days after the operation. AKI was diagnosed according to the KDIGO criteria (Eknoyan et al., 2014): ≥ 0.3 mg/dL increase in serum creatinine, 50% increase in serum creatinine from the initial value, or diuresis < 0.5 mL/kg/h for at least 6 h. Long-term kidney function was assessed using serum creatinine measurement taken at least 3 months after the operation. The onset or progression of CKD was diagnosed according to KDIGO guidelines (Eknoyan et al., 2014).

All patients enrolled in this investigation were classified as ASA II–III. General anesthesia was induced with 100 μg of fentanyl, 0.3 mg/kg etomidate, and 0.6 mg/kg rocuronium. After endotracheal intubation, anesthesia was maintained with sevoflurane (MAC = 1.0). Analgesia was maintained with 250 μg fentanyl boluses every 30–40 min; an additional dose of 500 μg fentanyl was administered prior to sternotomy. Repeated doses of 0.2 mg/kg rocuronium were administered according to the patient's requirements. After the initiation of normothermic CPB, mechanical ventilation was reduced to 50% of the initial tidal

TABLE 1 Comparison of the study (A) and control (B) group.

		Study group (A) (n = 44)	Control group (B) (n = 36)	p-value*
Age [years] mean ± SD (M)		66.52 ± 8.17 (68)	67.92 ± 8.02 (69.5)	0.375
Gender n, (%)	Female	10 (23%)	10 (28%)	0.615
	Male	34 (77%)	26 (72%)	
BMI mean ± SD (M)		28.63 ± 3.69 (28.2)	27.36 ± 3.78 (27.3)	0.283
ESL mean ± SD (M)		3.59 ± 2.56 (2.9)	3.99 ± 3.11 (3.5)	0.498
Ht_0 [%] mean ± SD (M)		41.06 ± 3.18 (41.7)	40.49 ± 3.56 (40.8)	0.411
$eGFR_0$ [ml/min/1.73m^2] mean ± SD (M)		79.57 ± 15.89 (80.5)	73.83 ± 20.98 (74)	0.223
Hypertension n, (%)		38 (86%)	26 (72%)	0.161
Diabetes n, (%)		19 (43%)	11 (31%)	0.353
CKD n, (%)		3 (7%)	6 (17%)	0.286
Dyslipidemia n, (%)		25 (57%)	20 (56%)	1
Operation n, (%)	CABG	25 (57%)	24 (67%)	0.489
	Valvular	5 (11%)	7 (19%)	0.359
	CABG + valvular	11 (25%)	3 (8%)	0.075
	Complex procedures	3 (7%)	2 (6%)	1
Total CPB time mean ± SD (M) [min]		77.84 ± 33.74 (72.5)	71.67 ± 34.75 (59.5)	0.312
Aortic cross-clamp time mean ± SD (M) [min]		55.02 ± 28.03 (48.5)	47.19 ± 26.68 (37.5)	0.169
Mean CPB pump flow mean ± SD (M) [l/min]		5.38 ± 0.59 (5.3)	4.92 ± 0.56 (5)	**0.002**
Mean $Ht_{CPB}1$ mean ± SD (M) [%]		26.93 ± 3.81 (27)	25.03 ± 4.63 (24)	**0.028**
Mean $Ht_{CPB}2$ mean ± SD (M) [%]		29.80 ± 3.65 (29.5)	27.74 ± 3.23 (27)	**0.007**
Mean iDO_2 during the CPB mean ± SD (M) [ml/min/m^2]		334.94 ± 46.23 (328.8)	301.40 ± 46.86 (297.6)	**0.001**
CSA-AKI n, (%)		12 (27%)	14 (39%)	0.339
Postoperative cerebral stroke n, (%)		0 (0%)	1 (3%)	0.450
Postoperative TIA n, (%)		1 (2%)	0 (0%)	1
Postoperative delirium n, (%)		5 (11%)	9 (25%)	0.143
Onset or progression of CKD n, (%)		1 (2%)	3 (9%)	0.316
eGFR after 3 months mean ± SD (M) [ml/min/1.73m^2]		82.98 ± 16.15 (82)	82.32 ± 19.76 (83.5)	0.882

BMI, body mass index; CABG, coronary artery bypassing graft; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; CSA-AKI, cardiac surgery-associated acute kidney injury, $eGFR_0$, preoperative estimated glomerular filtration rate; ESL, EuroSCORE logistic; Ht_0, preoperative hematocrit value; $Ht_{CPB}1$, first hematocrit value during the CPB; $Ht_{CPB}2$, second hematocrit value during the CPB; iDO2, oxygen delivery indexed for body surface area; M, median value; SD, standard deviation; TIA, transient ischemic attack; *, calculated using Mann-Whitney test for quantitative variables and Fisher exact test for qualitative variables. p values < 0.05 are put in bold.

volume and 50% of the initial respiratory rate. Endotracheal sevoflurane administration was ceased, and volatile anesthesia was continued at the same rate via the membrane oxygenator of the CPB circuit.

