Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

ROZPRAWA DOKTORSKA

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Znaczenie gospodarki żelazowej w patofizjologii ostrego zapalenia mięśnia sercowego

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PODZIĘKOWANIA

Składam szczególne podziękowania Pani Profesor Ewie Anicie Jankowskiej
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SPIS TREŚCI

1. WYKAZ PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

Wykaz publikacji stanowiących cykl

Paweł Franczuk

Lp	Opis bibliograficzny	IF	Punkty
1	**Franczuk Paweł**, Tkaczyszyn Michał, Kulak Maria, Domenico Esabel, Ponikowski Piotr, Jankowska Ewa Anita: Cardiovascular complications of viral respiratory infections and COVID-19, Biomedicines, 2023, vol. 11, nr 1, art.71 [12 s.], DOI:10.3390/biomedicines11010071	4,7*	100
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2. STRESZCZENIE W JĘZYKU POLSKIM

Zapalenie mięśnia sercowego (ang. *myocarditis* – MCD) jest chorobą zapalną, w której rozwijający się proces zapalny obejmuje mięsień sercowy (miokardium). Mimo zdumiewającego w ostatnich latach rozwoju diagnostyki i leczenia wielu chorób sercowo-naczyniowych, aktualna wiedza na temat patofizjologii i odpowiedniego postępowania w przypadku tego schorzenia wciąż jest bardzo ograniczona. MCD występuje zazwyczaj u osób młodych, przed 40 r.ż., a najczęstszy czynnik wywołujący chorobę stanowią infekcje wirusowe. Obraz kliniczny ostrej fazy choroby jest wyjątkowo heterogenny: od przypadków skąpoobjawowych przebiegających z niewielkim osłabieniem, poprzez zagrażające życiu zaburzenia rytmu serca i silne bóle stenokardialne, aż po gwałtownie postępującą ostrą niewydolność serca oraz nagły zgon sercowy. Ustępowanie procesu zapalnego może zakończyć się pełnym wyzdrowieniem, jednak u części chorych prowadzi do rozwoju pozapalnej kardiomiopatii rozstrzeniowej objawiającej się niewydolnością serca. Identyfikacja pacjentów o podwyższonym ryzyku rozwoju kardiomiopatii wciąż stanowi wyzwanie. Mimo że w trakcie ostrego okresu choroby zmienionych jest wiele parametrów laboratoryjnych, odzwierciedlających m.in. martwicę kardiomiocytów, aktywację neurohormonalną, czy proces zapalny, to żaden z nich nie okazał się istotnym czynnikiem w stratyfikacji ryzyka. Patofizjologia MCD obejmuje wzajemne zależności pomiędzy aktualnym stanem układu odpornościowego, uwarunkowaniami genetycznymi, współchorobowością oraz czynnikami zewnętrznymi, jednak większość mechanizmów odpowiedzialnych za rozwój choroby oraz jej konsekwencje wydaje się wciąż nieznana.

Z procesami odpowiedzi immunologicznej nieodłącznie związany jest metabolizm żelaza. Cytokiny zapalne inicjują całą kaskadę zmian w obrocie tego pierwiastka, mających na celu ograniczenie jego biodostępności. Część białek odpowiedzialnych za gospodarkę żelaza należy jednocześnie do białek ostrej fazy. Co ważne, żelazo odgrywa również kluczową rolę w procesach wewnątrzkomórkowych newralgicznych dla energetyki komórki. Optymalny stan gospodarki żelaza jest więc konieczny dla prawidłowego funkcjonowania wszystkich typów komórek uczestniczących w patogenezie zapalenia mięśnia sercowego – komórek układu odpornościowego, kardiomiocytów i kardiofibroblastów. Ponadto, zarówno niedobór żelaza, jak i jego nadmiar, wpływają szkodliwie na kardiomiocyty i mają udowodniony związek z rozwojem kardiomiopatii. Dlatego też żelazo, zaangażowane zarówno w patogenezę stanu zapalnego, jak i procesy energetyczne komórki, jawi się potencjalnie jako istotny modulator złożonej patofizjologii MCD.

Głównym celem przeprowadzonych badań była ocena związków gospodarki żelaza z przebiegiem MCD oraz weryfikacja hipotezy zakładającej, że zaburzenia gospodarki żelaza są związane z powstającym uszkodzeniem miokardium. Przeprowadzone analizy opierały się na prospektywnej ocenie kolejnych pacjentów hospitalizowanych z powodu ostrego MCD, uzyskanych podczas hospitalizacji oraz dwóch wizyt ambulatoryjnych, przeprowadzonych w ciągu sześciu miesięcy obserwacji.

W pracy przeglądowej pt. "*Cardiovascular Complications of Viral Respiratory Infections and COVID-19*" MCD zostało przedstawione w kontekście całego spektrum powikłań sercowo-naczyniowych wywołanych przez oddechowe infekcje wirusowe. Wirusy oddechowe są uważane za najczęstszą przyczynę zapalenia mięśnia sercowego, a mechanizmy prowadzące od infekcji do MCD wciąż nie są w pełni poznane.

W ramach badań opisanych w publikacji pt. "*Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study*" potwierdzono, że stan

gospodarki żelaza u pacjentów hospitalizowanych z powodu ostrego zapalenia mięśnia sercowego jest zaburzony. Mimo porównywalnych wartości parametrów czerwonokrwinkowych, obserwowano u nich wyższe stężenie ferrytyny i hepcydny oraz niższe stężenie żelaza i saturację transferyny w porównaniu do osób zdrowych. Do normalizacji wskaźników żelazowych doszło w ciągu sześciu tygodni obserwacji. Niskie stężenie żelaza i saturacja transferyny, wskazujące na czynnościowy niedobór żelaza, korelowały z większym nasileniem aktywacji neurohormonalnej oraz z utrzymującą się po sześciu tygodniach od zakończenia hospitalizacji łagodną dysfunkcją lewej komory w badaniu echokardiograficznym.

W artykule pt. "*Iron status and myocardial injury while recovering from acute myocarditis*" dokonano analizy szczegółowych parametrów rezonansu magnetycznego serca u pacjentów z MCD. W stosunku do grupy kontrolnej zidentyfikowano liczne nieprawidłowości, spośród których obecność ognisk późnego wzmocnienia pokontrastowego (ang. *late gadolinium enhancement* – LGE), regionalne nieprawidłowości w czasach relaksacji T1 i podwyższenie objętości pozakomórkowej utrzymywały się również w badaniu kontrolnym po sześciu miesiącach obserwacji. U pacjentów hospitalizowanych z powodu MCD stężenie ferrytyny korelowało z nasileniem obrzęku oraz rozległością ognisk LGE. Ponadto, po sześciu miesiącach od zakończenia hospitalizacji, wskaźniki czynnościowego niedoboru żelaza były związane z wielkością utrzymujących się ognisk LGE oraz z miejscowym podwyższeniem objętości pozakomórkowej.

Lepsze zrozumienie patofizjologii MCD i usprawnienie procesu diagnostyczno-terapeutycznego stanowi ważne wyzwanie dla współczesnej kardiologii. W powyższych publikacjach potwierdzono istotną rolę gospodarki żelaza w patogenezie MCD i jego następstw. Przeprowadzone analizy dostarczyły dowodów na związek pomiędzy zaburzonymi wskaźnikami gospodarki żelaza a cechami uszkodzenia miokardium w przebiegu choroby.

3. STRESZCZENIE W JĘZYKU ANGIELSKIM

SUMMARY

Myocarditis (MCD) is an inflammatory disease, in which inflammation affects the heart muscle (myocardium). Despite the tremendous progress that we have witnessed over the recent years, regarding diagnostics and treatment of numerous cardiovascular diseases, the current knowledge on acute MCD and its pathophysiology remains limited. MCD affects mainly young subjects, aged <40 years old, and the most common etiological factor is viral infection. The clinical manifestation of the disease is highly heterogeneous: from oligosymptomatic cases with subtle weakness or palpitations, through life-threatening arrhythmias and severe chest pain, up to rapidly progressing acute heart failure and sudden cardiac death. In the majority of patients with acute MCD, the disease spontaneously regresses without significant clinical sequelae. However, there are subjects who develop post-myocarditis non-ischemic cardiomyopathy, and such patients – who are at higher risk of poor outcomes – are difficult to identify. Although numerous laboratory parameters are altered in MCD – including biomarkers of cardiac necrosis, inflammatory or neurohormonal activation – no significant indicator for poor outcome in acute MCD has been found yet. The pathophysiology of MCD and subsequent recovery involves a complex interplay between the virulence of the pathogen, the host immunity with possible genetic-based immune dysregulation, comorbidities and environmental factors.

The pathogenesis of inflammation is closely linked to iron metabolism. The release of inflammatory cytokines upregulates the synthesis of hepcidin and the secretion of iron-poor ferritin by macrophages, which eventually leads to limiting the availability of iron to microorganisms during infection. Ferritin and hepcidin are well known as acute phase reactants. What is of note, iron also plays an important role in cellular energetics. An optimal iron status is essential for the functioning of all cells involved in the pathogenesis of MCD – immune cells, cardiomyocytes and cardiofibroblasts. Moreover, both iron deficiency and iron overload are detrimental for cardiomyocytes, and are associated with the occurrence of cardiomyopathy. Therefore, iron status, which is not only a hallmark of immune activation, but also appears to be involved in myocardial energetics, may become a significant modulator of the complex pathophysiology of MCD.

The aim of the presented studies was to recognize the relationships of iron status with the course of acute MCD and to verify the hypothesis that peripheral blood iron status is related to myocardial injury during recovery from MCD. We prospectively assessed consecutive patients with acute MCD during hospitalization and at two ambulatory visits, performed within six months of observation.

In the review article entitled '*Cardiovascular Complications of Viral Respiratory Infections and COVID-19*', an up-to-date presentation of diverse cardiovascular complications of viral respiratory infections, including acute MCD, was provided. Respiratory viruses are considered the most prevalent trigger of MCD. However, the pathomechanisms leading from infection to MCD remain unclear.

In the study described in the article entitled '*Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study*', we have demonstrated that iron status in patients hospitalized for acute MCD was altered. Despite comparable red blood cell indices, they presented increased concentration of serum ferritin and hepcidin, and lower serum iron and transferrin saturation, compared with healthy controls. The deranged iron status

normalized within six weeks of recovery. Lower serum iron and transferrin saturation (indicators of functional iron deficiency) correlated with a greater in-hospital neurohormonal activation and a subtle persistent left ventricular dysfunction detected in echocardiography.

In the study summarized in the paper entitled '*Iron status and myocardial injury while recovering from acute myocarditis*', we comprehensively analyzed data from cardiac magnetic resonance performed in patients with acute MCD. Out of numerous abnormalities that were identified during baseline hospitalization in comparison to control group, the following persisted after six months of recovery: presence of LGE, regional abnormalities in myocardial T1 relaxation time and elevated extracellular volume. During hospitalization for acute MCD, serum ferritin was related to myocardial injury (presence of edema, extent of LGE). In the control assessment, six months after discharge, the extent of residual fibrosis correlated with the indices of functional iron deficiency.

The current knowledge of the pathophysiology of MCD remains incomplete and the treatment options require further improvement. The results of our research confirmed an important role of iron status in the pathogenesis of the disease and its complications. The aforementioned papers demonstrated that circulating indices of iron status are related to myocardial injury while recovering from acute MCD.

4. WYKAZ STOSOWANYCH SKRÓTÓW

CK-MB – ang. *creatine kinase myocardial band* (izoforma sercowa kinazy kreatynowej)

COVID-19 – ang. *coronavirus disease 2019*

LGE – ang. *late gadolinium enhancement* (późne wzmocnienie pokontrastowe)

MCD – ang. *myocarditis* (zapalenie mięśnia sercowego)

MR-proADM – ang. *mid regional pro-adrenomedullin* (środkowy fragment propeptydu adrenomeduliny)

NT-proBNP – ang. *N-terminal pro-B-type natriuretic peptide* (N-końcowy fragment propeptydu natriuretycznego typu B)

5. WPROWADZENIE

Zdumiewający rozwój medycyny, jaki dokonał się w ostatnich latach w zakresie diagnostyki i leczenia chorób układu sercowo-naczyniowego, pozwolił na wypracowanie wielu ścieżek diagnostycznych oraz opracowanie wysoce skutecznych sposobów leczenia. Wciąż jednak w przypadku niektórych jednostek chorobowych aktualna wiedza na temat patofizjologii czy odpowiedniego postępowania pozostaje bardzo ograniczona. Niewątpliwie, właśnie do takich schorzeń należy zapalenie mięśnia sercowego (ang. *myocarditis*).

Zapalenie mięśnia sercowego jest chorobą zapalną, w której rozwijający się proces zapalny obejmuje mięsień sercowy (miokardium) [1-2]. Na histologiczny obraz zapalenia mięśnia sercowego składają się nacieki komórek zapalnych w miokardium z towarzyszącymi im zmianami degeneracyjnymi i/lub nekrotycznymi w kardiomiocytach, o układzie innym niż typowy dla zawałowego uszkodzenia mięśnia sercowego [2-4]. Szacunki dotyczące częstości występowania zapalenia mięśnia sercowego są wysoce nieprecyzyjne, co zapewne ma związek z dużą różnorodnością prezentacji klinicznej choroby [2-4]. Przyjmuje się, że rocznie diagnozowanych jest ok. 22 nowych przypadków na 100 000 osób [5]. Zdecydowaną większość z nich stanowią osoby młode – między 20. a 60. rokiem życia, a szczyt zachorowań przypada ok. 30. roku życia [4,6]. Jednakże zdecydowanie wyższą częstość występowania choroby mogłyby sugerować badania patomorfologiczne, raportujące zapalenie mięśnia sercowego jako jedną z głównych przyczyn nagłej śmierci sercowej osób młodych [4,7]. Zgodnie z szacunkami liczbowymi, podczas ostrych infekcji wirusowych proces zapalny może, w mniejszym lub większym stopniu, obejmować miokardium nawet w 1-5% przypadków [8].

Obraz kliniczny ostrej fazy zapalenia mięśnia sercowego cechuje wyjątkowa heterogenność: od przypadków skąpoobjawowych, manifestujących się jedynie niewielkim osłabieniem lub kołataniem serca, poprzez silne bóle stenokardialne, zagrażające życiu zaburzenia rytmu serca, objawy gwałtownie postępującej ostrej niewydolności serca (wymagające zastosowania mechanicznego wspomagania krążenia lub pilnej transplantacji serca), aż po nagły zgon sercowy [2-4,8-10]. W dalszym przebiegu ustępowanie procesu zapalnego może zakończyć się pełnym wyzdrowieniem, jednak u części chorych prowadzi do rozwoju nie-niedokrwiennej pozapalnej kardiomiopatii rozstrzeniowej, odpowiedzialnej za wystąpienie objawów niewydolności serca [2-4,8-10].

Mimo dotychczasowych starań, identyfikacja pacjentów z zapaleniem mięśnia sercowego o podwyższonym ryzyku następczego rozwoju kardiomiopatii wciąż jest problematyczna [3,10-13]. Chociaż w trakcie ostrego okresu choroby zmienionych jest wiele parametrów laboratoryjnych, to nadal nie opisano wartościowych klinicznie czynników predykcyjnych niekorzystnej progresji choroby [3,10-13]. Jak dotąd, spośród kompleksowo analizowanych markerów laboratoryjnych odzwierciedlających martwicę kardiomiocytów (troponina, CK-MB), zapalenie (białko C-reaktywne, morfotyczne parametry białokrwinkowe), przeciążenie objętościowe (NT-proBNP), stres endogenny (kopeptyna) czy dysfunkcję mikrokrążenia (MR-proADM), jedynie wybitnie wysokie wartości NT-proBNP (≥4,245 pg/ml) wykazywały związek z niekorzystnym rokowaniem, a przecież ryzyko rozwoju kardiomiopatii dotyczy również pacjentów z łagodnym przebiegiem ostrej fazy choroby [9,11,14-17]. Istotną wartość w stratyfikacji ryzyka w ogólnej populacji pacjentów z zapaleniem mięśnia sercowego stanowi analiza parametrów uzyskanych w obrazach rezonansu magnetycznego serca [13,18-20]. W ostatnio przeprowadzonych badaniach wykazano związek pomiędzy rozległością ognisk późnego wzmocnienia pokontrastowego (ang. *late gadolinium enhancement,* LGE) a długoterminowym rokowaniem po zapaleniu mięśnia sercowego [13,18-20]. Jednakże dostępność rezonansu magnetycznego w przypadku ostrych stanów klinicznych wciąż pozostaje ograniczona w wielu centrach kardiologicznych.

Patogeneza zapalenia mięśnia sercowego jest procesem złożonym, który opiera się na współoddziaływaniu pomiędzy aktualnym stanem układu odpornościowego, uwarunkowaniami genetycznymi, współchorobowością oraz czynnikami zewnętrznymi (zakaźnymi i niezakaźnymi) [4,9,10,12]. Wśród czynników zewnętrznych najczęstszą przyczynę choroby stanowią infekcje wirusowe [4,9,10]. Za dominujący patofizjologiczny mechanizm rozwoju zapalenia mięśnia sercowego i jego powikłań uważa się zaburzoną odpowiedź immunologiczną [4,9,10,12].

Z reakcją immunologiczną ściśle wiąże się metabolizm żelaza [21]. Hepcydyna i ferrytyna, należące do najważniejszych biomarkerów gospodarki żelaza, są jednocześnie znanymi od lat białkami ostrej fazy [21-26]. Natomiast żelazo jest unikalnym mikroelementem o znaczeniu kluczowym dla licznych procesów wewnątrzkomórkowych, do których, poza odpowiedzią immunologiczną, należą inne komponenty obrony przeciwinfekcyjnej, energetyka komórki czy mechanizmy przeciwzapalne [27-30]. Optymalny stan gospodarki żelaza jest niezbędny dla prawidłowego funkcjonowania wszystkich typów komórek zaangażowanych w patogenezę zapalenia mięśnia sercowego – komórek układu

odpornościowego, kardiomiocytów i kardiofibroblastów [21-30]. Co więcej, znane są dowody na to, że zarówno niedobór żelaza, jak i jego nadmiar, są szkodliwe dla kardiomiocytów, a zaburzenia jego metabolizmu mają związek z rozwojem kardiomiopatii [27,31-38]. Dlatego też wydaje się, że rola gospodarki żelaza w złożonej patofizjologii zapalenia mięśnia sercowego może być wyjątkowo istotna.

Zapalenie mięśnia sercowego, chociaż nie należy do częstych chorób, to stanowi niewątpliwie istotne wyzwanie dla dzisiejszej kardiologii [10]. Schorzenie dotyka zwykle osoby młode, co nadaje temu problemowi dodatkowe znacznie socjoekonomiczne, o szczególnej wadze dla już starzejących się społeczeństw [4,6]. Niestety, wiedza na temat patofizjologii tej choroby wciąż wydaje się mocno ograniczona oraz brak jest dokładnie sprecyzowanych schematów diagnostycznych i zaleceń terapeutycznych [4,10]. Niewątpliwie taki stan wynika w dużym stopniu z niewielkiej liczby badań klinicznych oraz rejestrów opisujących tę populację pacjentów. Ponadto, udział metabolizmu żelaza w patofizjologii zapalenia mięśnia sercowego nie był przedmiotem wcześniejszych badań.

6. CELE BADAŃ

Głównym celem przedstawionych badań była analiza związków gospodarki żelaza z przebiegiem ostrego zapalenia mięśnia sercowego. Na podstawie przeprowadzonych obserwacji zamierzano scharakteryzować zaburzenia gospodarki żelaza występujące u pacjentów z ostrym zapaleniem mięśnia sercowego oraz zweryfikować hipotezę zakładającą, że są one związane z uszkodzeniem miokardium, do którego dochodzi w trakcie choroby.

Szczegółowe cele publikacji pt. "*Cardiovascular Complications of Viral Respiratory Infections and COVID-19*":

- przybliżenie szerokiego spektrum powikłań sercowo-naczyniowych oddechowych infekcji wirusowych ze szczególnym uwzględnieniem COVID-19;
- przedstawienie istotnego miejsca zapalenia mięśnia sercowego pośród wszystkich powikłań sercowo-naczyniowych oddechowych infekcji wirusowych, stanowiących jednocześnie najczęstszą przyczynę tego schorzenia.