Fisher exact test was used to compare qualitative variables between the groups. Since most of the quantitative variables showed distributions significantly different from a normal distribution (p < 0.05, Shapiro-Wilk test), non-parametric tests were used: Mann-Whitney test to compare values of rank and continuous variables between groups, and Spearman rank correlation coefficient to measure association between continuous variables. Statistica 13 was used to perform the calculations. p < 0.05 was considered statistically significant.

Results

Twenty nine patients met the exclusion criteria, leaving eighty patients for the final analysis. The follow-up creatinine measurement was unavailable in three patients–Scheme 1.

There were no significant differences in age, gender, comorbidities, or initial laboratory results between the patients

TABLE 2 Comparison of AKI vs. no-AKI groups.

		AKI (n = 26)	no-AKI (n = 54)	p-value*
Age [years] mean ± SD (M)		66.54 ± 8.10 (71)	66.48 ± 8.06 68)	0.239
Gender n, (%)	Female	8 (31%)	12 (22%)	0.421
	Male	18 (69%)	42 (78%)	
BMI mean ± SD (M)		27.92 ± 3.94 (27.3)	28.12 ± 3.71 (27.9)	0.873
ESL mean ± SD (M)		4.11 ± 2.52 (3.9)	3.61 ± 2.95 (2.8)	0.208
Ht_0 [%] mean ± SD (M)		40.31 ± 3.84 (41.5)	41.04 ± 3.09 (41.5)	0.813
Hb_{A1C} [%] mean ± SD (M)		6.30 ± 0.89 (6)	6.18 ± 0.70 (6)	0.789
$eGFR_0$ [ml/min/1.73 m^2] mean ± SD (M)		69.58 ± 20.88 (68)	80.56 ± 16.20 (81)	**0.025**
Hypertension n, (%)		23 (88%)	41 (76%)	0.242
Diabetes n, (%)		11 (42%)	19 (35%)	0.624
CKD n, (%)		6 (23%)	3 (6%)	0.052
Dyslipidemia n, (%)		13 (50%)	32 (59%)	0.477
Preoperative NGAL/Cr mean ± SD (M) [ng/mg]		11.82 ± 24.74 (4.5)	5.66 ± 11.20 (2.9)	**0.024**
Preoperative IL-18/Cr mean ± SD (M) [ng/mg]		0.071 ± 0.047 (0.06)	0.049 ± 0.043 (0.04)	**0.013**
Preoperative MMP-9/Cr mean ± SD (M) [ng/mg]		8.91 ± 39.74 (0.09)	2.48 ± 13.55 (0.02)	**0.006**
Operation n, (%)	CABG	12 (46%)	37 (69%)	0.085
	Valvular	4 (15%)	8 (15%)	1
	CABG + valvular	6 (23%)	8 (15%)	0.366
	Complex procedures	4 (15%)	1 (2%)	**0.036**
Total CPB time mean ± SD (M) [min]		81.85 ± 34.96 (86.5)	71.80 ± 33.55 (60.5)	0.214
Aortic cross-clamp time mean ± SD (M) [min]		57.77 ± 29.64 (63)	48.48 ± 26.21 (40.5)	0.252
Postoperative noradrenaline dose mean ± SD (M) [mg/kg]		0.057 ± 0.078 (0.031)	0.042 ± 0.164 (0)	**0.005**
IL-8 6 h after the CPB mean ± SD (M)[pg/ml]		22.26 ± 19 (17)	14.79 ± 10.16 (11.9)	**0.045**
TNF-α 6 h after the CPB mean ± SD (M) [pg/ml]		9.18 ± 4.14 (8.2)	6.40 ± 2.19 (5.9)	**<0.001**
NGAL/Cr 6 h after the CPB mean ± SD (M) [ng/mg]		16.98 ± 29.44 (5)	8.10 ± 28.22 (3.4)	**0.014**
NGAL/Cr 24 h after the operation mean ± SD (M) [ng/mg]		32.21 ± 37.20 (26)	18.94 ± 12.98 (16.6)	**0.025**
IL-18/Cr 24 h after the operation mean ± SD (M) [ng/mg]		0.492 ± 0.457 (0.3)	0.378 ± 0.406 (0.2)	**0.029**
Onset or progression of CKD n, (%)		4 (17%)	0 (0%)	**0.008**
eGFR after 3 months mean ± SD (M) [ml/min/1.7 m^2]		70.04 ± 22.01 (71.5)	86.60 ± 13.94 (85)	**0.020**