Szczegółowe cele badań opisanych w publikacji pt. "*Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study*":

- ocena stanu gospodarki żelaza w populacji pacjentów z ostrym zapaleniem mięśnia sercowego;
- analiza dynamiki zmian biomarkerów żelazowych w ciągu 6-tygodniowej obserwacji;
- weryfikacja hipotezy mówiącej o tym, że systemowe wskaźniki żelazowe w ostrym zapaleniu mięśnia sercowego mają związek z nasileniem aktywacji neurohormonalnej oraz echokardiograficznymi wykładnikami uszkodzenia miokardium w trakcie 6-tygodniowej obserwacji.

Szczegółowe cele badań opisanych w publikacji pt. "*Iron status and myocardial injury while recovering from acute myocarditis*":

- ocena związku wskaźników gospodarki żelaza z cechami uszkodzenia miokardium w obrazach rezonansu magnetycznego serca w ostrym zapaleniu mięśnia sercowego w ciągu 6-miesięcznej obserwacji;
- analiza regresji zmian w rezonansie magnetycznym w badanej populacji w ciągu 6 miesięcy.

7. MATERIAŁY I METODY

Badania przedstawione w niniejszym opracowaniu zostały przeprowadzone w Ośrodku Chorób Serca 4. Wojskowego Szpitala Klinicznego we Wrocławiu, Oddziale Kardiologii Dolnośląskiego Szpitala Specjalistycznego im. T. Marciniaka - Centrum Medycyny Ratunkowej we Wrocławiu, Centrum oraz Instytucie Chorób Serca Uniwersytetu Medycznego we Wrocławiu. Zgodę na przeprowadzenie badań wydała Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu. Wszyscy pacjenci wyrazili świadomą zgodę na udział w badaniu.

Prospektywny rejestr pacjentów z ostrym zapaleniem mięśnia sercowego, którego wyniki zostały przedstawione w publikacjach pt. "*Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study*" oraz "*Iron status and myocardial injury while recovering from acute myocarditis*", objął kolejnych pacjentów hospitalizowanych z powodu ostrego zapalenia mięśnia sercowego. Kryteria stanowiące podstawę do rozpoznania choroby oparto na objawach klinicznych oraz wynikach badań laboratoryjnych i obrazowych. Włączeni do badania chorzy byli oceniani w trzech punktach czasowych: podczas hospitalizacji oraz podczas dwóch wizyt ambulatoryjnych – po 6 tygodniach i 6 miesiącach od wypisu ze szpitala. W każdym z punktów czasowych przeprowadzono wywiad lekarski i badanie fizykalne, przezklatkowe badanie echokardiograficzne, diagnostykę laboratoryjną z kompleksową oceną wskaźników stanu gospodarki żelaza oraz biomarkerów odpowiedzi neurohormonalnej, martwicy kardiomiocytów i stanu zapalnego. Podczas hospitalizacji i po upływie 6 miesięcy wykonywano rezonans magnetyczny serca. Dodatkowo, celem scharakteryzowania zaburzeń gospodarki żelazowej występujących w ostrym zapaleniu mięśnia sercowego w odniesieniu do zdrowej populacji, utworzono grupę kontrolną, do której włączono zdrowych ochotników. Szczegółowy opis przeprowadzonych badań oraz zastosowanych testów statystycznych został ujęty w odpowiednich sekcjach wyżej wymienionych publikacji.

Natomiast w publikacji pt. "*Cardiovascular Complications of Viral Respiratory Infections and COVID-19*" na podstawie dostępnej literatury dokonano przeglądu aktualnej wiedzy na temat patofizjologii i kliniki różnorodnych powikłań układu sercowo-naczyniowego wywołanych przez oddechowe infekcje wirusowe, uwzględniając wśród nich szczególne miejsce zapalenia mięśnia sercowego.

8. PUBLIKACJE

8.1. PUBLIKACJA 1

Cardiovascular Complications of Viral Respiratory Infections and COVID-19.

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Review

Cardiovascular Complications of Viral Respiratory Infections and COVID-19

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Abstract: Viral respiratory infections (VRI) are the most prevalent type of infectious diseases and constitute one of the most common causes of contact with medical care. Regarding the pathophysiology of the cardiovascular system, VRI can not only exacerbate already existing chronic cardiovascular disease (such as coronary artery disease or heart failure) but also trigger new adverse events or complications (e.g., venous thromboembolism), the latter particularly in subjects with multimorbidity or disease-related immobilization. In the current paper, we provide a narrative review of diverse cardiovascular complications of VRI as well as summarize available data on the pathology of the circulatory system in the course of coronavirus disease 2019 (COVID-19).

Keywords: respiratory viruses; respiratory infection; cardiovascular disease; myocarditis; COVID-19; heart failure

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1. Introduction

Viral respiratory infections (VRI) are among the most common reasons of contact with health care in both adults and children [1]. From a global perspective, respiratory infections are the most prevalent type of infectious diseases and one of the leading causes of death, following only ischemic heart disease, chronic obstructive pulmonary disease, and stroke, and are responsible for 120 million disability-adjusted life years worldwide [2–4]. Viral etiology remains the most common in both respiratory infections in total and also in the subgroup of subjects with pneumonia—the most severe type of infectious involvement of the respiratory tract [5,6].

The most frequently identified viruses in patients with acute presentations of VRI are influenza virus, rhinoviruses, respiratory syncytial virus (RSV), parainfluenza virus, human metapneumovirus, respiratory adenoviruses, and coronaviruses [1,7–9]. However, it needs to be acknowledged that multiple viral pathogens are found in many subjects [10]. Respiratory viruses are transmitted predominantly via inhalation of infectious droplets or contact with contaminated secretions [1]. Clinical manifestations of VRI are heterogeneous and may involve the upper and/or lower respiratory tract, comprising rhinosinusitis, pharyngitis, the common cold, laryngotracheitis, bronchitis, bronchiolitis, and eventually overt pneumonia [11]. From the point of view of the cardiovascular system, VRI may not only exacerbate already existing chronic cardiovascular disease (such as coronary artery disease or heart failure) but also trigger new adverse cardiovascular events/conditions, the latter particularly in subjects with multimorbidity or immune deficits (Figure 1). Currently, due to the latest research boosted by the coronavirus disease 2019 (COVID-19) pandemic, our knowledge of and interest in the pathophysiology of VRI have considerably increased. In the current paper we provide a narrative review on diverse cardiovascular complications

of VRI, as well as a summary of available data on the involvement of the cardiovascular system in the course of COVID-19.

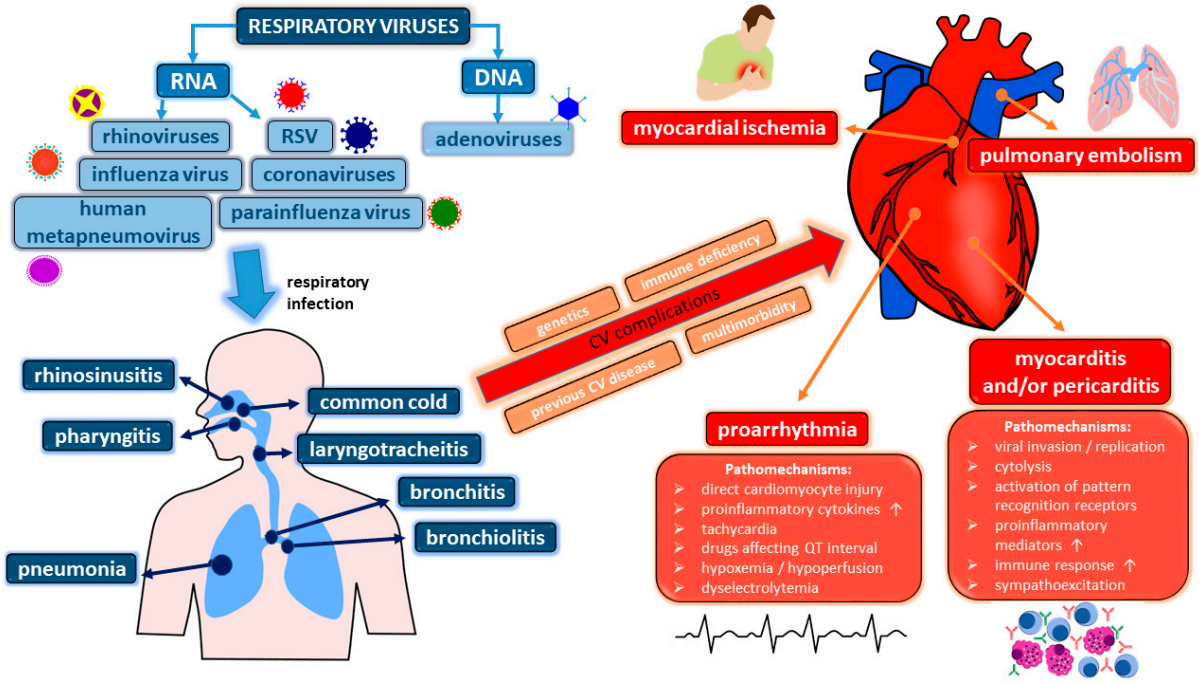

Figure 1. In predisposed patients, common upper and lower respiratory tract infections of viral etiology may be complicated by adverse cardiovascular events and conditions, the pathophysiology of which is diverse and not always thoroughly investigated. The pathomechanisms of myocardial ischemia and pulmonary embolism are presented in Figure 2. Abbreviations: CV—cardiovascular, DNA—deoxyribonucleic acid, RNA—ribonucleic acid, RSV—respiratory syncytial virus.

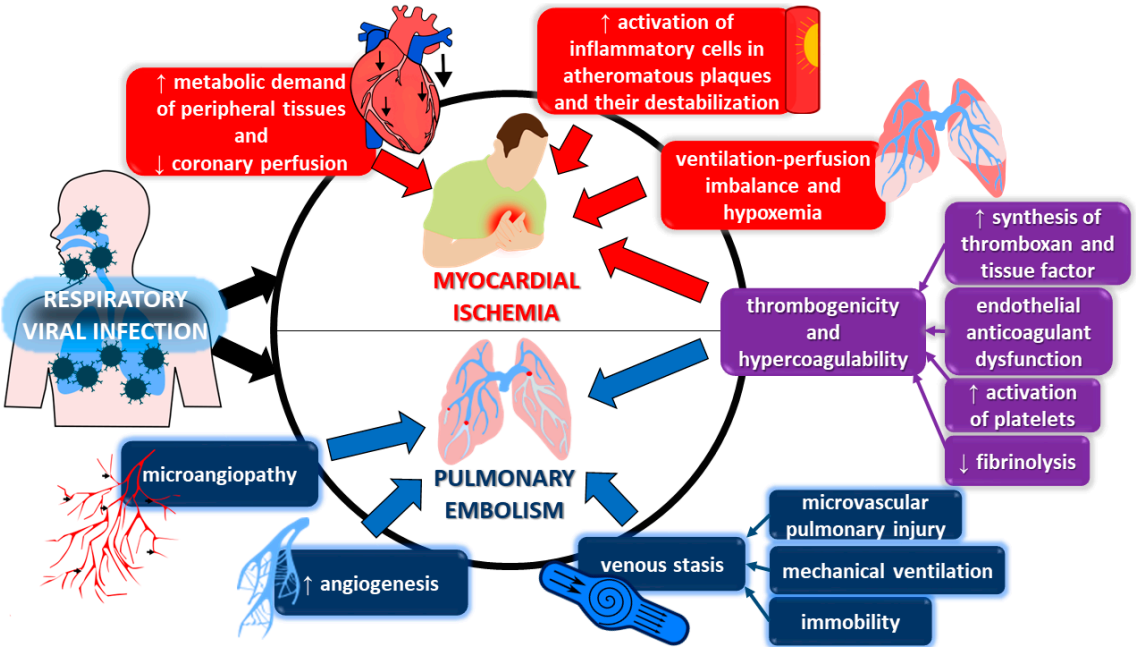

Figure 2. Multifaceted and overlapping mechanisms of arterial ischemic and venous thromboembolic complications of viral respiratory infections.

2. Ischemic Complications

From a pathophysiological point of view, myocardial 'ischemia' results from an imbalance between myocardial oxygen demand/supply, whereas myocardial 'injury' is defined as any damage to myocardial cells that is accompanied by the release of cardiac necrotic biomarkers [12]. It needs to be acknowledged that the prevalence of myocardial infarction (MI) varies seasonally and is highest in the winter [13]. The number of daily hospitalizations rises starting in August and reaches its peak in January [13]. This seasonality is not fully explained, but the increased incidence of upper respiratory tract infections is considered to play a role due to their multifaceted impact on blood rheology and therefore the functioning of the cardiovascular system [13]. The total risk for cardiovascular complications is determined primarily by the severity of the respiratory infection [14,15]. Although cardiac troponins above the upper limit of normal are frequently detected in the peripheral blood of patients with ongoing severe VRI [16,17], the most frequent pathomechanism is presumably the direct/indirect influence of the viruses themselves on cardiomyocytes (myocardial injury) [14].

The risk of MI during the first week following VRI is significantly increased (up to 6-fold) and remains elevated during one month of observation in Scottish records of the 10-year national infections registry, including 1989 individuals with acute ischemic cardiovascular events [18]. Similar trends have also been demonstrated for incident stroke, and therefore it should be assumed that the increased risk should be attributed to the entire spectrum of atherosclerotic cardiovascular disease (ASCVD). It is worth noting that the risk of an acute cardiovascular event was also related to previous ASCVD burden (the highest in patients with a history of previous MI) and the type of infection (the highest in influenza) [19,20]. There is evidence from longitudinal observations for an increased risk for ASCVD-related morbidity and mortality (including MI, stroke, or cardiovascular death) for a 10-year period following the hospitalization for any severe or non-severe pneumonia [21].

There are several pathophysiological links between VRI and the triggering or worsening of myocardial ischemia, including (i) inflammation; (ii) prothrombotic imbalance; (iii) hypercoagulability; and (iv) increased metabolic demands of the myocardium [22–24] (Figure 2). The process of inflammation not only activates platelets but also stimulates inflammatory cells within atherosclerotic plaques. The latter results in the release of metalloproteinases and peptidases, which can contribute to plaque destabilization [23,24]. Moreover, circulating pro-inflammatory cytokines can negatively impact the process of atherosclerotic remodeling of the vessel wall through modulating monocyte adhesion, macrophage activation, and proliferation of smooth muscle cells [24]. In parallel, up-regulated synthesis of thromboxane and tissue factor expression on immune cells, as well as the impairment of fibrinolysis and anticoagulant function of the endothelium, lead to increased thrombogenicity and a hypercoagulability state [24]. The anticoagulant dysfunction is associated with the downregulation of protein C, while the disturbance of fibrinolysis is associated with an increase in plasminogen activator inhibitor 1 [24].

3. Thromboembolism

Infections per se augment the risk of venous thromboembolism (VTE) up to about two times in records from over 10,000 individuals with urinary or respiratory tract infections [25]. Respiratory infections are associated with increased risk of both components of VTE, analyzed separately: deep vein thrombosis (DVT) and pulmonary embolism (PE) [25]. The overlapping of symptoms between PE and respiratory infection makes it frequently difficult to establish the chronology of these clinical entities in clinical practice [25].

The established pathomechanisms linking infection and thromboembolism include not only platelet activation and up-regulated synthesis of pro-coagulant proteins but also the impairment of fibrinolysis and anticoagulant function of the endothelium [26] (Figure 2). Moreover, the activation of leukocytes, triggered by infection, is associated with the release of damage-associated molecular patterns (such as deoxyribonucleic acid or histones), which further promotes thrombus formation [26]. It also needs to be acknowledged that local

inflammatory reactions, for example in the lungs, result in the disruption of endothelial cell membranes, which is followed by vascular thrombosis, microangiopathy, and increased angiogenesis [27,28]. Venous stasis, which is prevalent in immobile critically ill patients undergoing mechanical ventilation and presenting with microvascular pulmonary injury, is another pathomechanism increasing thromboembolic events in such patients [29].

4. Viral Myocarditis and (Post-)Inflammatory Cardiomyopathy

Despite many new experimental studies, our understanding of the development, evolution/progression, and recovery (or not) from an acute/sub-acute myocarditis is still not sufficient, and several pathways/mechanisms are constantly being explored, including the role of immune cells (also autoimmunity), the pathobiology of particular viruses, and iron metabolism, to name but a few [30–33]. Respiratory viruses are established to be the most common triggers of myocarditis, and the most frequently identified/isolated ones are adenoviruses, enteroviruses, influenza virus, and coronaviruses [30,34,35]. The incidence of particular viral infections fluctuates seasonally, with the peak of influenza in the winter and enteroviruses in the summer and autumn [30]. Clinical presentation of viral myocarditis is heterogeneous and comprises a broad spectrum of symptoms, from chest pain (ischemic-like or pleuritic-like), dyspnea, and fatigue, through less specific palpitations or syncope, to fulminant life-threatening conditions such as cardiogenic shock, ventricular arrhythmias, or even sudden cardiac death [36].

Adenoviruses and enteroviruses are positioned among the most common etiological factors of myocarditis [34]. They represent a group of primary cardiotropic viruses, responsible for direct damage to myocardial tissue. Viral invasion into cardiomyocytes occurs via the transmembrane receptor and is followed by viral replication inside, leading to the destruction of the cytoskeleton, cytolysis, and eventually an immune cell reaction [30,37,38]. Persistent viral activity following the acute phase of the disease can result in progressive cardiac dysfunction with a poor prognosis [35]. There is evidence that, for example, in enteroviral myocarditis, the recovery from an acute condition defined as complete virus clearance occurs in only half of subjects [39]. In this context, it is worth noting that entero- or adenoviral genomes were detected in 26% of patients with idiopathic left ventricular dysfunction and in 13% of patients with idiopathic dilated cardiomyopathy. However, it should be stipulated that this does not prove causality [35,40].

Influenza A and influenza B viruses (together with the Coronaviridae family described below) are classified as cardiotoxic agents, provoking myocarditis indirectly; these viruses activate the immune system responses, leading to augmented cytokine release and cytokine-mediated myocardial damage [30,41]. Influenza myocarditis is considered infrequent but associated with a poor outcome, with a mortality rate ranging up to 30% in H1N1 subtype infections [41].

5. Pericardial Disease

In developed countries, viral etiology is the most common in both acute pericarditis and pericardial disease as a whole [42,43]. Acute pericarditis is an inflammatory disease characterized by infiltrates of immune cells into the pericardium triggered mainly by viruses and resulting in a clinical syndrome characterized by typical signs and symptoms (pericarditic type of chest pain, specific electrocardiogram (ECG) abnormalities, and pericardial effusion) [42,44]. The common course of the disease is benign with mild to moderate symptoms that can be successfully treated outpatiently with non-steroidal anti-inflammatory agents and colchicine. More severe complications, including cardiac tamponade with a worse prognosis, are rather rare [44,45]. 33% of patients with acute pericarditis have a history of a recent upper respiratory tract infection [46]. Among respiratory viruses, enteroviruses, adenoviruses and influenza virus are the most prevalent in patients with pericarditis, being identified in 25%, 19%, and 6% of patients, respectively [47]. Differences in the clinical course of the disease according to particular groups of viruses have not been investigated. Not infrequently, pericarditis is accompanied by the involvement of

myocardial muscle, which results in a syndrome of 'myopericarditis' [47,48]. This condition is associated with enteroviral infection in 15% and adenoviral, influenza, or parainfluenza in 10% each [47,48].

6. Pro-Arrhythmia

Diverse cardiovascular and non-cardiovascular factors (the latter including, for example, dehydration and electrolyte disturbances caused by hyperthermia or diarrhea) contribute to pro-arrhythmia in the course of VRI. Not surprisingly, the patients most vulnerable to severe arrhythmic complications are those who already have a chronic cardiovascular disease (such as heart failure or non-revascularized coronary artery disease) that may be a substrate for life-threatening ventricular arrhythmias [30,49,50]. Obviously, both supraventricular and ventricular arrhythmias can also be triggered by direct (e.g., cardiomyocyte invasion in acute myocarditis complicating VRI) or indirect (e.g., in the course of excessive pro-inflammatory cytokine release) myocardial injury associated with an infection that is initially limited to the respiratory system [30]. Regarding the impact of severe respiratory infection on the functioning of the cardiovascular system, it also needs to be acknowledged that coexistent (sub-)acute myocardial ischemia (resulting from, e.g., hypoxemia, hypoperfusion, or tachycardia, to name but a few) can also promote arrhythmic episodes [22–24].