BMI, body mass index; CABG, coronary artery bypassing graft; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; $eGFR_0$, preoperative estimated glomerular filtration rate; ESL, EuroSCORE logistic; Hb_{A1C}, preoperative glycated hemoglobin percentage; Ht_0, preoperative hematocrit value; IL-8, serum interleukin 8 concentration; IL-18/Cr, serum interleukin 18 concentration; M, median value; MMP-9, urine matrix metalloproteinase 9 concentration normalized for creatinine excretion; NGAL/Cr, urine neutrophil gelatinase-associated lipocalin concentration normalized for creatinine excretion; SD, standard deviation; TNF-α, serum tumor necrosis factor-alpha concentration; *, calculated using Mann-Whitney test for quantitative variables and Fisher exact test for qualitative variables. p values < 0.05 are put in bold.

from the included and the excluded groups. The only differences included the Euro Score Logistic value and percentage of complex procedures, which were both higher in the excluded patient group–Supplementary Table S1.

The study (A) and control (B) groups did not differ in terms of age, gender, comorbidities, or initial laboratory results. Patients in the study group maintained higher hematocrit values during the CPB. With greater CPB pump flow, there was a higher iDO_2 in this patient group. There were no differences in postoperative complications between the study and control group. Target MAP of > 90 mmHg was achieved in 31.82% of the study group and 8.33% of the control group. In the control group, the dominant MAP range was 70–90 mmHg (50%), the same as in the study group (52.27%). There was a relatively high percentage of MAP < 70 mmHg in the

TABLE 3 Comparison of patients subjected to different MAP ranges during the CPB. Each MAP range was coded with a letter (C–E) for more transparent data presentation.