Epidemiological data show interesting trends: seasons with higher influenza activity are characterized by an increased risk of device-detected ventricular arrhythmias treated with appropriate therapies in patients with implantable cardioverter-defibrillators [51]. In one analysis of a large cohort of patients, it has been demonstrated that the prevalence of ventricular arrhythmia requiring high-energy discharge or antitachycardia pacing therapy followed the community activity of the influenza virus [51]. This relationship can be potentially explained by inflammation, exacerbation of heart failure or coronary artery disease, and increased myocardial oxygen demand [51]. Furthermore, among adult patients hospitalized due to RSV infection, 8% developed a new arrhythmia, and after considering all cardiovascular complications, only exacerbation of heart failure symptoms was slightly more frequent in this group of subjects [52].

Life-threatening ventricular arrhythmias or severe cardiac conductance disorders are most likely to occur in the course of giant-cell myocarditis [30,49,53]. The pathomechanism of significant (ventricular) arrhythmias in patients with (sub-)acute myocarditis is complex and there is evidence on the contribution of direct viral invasion within cardiomyocytes, microvascular ischemia, proarrhythmic properties of particular cytokines, abnormal calcium handling, and deranged ion channel functioning [54,55]. Pericarditis can also be complicated by arrhythmias, although it is considerably less prevalent than myocarditis [48].

7. Coronaviruses and Severe Acute Respiratory Syndrome Coronavirus 2

Although common coronaviruses are an etiological factor for mild respiratory infections [56], a few particular coronaviruses responsible for epidemic outbreaks occurring in the last two decades (Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1—2002, China); Middle East Respiratory Syndrome Coronavirus (MERS-CoV—2012, Saudi Arabia)) have been linked to greater morbidity and mortality in humans [15]. Although 20 years have elapsed since the outbreak of severe acute respiratory syndrome (SARS), our knowledge regarding this pathogen is still based on small cohorts' descriptions [15,57]. The most prevalent cardiovascular symptoms in patients with SARS-CoV-1 were tachycardia (72%) and hypotension (50%) [57,58]. The echocardiographic evaluation of 46 patients revealed transient diastolic dysfunction without systolic impairment in the entire group of infected subjects, whereas in patients who required mechanical ventilation, a decrease in left ventricular ejection fraction was noted [59]. Cases of MI and PE have also been documented during SARS-CoV-1 infection [60]. The Middle East respiratory syndrome (MERS) epidemic occurred 10 years after SARS, and there are only anecdotal records on

how it affects the cardiovascular system or impacts concomitant chronic cardiovascular disease [61].

We have much more high-quality data for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) due to the global impact of the COVID-19 pandemic and the great social need for large-scale research. The multidimensional impact of SARS-CoV-2 infection on the human organism has been demonstrated in both experimental studies and patient data analyses. Due to the pleiotropic effects of SARS-CoV-2 infection, the spectrum of COVID-19 complications is wide and heterogeneous and without doubt requires a multidisciplinary approach. For example, COVID-19 has been linked with neurological and psychiatric conditions (stroke, encephalitis, psychosis), reproductive system disturbances in males (infertility, erectile dysfunction), and gestational complications in females (preeclampsia, hypertension) [62–64]. With regard to the circulatory system, analogously to other respiratory viruses, SARS-CoV-2 not only can exacerbate (decompensate) pre-existing cardiovascular disease (such as heart failure), but in predisposed patients it may also be responsible for new adverse cardiac events (Figure 3). Acute myocardial injury as reflected by elevated cardiac troponin levels is found in 7–36% of COVID-19 patients and correlates with increased in-hospital mortality and the need for mechanical respiratory support [65–71]. Moreover, individual cases of fulminant heart failure with severe systolic dysfunction have also been published [72,73].

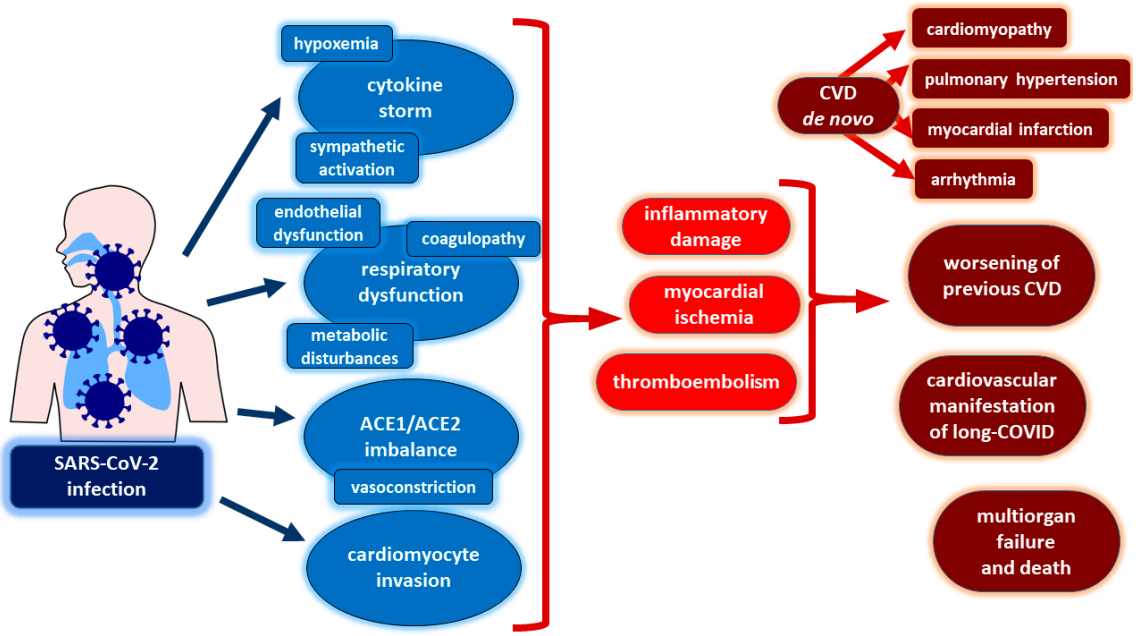

Figure 3. Cardiovascular complications of COVID-19 and diverse proven underlying pathomechanisms. Abbreviations: ACE1—angiotensin-converting enzyme 1, ACE2—angiotensin-converting enzyme 2, CVD—cardiovascular disease, SARS-CoV-2—Severe Acute Respiratory Syndrome Coronavirus 2.

There are a few different pathomechanisms of myocardial injury in patients with COVID-19. They include, for example, direct myocardial damage due to uncontrolled cytokine release [67,74] or myocardial ischemia triggered by respiratory dysfunction with hypoxemia in the course of severe respiratory insufficiency [75]. Furthermore, ACE2 downregulation by interfering with the balance between angiotensin-converting enzyme 1 (ACE1) and angiotensin-converting enzyme 2 (ACE2) can lead to the suppression of the cardioprotective, anti-inflammatory, and vasodilative effects of the ACE2–angiotensin axis [76]. Additional pathomechanisms contributing to myocardial injury in COVID-19 are endothelial dysfunction, coagulopathy, and metabolic disturbances with insulin resistance and pericardial lesions [75,77]. SARS-CoV-2 is proven to directly invade car-

diomyocytes in vitro in a cathepsin- and ACE2-dependent way [78]. Regarding autopsy studies, high cardiac viral loads were found in 41% of subjects [79] and interstitial infiltrates of mononuclear immune cells, macrophages with viral particles, and endotheliitis were demonstrated [72,80,81].

There have been documented cases of acute myocarditis in the course of symptomatic COVID-19 [73,82]. However, the causal relationship has not been fully elucidated, and the prevalence of this coincidence is not precisely established [65]. Among patients recovered from recent COVID-19, in magnetic resonance imaging (MRI), cardiac involvement was found in 78% of subjects, while myocardial inflammation was present in 60% of enrollees. It is worth noting that cardiac magnetic resonance (CMR) abnormalities are more prevalent than abnormal cardiac biomarkers in patients with a recent history of COVID-19 [83–85]. In the recent meta-analysis, heart failure symptoms were described in 11.5% of patients with COVID-19 and were related to higher mortality [86]. Analogously, elevated natriuretic peptides predict increased mortality in patients hospitalized with COVID-19 [87].

COVID-19 is related to an increased risk for ischemic complications. The risk of MI is five times higher and the risk of stroke is ten times higher during the first 2 weeks after diagnosis, and persists for at least 1 month [88]. MI is diagnosed in 7–17% of COVID-19 inpatients and may have a heterogeneous etiology: plaque rupture, spasm of the coronary artery, micro-thrombi or insufficient oxygen supply due to hypoxemia (type 2 MI according to guidelines) or endothelial or vascular injury [89]. The incidence of ischemic stroke in hospitalized patients reaches 2.5–5% [90], and cases of aortic thrombosis, acute limb, or mesenteric ischemia have also been described [91]. Thromboembolic events are prevalent and related mainly to hyperinflammatory reactions and microvascular dysfunction [67,92–94]. VTE occurs in 29-37% of subjects (predominantly PE—18%), with a demonstrated reduction to 24% (15% in the case of PE) when antithrombotic prophylaxis is implemented [27]. In autopsy, alveolar capillary microthrombi in COVID-19 patients are almost 10 times more frequent than in influenza [28]. VTE is considerably more prevalent in ARDS associated with COVID-19 than in non-COVID-19 ARDS [95]. Furthermore, arrhythmias affect almost every fifth patient and are also related to worse outcomes [86]. However, arrhythmic burden is not associated with the severity of lung injury [96,97]. New-onset atrial fibrillation was found in up to 6% of patients hospitalized due to COVID-19 [66,97,98].

Long-COVID (persistence of signs or symptoms over 4 weeks from acute onset) consists of two stages: ongoing symptomatic phase (4–12 weeks) and post-COVID-19 syndrome (>12 weeks), and is manifested in 43–89% of the patients by cardiopulmonary symptoms (chest pain, breathlessness, palpitations, and fainting) [99–101]. In one study, at least 4 months after COVID-19 the convalescents had higher troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels together with slight biventricular contractile dysfunction as assessed by echocardiography in comparison to non-COVID controls [102].