		C	D	E	*p*-value*		
		MAP: < 70 mmHg	MAP: 70–90 mmHg	MAP: > 90 mmHg	C vs. D	C vs. E	D vs. E
Age [years] mean ± SD (M)		64.45 ± 8.14 (67)	68.22 ± 7.99 (69)	68.06 ± 7.88 (69)	**0.049**	0.178	0.837
Gender n, (%)	Female	2 (9%)	11 (27%)	7 (41%)		**0.020**	
	Male	20 (91%)	30 (73%)	10 (59%)			
BMI mean ± SD (M)		26.96 ± 3.98 (27)	27.98 ± 3.78 (27)	29.67 ± 2.98 (29)	0.569	**0.039**	**0.043**
ESL mean ± SD (M)		3.33 ± 2.48 (2.8)	3.67 ± 2.92 (2.8)	4.57 ± 2.93 (3.9)	0.584	0.113	0.245
Ht_0 [%] mean ± SD (M)		40.53 ± 2.91 (41.2)	40.99 ± 3.33 (41.2)	40.71 ± 4.03 (41.8)	0.639	0.552	0.993
$eGFR_0$ mean ± SD (M) [ml/min/1.73m^2]		76.27 ± 20.64 (75.5)	79.49 ± 15.89 (80)	74.29 ± 21.85 (79)	0.512	0.966	0.489
CKD n, (%)		2 (9%)	4 (10%)	3 (18%)		0.442	
Preoperative KIM-1/Cr mean ± SD (M) [ng/mg]		0.756 ± 1.147 (0.25)	0.562 ± 0.701 (0.32)	1.620 ± 2.657 (0.80)	0.751	0.079	**0.021**
Operation n, (%)	CABG	12 (55%)	25 (61%)	12 (71%)		0.321	
	Valvular	3 (14%)	8 (20%)	1 (6%)		0.604	
	CABG + valvular	4 (18%)	6 (15%)	4 (24%)		0.731	
	Complex procedures	3 (14%)	2 (5%)	0 (0%)		0.074	
Total CPB time mean ± SD (M) [min]		83.86 ± 37.11 (73.5)	71.02 ± 29.78 (71)	73.41 ± 39.66 (58)	0.136	0.315	0.925
Aortic cross-clamp time mean ± SD (M) [min]		57.32 ± 31.11 (48)	49.39 ± 25.17 (43)	49.06 ± 28.73 (42)	0.296	0.590	0.912
MAP after the induction of general anesthesia mean ± SD (M) [mmHg]		84.68 ± 12.30 (83)	90.61 ± 12.14 (93)	93.88 ± 8.14 (96)	**0.040**	**0.007**	0.434
Intraoperative noradrenaline dosemean ± SD (M) [mg/kg]		0.012 ± 0.010 (0.01)	0.006 ± 0.006 (0.01)	0.005 ± 0.006 (0)	**0.008**	**0.008**	0.532
Diuresis during the CPB mean ± SD (M) [ml/kg/h]		2.90 ± 1.78 (2.38)	3.87 ± 2.72 (3.48)	4.97 ± 2.89 (4.54)	0.198	**0.006**	0.107
Δ CaO_2 mean ± SD (M) [%]		63.19 ± 7.27 (63.9)	65.82 ± 8.41 (66.3)	68.15 ± 8.08 (66.3)	**0.040**	**0.036**	0.688
Mean iDO_2 during the CPB mean ± SD (M) [ml/min/m^2]		305.90 ± 44.44 (305)	319.47 ± 52.90 (315)	338.79 ± 41.27 (335)	0.299	**0.002**	0.114
Δ Renin M (Q1-Q3) [%]		364.28 (213.99–4.95.26	286.28 (163.82–532.99)	166.89 (101.59–266.33)	0.428	**0.008**	**0.048**
Δ $Creatinine_C$ mean ± SD (M) [%]		77.68 ± 48.61 (74.6)	74.70 ± 46.48 (67.4)	98.57 ± 67.10 (91.5)	0.719	0.350	0.135
CSA-AKI n, (%)		6 (27%)	16 (39%)	4 (24%)		0.929	
Postoperative cerebral stroke n, (%)		1 (5%)	0 (0%)	0 (0%)		0.171	
Postoperative TIA n, (%)		0 (0%)	1 (2%)	0 (0%)		0.907	
Postoperative delirium n, (%)		7 (32%)	5 (12%)	2 (12%)		0.077	

BMI, body mass index; CABG, coronary artery bypassing graft; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; CSA-AKI, cardiac surgery associated acute kidney injury, eGFR0, preoperative estimated glomerular filtration rate; ESL, EuroSCORE logistic, Ht0, preoperative hematocrit value; iDO2, oxygen delivery indexed for body surface area; KIM-1/Cr, urine kidney injury molecule 1 concentration normalized for creatinine excretion; M, median value; MAP, mean arterial pressure; SD, standard deviation; TIA, transient ischemic attack, Q1-Q3, first and third quartile values; Δ CaO2, delta of preoperative and mean intraoperative blood oxygen-carrying capacity; Δ CreatinineC, delta of 6-hour-postoperative and preoperative creatinine clearance; Δ Renin, delta of 6-hour-postoperative and preoperative plasma renin concentration; *, calculated using Mann-Whitney test for differences in quantitative variables between the MAP groups, and also for associations of MAP range treated as rank variable with qualitative variables. *p* values < 0.05 are put in bold.

TABLE 4 Correlation between diuresis during the CPB and perioperative and follow-up serum creatinine concentration.

	Preoperative serum creatinine	$Creatinine_1$	$Creatinine_2$	$Creatinine_3$	$Creatinine_4$	Follow-up serum creatinine
Diuresis during the CPB	R = −0.256 p = 0.026	R = −0.327 p = 0.004	R = −0.319 p = 0.005	R = −0.317 p = 0.005	R = −0.271 p = 0.039	R = −0.243 p = 0.038

CPB, cardiopulmonary bypass; $Creatinine_{1-4}$, consecutive postoperative serum creatinine measurements; p, p-value (calculated using Mann-Whitney test); R, Spearman's correlation coefficient.

control group (41.67%) compared to the study group (15.91%). Results are summarized in Table 1.

As many patients in the study group did not reach the target MAP of > 90 mmHg, the primary outcomes analysis focused on patients from different MAP ranges and those who eventually developed and did not develop CSA-AKI.

The patients who suffered from CSA-AKI had worse preoperative kidney function, which was also demonstrated with higher preoperative biomarkers' concentration. The percentage of complex procedures and the postoperative use of Noradrenaline (NA) were higher in this group. CSA-AKI was associated with the onset or progression of CKD in this study population, and also with higher postoperative biomarkers concentration. No other significant differences were observed–Table 2.

MAP decreased in 78.75% of the study population immediately after the initiation of CPB. The average decrease in MAP was 14.38%. Patients with higher MAP after the induction of general anesthesia had higher MAP during the CPB. The highest MAP maintained during CPB in this investigation was 110 mmHg.

Maintaining a higher MAP during CPB in this study population did not affect CSA-AKI incidence. It did, however, increase the intraoperative and postoperative diuresis, as well as decreased renin release associated with CPB. On the other hand, patients in the lowest MAP group had greater CaO2 and iDO2 decrease as well as higher NA demand compared to patients in the highest MAP group. Patients in the higher MAP groups were older, had higher BMI, higher preoperative urine KIM-1/Cr concentration, and statistically more women were amongst them. Patients with lower MAP during CPB had a greater decrease in creatinine clearance 6 h after the surgery, but the result was not statistically significant. Higher MAP during the CPB did not increase the incidence of cerebrovascular complications after the operation; patients in the highest MAP group had the smallest percentage of complications, but the difference was not statistically significant–Table 3.

There was a negative correlation between diuresis during the CPB and perioperative serum creatinine concentrations, as well as the follow-up creatinine concentration–Table 4.

Discussion

This investigation aimed to determine whether a higher perfusion pressure during CPB can alleviate kidney injury associated with this procedure. The obtained results suggest that it can. Mayor benefits of maintaining high MAP during the CPB included greater diuresis and decreased renin increase after the operation. Diuresis is a direct indicator of kidney function (Yao and Gao, 2021), and a lower renin increase proves reduced kidney hypoperfusion (Küllmar et al., 2021). Greater urine output in the higher MAP groups could be partially attributed to a smaller decrease in CaO2 and iDO2 during the CPB. However, renin release is irrespective of these two parameters and depends solely on perfusion pressure. When the RAA axis response is triggered within the juxtaglomerular cells of the afferent arteriole, it means that the current MAP is below the kidneys' autoregulatory range. The kidneys strive to raise the systemic pressure and maintain glomerular filtration pressure at the expense of peritubular and medullary blood flow. Thus, there is a tight dependency between renin release and reduced blood flow to the post-glomerular capillaries, which can lead to ischemic kidney injury. Lower renin increase after the operation indicates that kidneys received more adequate perfusion and endured less ischemic stress.

There was no statistically significant difference in CSA-AKI incidence between the different MAP groups, which can be attributed to the modest sample size in this study. Comparing these results with the results of other authors is difficult, as higher MAP values in these studies were achieved using NA infusion (Azau et al., 2014; Vedel et al., 2018; De La et al., 2022), which can have an adverse impact on the kidneys (Huette et al., 2022). There is, however, scientific evidence that increasing CPB pump flow can improve renal blood flow during the CPB (Lee et al., 2020). Such an approach is all the more convincing as it mimics the physiological circulatory response to decreased CaO2, which is increasing the cardiac output. The authors of this study did not encounter any scientific investigations where target MAP during the CPB was achieved by increasing the pump flow. There are, however, reports that higher iDO2 during the CPB (achieved by increasing the pump flow) can reduce the risk of CSA-AKI (Mukaida et al., 2019; de et al., 2011). Taking advantage of the dual benefit of increasing the CPB pump flow (simultaneous MAP and iDO2 adjustment) appears optimal for preserving kidney function.

Determining an optimal MAP range for kidney function during the CPB is a complicated issue. As was mentioned in the Introduction section, under physiological conditions, the lower autoregulatory threshold of renal blood flow is 70–80 mmHg. In this investigation, the most distinct differences in outcomes can be noticed between the lowest (<70 mmHg) and the highest (>90 mmHg) MAP groups. This suggests that MAP < 70 mmHg is disadvantageous to the kidneys, while MAP > 90 mmHg is sufficient to maintain kidney function. The results in the middle MAP group (70–90 mmHg) vary, which suggests that the lower kidney autoregulatory threshold during CPB is somewhere in this MAP range.