Although SARS-CoV-2 infection in children is usually mild or asymptomatic, a rare but severe complication among the youngest constitutes multisystem inflammatory syndrome in children (MIS-C; also described as pediatric inflammatory multisystem syndrome, or PIMS), which in the majority of cases affects the heart and coronary arteries [103,104]. The postulated underlying mechanisms are immune-driven, induced by a hyperimmune response to the virus in genetically vulnerable subjects [103]. The most prevalent symptoms are persistent fever and gastrointestinal manifestations, while the most common cardiac complications include left ventricular systolic dysfunction, coronary artery aneurysms, and electrical abnormalities (arrhythmias or conduction disturbances) [103]. The described complications are similar to Kawasaki disease, toxic shock syndrome, macrophage activation syndrome, bacterial sepsis, and cytokine release syndrome, which only confirms their common immunological denominator [103,105]. In severe cases requiring inotropic agents, mechanical ventilation or extracorporeal membrane oxygenation (ECMO) are required. Troponin elevation can be found in 64-95% of children with MIS-C [103,106]. The majority of patients recover within several weeks, with the mortality rate estimated at approxi-

mately 2%. However, the long-term consequences have not been elucidated yet [103–106]. Established risk factors for poor prognosis comprise older age and high serum ferritin [107].

8. Conclusions

Some cardiovascular complications of VRI are well characterized; for example, we know in detail how such infections adversely affect blood rheology or endothelial function. In the course of, for example, COVID-19, pathophysiological aspects such as hypoxemia due to severe respiratory failure or a cytokine storm have also been intensively studied in the context of the impact on the circulatory system. On the other hand, we still do not know much about what happens at the virus-cardiomyocyte level, i.e., which factors determine, for example, the development of acute/sub-acute myocarditis (complicating a common viral upper respiratory tract infection) or the conversion of acute inflammatory myocardial involvement to chronic post-inflammatory cardiomyopathy. A more precise understanding of these pathomechanisms will not only allow us to identify more precisely subjects at risk of the most severe VRI cardiovascular complications (cardiomyopathy with severe symptoms of heart failure), but it may also allow us to develop effective causal or even prophylactic anti-inflammatory/immunosuppressive therapies, which in a carefully selected group of patients may reduce morbidity and mortality.

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8.2. PUBLIKACJA 2

Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study.

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Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study

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Abstract: Pathomechanisms responsible for recovery from acute myocarditis (MCD) or progression to non-ischemic cardiomyopathy have not been comprehensively investigated. Iron, positioned at the crossroads of inflammation and the energy metabolism of cardiomyocytes, may contribute to the pathophysiology of inflammatory myocardial disease. The aim of this study was to evaluate whether systemic iron parameters are related to myocardial dysfunction in MCD patients. We prospectively enrolled 42 consecutive patients hospitalized for MCD. Their iron status and their clinical, laboratory, and echocardiographic indices were assessed during hospitalization and during ambulatory visits six weeks after discharge. A control group comprising healthy volunteers was recruited. The MCD patients had higher serum ferritin and hepcidin and lower serum iron concentration and transferrin saturation (TSAT) than the healthy controls (all $p < 0.01$). Six weeks after discharge, the iron status of the MCD patients was already comparable to that of the control group. During hospitalization, lower serum iron and TSAT correlated with higher NT-proBNP (both $p < 0.05$). In-hospital lower serum iron and TSAT correlated with both a lower left ventricular ejection fraction (LVEF) and worse left ventricular global longitudinal strain at follow-up visits (all $p < 0.05$). In conclusion, in patients with acute MCD, iron status is altered and normalizes within six weeks. Low serum iron and TSAT are related to greater in-hospital neurohormonal activation and subtle persistent left ventricular dysfunction.

Keywords: myocarditis; iron status; ferritin; hepcidin; inflammation; myocardial dysfunction

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1. Introduction

In the majority of patients with acute myocarditis (MCD), the disease spontaneously regresses without significant clinical sequelae [1–3]. However, there are subjects who develop post-myocarditis non-ischemic cardiomyopathy, and such patients—who are at higher risk of poor outcomes—are difficult to identify [1–3]. Our knowledge of the mechanisms behind recovery from MCD or the development of subsequent cardiomyopathy is limited, and various factors responsible for this process have been postulated, including innate immune competence, comorbidities, and genetics [1,4–7].

There are pathophysiological links between disordered iron status and cardiomyopathy. Both iron deficiency and iron overload are detrimental for cardiomyocytes. This

provides an insight into the U-shaped relationship between a (sub-)cellular iron level and cardiomyocyte homeostasis [8–15]. An abnormal immune response is considered to be the major pathophysiological mechanism promoting MCD, and circulating biomarkers of iron metabolism are also linked to immunological reactions [1,2,16–19]. Ferritin and hepcidin are widely recognized as acute phase reactants and biomarkers of inflammation [20–24]. The release of inflammatory cytokines upregulates hepcidin synthesis and the secretion of iron-poor ferritin by macrophages, which eventually leads to limiting the availability of iron to microorganisms during infection [25–27]. Nevertheless, whether or not peripheral blood iron status relates to the recovery from acute MCD remains unexplored.

The aim of the current study was to evaluate whether systemic iron parameters are related to myocardial dysfunction in acute MCD patients.

2. Materials and Methods

2.1. Patients Population

The prospective MCD registry consisted of patients who were hospitalized consecutively for acute MCD during 2014–2019 in two tertiary referral cardiology centers: the Cardiology Department of the Center for Heart Diseases in the 4th Military Hospital in Wroclaw and the Department of Cardiology of the Tadeusz Marciniak Lower Silesia Specialist Hospital—Emergency Medicine Center in Wroclaw.

MCD was diagnosed according to the criteria presented in Table 1. The follow-up period for analysis was 6 weeks after discharge. A control group comprising healthy adult age-matched and gender-matched volunteers was recruited among hospital personnel and relatives in order to constitute a reference for laboratory tests and imaging.

Table 1. The diagnostic criteria for acute myocarditis in the current study.

All Diagnostic Criteria for Acute Myocarditis Must Have Been Met:
(1) new onset symptoms suggestive of myocarditis (shortness of breath, effort intolerance, fatigue, palpitations, or chest pain),
(2) elevated high sensitivity cardiac troponin I,
(3) exclusion of obstructive coronary artery disease in coronary angiography or coronary computed tomographic angiography,
(4) features suggestive of myocarditis in cardiac magnetic resonance, and
(5) age $\geq$ 18 years.

The study protocol was approved by the local ethics committee (the Bioethics Committee, Wroclaw Medical University, Wroclaw, Poland). All patients provided written informed consent to participate in the study. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Study Scheme

During their hospitalization for acute MCD, the patients were assessed at the emergency department and 3 $\pm$ 1 days after admission to the cardiology department. A control ambulatory visit was scheduled 6 $\pm$ 1 weeks after discharge. The study design scheme is presented in Figure 1.

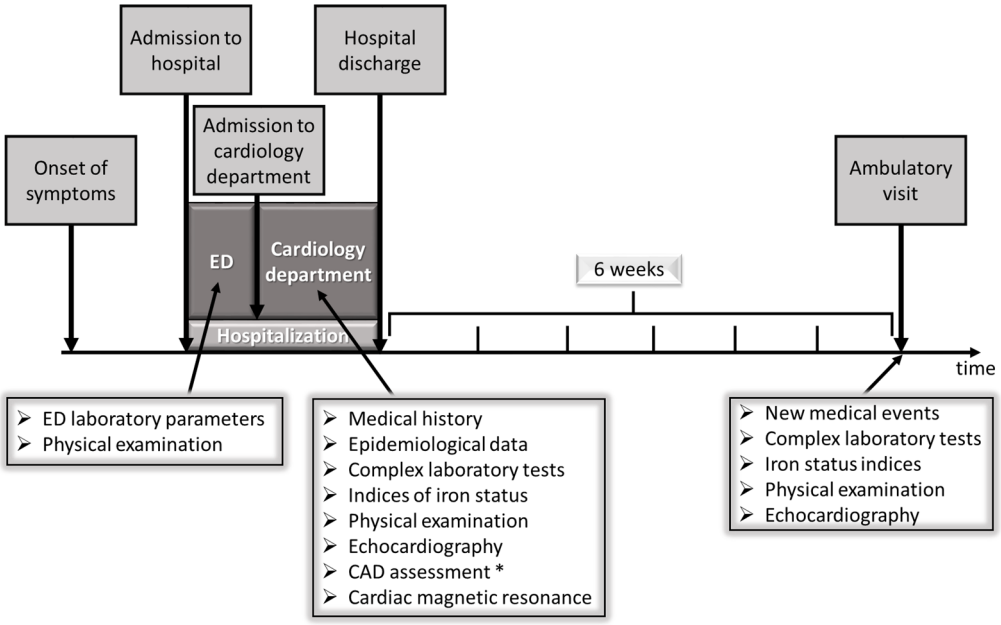

Figure 1. The study scheme comprised two assessments of patients with acute myocarditis during hospitalization and one at ambulatory visit after six weeks of recovery. Abbreviations: CAD, coronary artery disease; ED, Emergency Department. * coronary angiography or coronary computed tomographic angiography.

2.3. Basic Clinical Evaluation

The demographic and anthropometric characteristics, medical history, comorbidities, and the characteristics of clinical presentation (signs, symptoms) of acute MCD were collected at the cardiology department (detailed medical history). At each timepoint (at the emergency department, at the cardiology department, and at the ambulatory visit), assessment of the vital signs and physical examination were performed. Mean systolic blood pressure, mean diastolic blood pressure, and mean heart rate were calculated as an average from 3 consecutive measurements.

2.4. Laboratory Parameters

We analyzed the following emergency department laboratory tests: serum hemoglobin, white blood cell count, high-sensitivity cardiac troponin I (hs-cTnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), serum creatinine, and alanine transaminase (ALT). The following basic laboratory parameters were measured - in fresh venous blood: in patients with acute MCD at the cardiology department and during ambulatory visit: serum hemoglobin, red blood/white blood cell/neutrophil/lymphocyte/monocyte count, reticulocyte hemoglobin content, reticulocyte count, hs-cTnI, NT-proBNP, CRP, ALT, serum creatinine, serum insulin, and thyroid-stimulating hormone.