Novel kidney injury biomarkers (IL-6, IL-8, TNF-α, NGAL, KIM-1, MMP-9, and IL-18) were used in this investigation to assess kidney damage more accurately. They proved efficient in the early detection of CSA-AKI, as there were significant differences in their postoperative concentration between the AKI and no-AKI groups. There was no significant difference in postoperative biomarkers' concentration between the different MAP groups. Several reasons can explain this result, such as the limited study population or the unknown hydration status of the enrolled patients.

There was a constant negative correlation between diuresis during the CPB and postoperative serum creatinine concentration. This demonstrates that better intraoperative kidney function (indicated by greater diuresis) directly impacts early postoperative kidney function. Hence, maintaining higher MAP during the CPB improves the kidney's filtration function after the surgery.

Some patients in this investigation who suffered from CSA-AKI experienced the onset or progression of CKD. The impact of AKI on patients' morbidity and mortality is well established (Harty; Gameiro et al., 2020), and so nephroprotection during cardiac surgeries is of great importance. It is worth mentioning that diuresis during the CPB (enhanced by MAP > 90 mmHg) presented a significant negative correlation with serum creatinine concentration after 3 months. This suggests a positive long-term impact of higher perfusion pressure on postoperative kidney function.

The analysis of cerebrovascular complications proved that MAP values > 90 mmHg during the CPB are safe for the central nervous system. The same applies to the increased CPB pump flow, as there was no higher complication rate in the study group, which had a significantly greater pump flow. Looking at the incidence of postoperative delirium (Table 3), it is justified to state that increasing MAP during the CPB could decrease the risk of this complication. These findings are consistent with other researchers' discoveries (Siepe et al., 2011; Brown et al., 2019).

This study had several limitations. Its primary limitation is a modest sample size. The statistical power of our study with 44 and 36 subjects in the study and control group respectively was sufficient to detect the real differences between the groups with 80% probability. This corresponds to 0.64 standard deviations of the studied parameters. Smaller differences could remain undetected. Furthermore, this study population had no set fluid intake regimen. The patients were allowed to intake fluids at will on the day preceding the operation. Only a dominant MAP range during the CPB was recorded during this investigation. Due to technical reasons, there was no continuous recording of MAP or pump flow, which could provide valuable data for this study.

Conclusions

Maintaining MAP > 90 mmHg during the CPB positively impacts intraoperative and postoperative kidney function. It significantly reduces renal hypoperfusion during the procedure compared to MAP < 70 mmHg. MAP > 90 mmHg is safe for the central nervous system, and preliminary results suggest that it may have a beneficial impact on the incidence of postoperative delirium.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Komisja Bioetyczna Pomorskiego Uniwersytetu Medycznego w Szczecinie. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JU: Conceptualization, Investigation, Methodology, Writing–original draft. JP: Supervision, Writing–review and editing. AB: Supervision, Writing–review and editing. KS: Data curation, Formal Analysis, Writing–review and editing. IW-K: Investigation, Validation, Writing–review and editing. PK: Investigation, Validation, Writing–review and editing. PR: Investigation, Validation, Writing–review and editing. KR: Investigation, Validation, Writing–review and editing. VD: Investigation, Validation, Writing–review and editing. ZM: Investigation, Validation, Writing–review and editing. SK: Funding acquisition, Writing–review and editing. EK: Conceptualization, Investigation, Supervision, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The project was financed by the Minister of Science and Higher Education program under the name "Regional Initiative of Excellence" in 2019–2022. Project number: 002/RID/2021/22.

Acknowledgments

The authors want to express their appreciation and gratitude to the following medical professionals involved in this investigation: members of the Perfusionists' Team (Ryszard Biskup, Marlena Polk, and Marek Nowak)–for their cooperation and meritorical support; members of the Anesthesia Team (Iwona Sell, Marzena Zajdel)–for their contribution in obtaining samples and data for this study; and members of the Postoperative Care Team (Kamil Feculak, Ada Fic, Alicja Fronczek, Lidia Janikowska, Małgorzata Juszczak, Małgorzata Kaźmierczak, Izabella Szatanek, Halina Ługowska-Bogacz, Anna Małagocka, Dominika Małyszko, Aleksandra Mruk, Gabriela Mysza, Lucyna Olek, Adrian Owczarek, Dorota Rzelewska, Jolanta Samborska, Anna Stasiaczyk, and Beata Szklar)–for their invaluable help in collecting samples for this investigation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2024.1257631/full#supplementary-material

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