The following blood biomarkers/parameters, reflecting iron metabolism, were measured directly (from fresh venous blood): serum ferritin (μg/L)—with an immunoassay based on electrochemiluminescence with the Elecsys 2010 System (Roche Diagnostics GmbH, Mannheim, Germany); iron (μg/dL); and unsaturated iron-binding capacity - based on a substrate method with Feren S (Thermo Fisher Scientific, Waltham, MA, USA). The total iron-binding capacity (μg/dL) was automatically calculated using serum iron and unsaturated iron-binding capacity. Transferrin saturation (TSAT) was calculated as the ratio of serum iron (μg/dL) and total iron-binding capacity (μg/dL), and expressed as a percentage. Soluble Transferrin Receptor (sTfR, mg/L) and hepcidin (ng/mL) were measured in frozen sera, after obtaining and preparing biological material from all study enrollees. Clotted blood samples were centrifuged and the supernatants were collected and frozen in −80 °C for further analysis. STfR was measured using immunonephelom-

etry (Siemens Healthcare Diagnostics, Inc., Deerfield, IL, USA). Hepcidin was assessed using a commercially available, enzyme-linked immunosorbent assay (BACHEM s-1337 (Bachem AG, Bubendorf, Switzerland) for detecting human hepcidin-25, dedicated for research use only. This is a unique hepcidin ELISA kit which has been validated with a gold standard for hepcidin assessment—liquid chromatography mass spectrometry (LC MS) [28]. For accurate hepcidin detection, all samples were 5 times diluted and were within the linear range of the curve. The optical density of the samples was measured at 450 nm, with a reading time of 1 sec, using a microtiter plate reader Biotek Synergy HTX (Agilent Technologies, Inc., Santa Clara, CA, USA). For the assessment of the neurohormonal activation, plasma level of NT-proBNP (pg/mL) was measured using an immunoassay based on chemiluminescence with Dimension RxL system (Siemens Healthcare Diagnostics, Inc., Deerfield, IL, USA). For the evaluation of the inflammatory response, serum level of CRP (mg/L) was assessed using immunonephelometry with BN II System (Siemens Healthcare Diagnostics, Inc., Deerfield, IL, USA). For the assessment of the cardiomyocyte necrosis, hs-cTnI (μg/L) was measured using chemiluminescence (technology LOCI) on the Dimension EXL System (Siemens Healthcare Diagnostics, Inc., Deerfield, IL, USA). The serum hemoglobin concentration (g/dL), red or white cell indices and reticulocytes, were measured using the ADVIA 120 hematology system (Siemens Healthcare Diagnostics, Inc., Deerfield, IL, USA). Except for hepcidin, all diagnostic laboratory assessments were performed in the central laboratory of the Military Hospital in Wroclaw (Poland).

2.5. Echocardiography

A standard transthoracic echocardiography was performed at the cardiology department and during ambulatory visit six weeks after discharge. For the purposes of this study, the following variables were analyzed: left ventricular ejection fraction (LVEF), estimated using Simpson's planimetric method; left ventricular global longitudinal strain (LV GLS), measured by the speckle tracking technique; indices of left ventricular diastolic function (including E/A, e' sep, e' lat and E/e'), assessed with the use of continuous wave and tissue doppler imaging; tricuspid annular plane systolic excursion (TAPSE) and segmental myocardial contractility dysfunction, estimated visually by an experienced sonographer.

2.6. Other Diagnostic Procedures

We analyzed the following other diagnostic procedures, performed during the index hospitalization in the cardiology ward:

- coronary angiography or coronary computed tomographic angiography—to exclude obstructive coronary artery disease;
- cardiac magnetic resonance—in search for the indices of MCD, to confirm the diagnosis.

2.7. Statistical Analyses

Most of the continuous variables had a normal distribution, and were expressed as mean (standard error of the mean). NT-proBNP, hs-cTnI, CRP, serum hepcidin, reticulocyte count, ALT, alcohol consumption, and neutrophil-to-lymphocyte ratio had a skewed distribution and were expressed as median with lower and upper quartiles (interquartile range). These variables were log-transformed (a natural logarithm, ln) before inclusion in further analyses. The intergroup differences between the patients with acute MCD and the healthy controls were tested using the *t*-test for unpaired samples. The categorical variables were expressed as numbers (with percentages). The intergroup differences regarding the categorized variables were tested using the Pearson's Chi-square test. The associations between the iron status indices and the laboratory or echocardiographic parameters were tested using Pearson's correlation coefficients. The changes in laboratory parameters between the hospitalization and the ambulatory visit were tested using t-test for paired samples. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the Statistica 13 data analysis software system (TIBCO Software Inc., Palo Alto, CA, USA).

3. Results

3.1. Patients Characteristics

Out of 63 patients admitted to the hospital with suspected acute MCD, 21 initially evaluated subjects were excluded:

- 3 with normal level of high sensitivity cardiac troponin I;
- 18 without indices of MCD in cardiac magnetic resonance.

The final study group of patients hospitalized for acute MCD comprised 42 subjects.

The baseline demographic, clinical, laboratory, and echocardiographic characteristics of the study group versus controls, who were 15 age-matched and gender-matched healthy volunteers, are presented in Table 2. Co-morbidities were not prevalent in the patients with acute MCD. Only three (7%) of them had a history of a previous MCD. During the hospitalization and the subsequent observation, none of the subjects died, was rehospitalized for unplanned reasons (including cardiovascular and non-cardiovascular causes), nor required a heart transplantation or a ventricular assist device.

Table 2. The baseline demographic and clinical characteristics, laboratory parameters and echocardiographic indices in patients hospitalized for acute myocarditis in comparison with a control group of age- and gender-matched healthy volunteers.

Variables, Units	MCD Patients (n = 42)	Control Group (n = 15)	p-Value
Age, year	32 (1)	31 (1)	0.66
Male gender, yes	41 (97%)	13 (87%)	0.10
Smoking, packet-year	0.2 (0.0–6.5)	0.0 (0.0–0.0)	0.20
Alcohol, g per week	90 (25–155)	25 (25–50)	0.01
SBP on admission, mmHg	135 (3)	118 (3)	0.003
DBP on admission, mmHg	80 (3)	77 (3)	0.62
HR on admission, mmHg	86 (3)	73 (4)	0.02
Basic laboratory parameters (cardiology department)			
Serum hemoglobin, g/dL	15.0 (0.2)	15.2 (0.3)	0.59
Red blood cell count, $10^6/\mu L$	5.0 (0.1)	5.0 (0.1)	0.65
White blood cell count, $10^3/\mu L$	7.9 (0.4)	6.3 (0.4)	0.03
Neutrophil count, $10^3/\mu L$	5.0 (0.3)	3.2 (0.3)	0.004
Lymphocyte count, $10^3/\mu L$	2.0 (0.1)	2.3 (0.2)	0.19
Monocyte count, $10^3/\mu L$	0.7 (0.1)	0.4 (0.1)	0.008
Neutrophil-to-lymphocyte ratio	2.3 (1.9–3.0)	1.2 (1.1–1.9)	<0.001
Reticulocyte hemoglobin content, pg	30 (3)	37 (5)	0.03
Reticulocytes, %	0.98 (0.82–1.30)	1.26 (1.06–1.56)	0.60
C-reactive protein, mg/L	54 (5)	3 (0)	<0.001
NT-proBNP, pg/mL	340 (185–594)	31 (18–46)	<0.001
Hs-cTnI, µg/L	2.44 (0.53–6.33)	0.01 (0.01–0.01)	<0.001
Serum creatinine, mg/dL	0.91 (0.02)	0.98 (0.03)	0.11
ALT, U/L	38 (27–48)	20 (13–30)	<0.001
Serum insulin, uIU/mL	13.4 (1.1)	7.9 (1.3)	0.01
TSH, mIU/L	2.0 (0.2)	2.7 (0.3)	0.07
Iron status indices			
Serum iron, µg/dL	70 (5)	101 (12)	0.006
Serum ferritin, µg/L	285 (30)	139 (18)	0.007
TSAT, %	21 (1)	30 (4)	0.007
sTfR, nmol/L	1.28 (0.05)	1.17 (0.06)	0.25
Serum hepcidin, µg/L	44 (24–131)	21 (13–44)	0.009

Table 2. *Cont.*

Variables, Units	MCD Patients (*n* = 42)	Control Group (*n* = 15)	*p*-Value
Transthoracic echocardiography			
LVEF, %	56 (1)	63 (1)	0.01
TAPSE, mm	21 (1)	23 (1)	0.045

The data are presented as mean (SEM) or median with interquartile range for continuous variables and counts (percentages) for nominal variables. Abbreviations: ALT, alanine transaminase; BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; hs-cTnI, high-sensitivity cardiac troponin I; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; SBP, systolic blood pressure; sTfR, soluble transferrin receptor; TAPSE, tricuspid annular plane systolic excursion; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone. The conversion factors to SI units are as follows: for hemoglobin (g/dL), 10; for white blood cells, neutrophils, lymphocytes, and monocyte count (all in 103/μL) 1; for NT-proBNP (in pg/mL), 0.118; for serum creatinine (in mg/dL), 88.42; for serum insulin (in uIU/mL), 6.945; for serum iron (in μg/dL), 0.179; for serum ferritin (in μg/L), 2.247; for serum hepcidin (in μg/L), 0.3584.

3.2. Clinical Manifestation of MCD

The most prevalent symptoms of acute MCD were chest pain—in 39 (93%) patients, dyspnea—in 13 (31%), and palpitations—in 6 (14%). Two (5%) patients presented symptoms of acute heart failure at the time of admission. Within 30 days before admission to the hospital, fever (T > 38 °C) was present in 26 (62%) of the patients, pharyngitis in 25 (60%), arthritis in 22 (52%), cough in 18 (43%), rhinitis in 15 (36%), nausea/vomiting in 10 (24%), stomach pain in 4 (10%), diarrhea in 3 (7%), and sinusitis, rash, and dysuria in two (5%) patients. Twenty-two (52%) subjects still presented symptoms of infection at the time of admission.

In transthoracic echocardiography, the patients hospitalized for acute MCD presented lower LVEF, higher LV GLS, and worse parameters of diastolic function—lower values of E/A, e' lat and higher of E/e'—compared to the control group (Table 2). A segmental myocardial contractility dysfunction was present in more than half of the subjects.

3.3. Follow-Up Visit

The ambulatory visit at six weeks after discharge was missed by 7 patients—data for 35 subjects were available. No differences regarding baseline clinical characteristics were found between the 35 patients, who attended the ambulatory visit, and the 7 patients, who were lost to follow-up.

At the ambulatory visit, NT-proBNP, high-sensitivity troponin I, and CRP were lower than during the hospitalization (all *p*-values < 0.001), and already comparable to the healthy controls (*p*-values: 0.36, 0.16, 0.17, respectively). The changes in the indices of iron status after six weeks of recovery together with the comparison to the control group are presented in Figure 2.

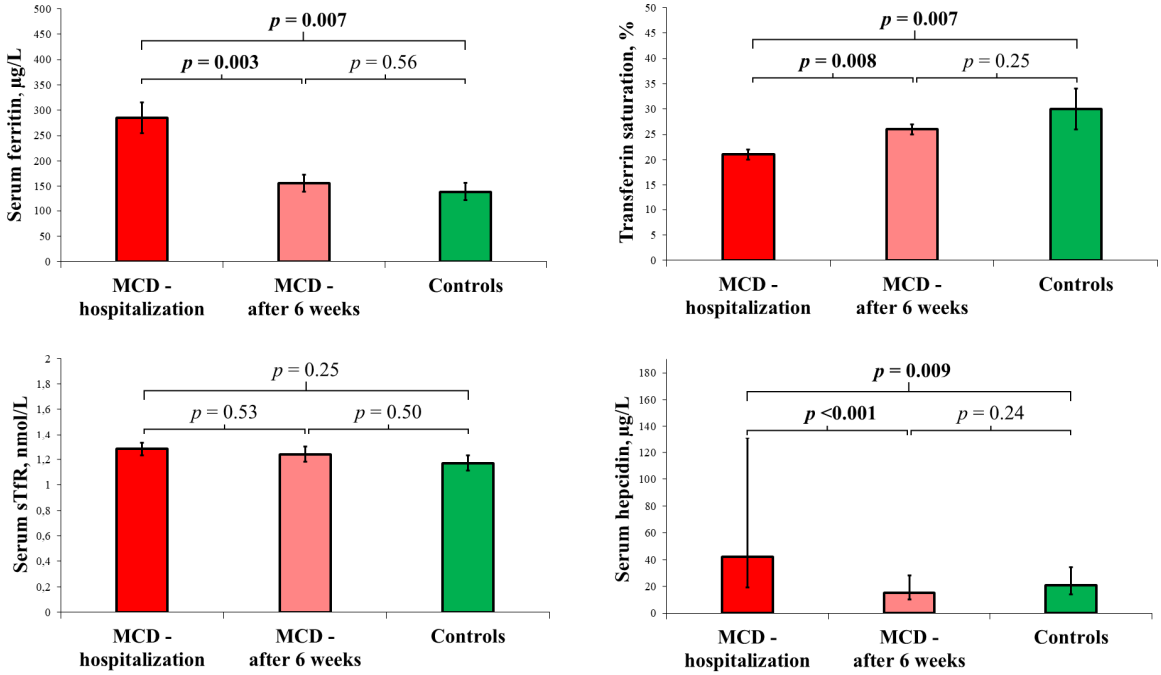

Figure 2. Serum ferritin, transferrin saturation, serum soluble transferrin receptor (mean (bar) with SEM (whiskers)), and serum hepcidin (median (bar) with interquartile range (whiskers)) in the patients with acute myocarditis during hospitalization (n = 42) and at the follow-up visit 6 weeks after discharge (n = 35), in comparison with age- and gender-matched healthy volunteers (n = 15). The MCD patients during hospitalization had higher serum ferritin and hepcidin and lower transferrin saturation than the healthy controls. Six weeks after discharge, in the MCD patients, serum ferritin and hepcidin decreased, while transferrin saturation increased, and the iron status was already comparable to that of the control group. For details, see "Section 2.7".

3.4. Relationship of Neurohormonal Activation, Cardiomyocyte Necrosis, Inflammatory Response, and Cardiac Dysfunction with In-Hospital Iron Status

The relationships of the in-hospital indices of iron status with the in-hospital laboratory markers of neurohormonal activation, cardiomyocyte necrosis, and inflammatory response, and with the echocardiographic measures of cardiac dysfunction from the index hospitalization, are presented in Table 3.

Table 3. The relationships between the baseline iron indices, the biomarkers of neurohormonal activation, cardiomyocyte necrosis or inflammation, and the main laboratory or echocardiographic parameters from the index hospitalization in the patients with acute myocarditis.

Variables #, Units	Cardiology Department					
	NT-proBNP, 1 ln pg/mL	Hs-cTnI, 1 ln µg/L	CRP, 1 ln mg/L	LVEF, 1%	LV GLS, 1	TAPSE, 1 mm
Serum iron, 1 µg/dL	−0.345 *	−0.086	−0.315 *	0.169	−0.029	0.037
Serum ferritin, 1 µg/L	0.093	0.155	0.309 *	0.019	−0.135	0.167
TSAT, 1%	−0.319 *	0.018	−0.281	0.223	−0.093	0.122
sTfR, 1 nmol/L	−0.101	0.094	0.052	−0.020	0.235	−0.101
Serum hepcidin, 1 ln µg/L	0.283	0.095	0.308 *	−0.113	−0.196	0.229
NT-proBNP, 1 ln pg/mL	X	−0.022	0.166	−0.614 ***	0.111	−0.031
Hs-TnI, 1 ln µg/L	−0.022	X	0.245	0.082	0.188	0.078
CRP, 1 ln mg/L	0.166	0.245	X	−0.029	0.040	−0.173

Data are presented as Pearson's correlation coefficient. * p-value < 0.05, *** p-value < 0.001. # Assessed at the cardiology department. Abbreviations: see Table 2; LV GLS, left ventricular global longitudinal strain. Conversion factors to SI units: see Table 2.

During the index hospitalization, serum iron and acute phase reactants (ferritin and hepcidin) correlated with CRP. Lower in-hospital serum iron and TSAT were associated with higher in-hospital NT-proBNP.

Moreover, an analysis of echocardiographic evaluation, performed six weeks after discharge, demonstrated that lower serum iron and TSAT, measured during the hospitalization, were associated with a persistent left ventricular dysfunction (lower LVEF and higher LV GLS) at the follow-up visit (Table 4).

Table 4. The correlation of the baseline iron indices with the biomarkers of neurohormonal activation, cardiomyocyte necrosis or inflammation, and with echocardiographic parameters after six weeks of recovery in the patients with acute myocarditis.

Baseline	6 Weeks after Hospital Discharge					
Variables, Units	**NT-proBNP, 1 ln pg/mL**	**hs-cTnI, 1 ln µg/L**	**CRP, 1 ln mg/L**	**LVEF, 1%**	**LV GLS, 1**	**TAPSE, 1 mm**
Serum iron, 1 µg/dL	−0.012	−0.014	−0.067	0.388 *	−0.392 *	0.327
Serum ferritin, 1 µg/L	−0.104	−0.020	0.325	0.134	−0.279	0.126
TSAT, 1%	0.031	0.037	−0.104	0.391 *	−0.408 *	0.285
sTfR, 1 nmol/L	−0.013	0.219	−0.213	−0.209	0.241	0.067
Serum hepcidin, 1 ln µg/L	−0.263	−0.034	0.110	0.179	0.073	0.142

Data are presented as Pearson's correlation coefficient. * p-value < 0.05. Abbreviations: see Tables 2 and 3. Conversion factors to SI units: see Table 2.

The levels of hs-TnI, NT-proBNP, LVEF and LV GLS, assessed during the follow-up visit, were neither related to CRP, nor to white blood cell indices (white blood cell count, neutrophil, lymphocyte or monocyte count and neutrophil-to-lymphocyte ratio) from the index hospitalization.

4. Discussion

The major findings arising from the current study are (1) the patients with acute MCD had comparable red blood cell indices but altered indices of iron status, compared with the healthy controls, (2) disordered iron parameters normalized within six weeks after the index hospitalization, (3) low serum iron and TSAT, which constitute indices of iron deficiency but not acute phase reactants, were correlated with greater in-hospital neurohormonal activation (measured via the concentration of natriuretic peptides), together with a subtle persistent left ventricular dysfunction, detected after six weeks of recovery (assessed via LVEF and LV GLS).

There is evidence, from experimental animal and cell cultures, that systemic iron deficiency relates to multifaceted myocardial dysfunction [8,10,12,18]. For example, systemic ID, induced in animals through bleeding or an iron-depleted diet, resulted in mitochondrial dysfunction, abnormal intracellular metabolism, and destruction or apoptosis of cardiomyocytes [29–32]. All those adverse alterations were associated with progression to cardiomyopathy with systolic dysfunction, and development of overt heart failure [12,33,34]. Recently, experimental models have demonstrated that the detrimental impact of iron deficiency on cardiac muscle can be reversed via iron supplementation [11,35,36]. In addition, clinical data have confirmed beneficial effects of iron supplementation in iron-deficient subjects in chronic conditions [37,38]. In patients with heart failure with left ventricular dysfunction, intravenous iron therapy leaded to improvement of symptoms, exercise capacity, and quality of life in randomized clinical trials, and was even associated with better prognosis in further meta-analysis [37,38]. Recently, clinical data have shown favorable results of treatment of iron depletion in a post-acute clinical scenario: in patients who were stabilized after an episode of acute heart failure, a treatment with ferric carboxymaltose reduced the risk of heart failure hospitalizations in a randomized clinical trial [39]. Whether iron supplementation in patients with acute MCD, with peripheral indices of iron deficiency, may be beneficial and prevent progression to post-myocarditis non-

ischemic cardiomyopathy, has never been explored. It may be an interesting direction for future research.

Although we have no data on the cardiomyocyte iron status in patients with acute MCD, there have been documented links between the systemic iron status and myocardial iron metabolism [31,40,41]. Cardiomyocytes cultured in iron-depleted environment were revealed to exhibit an overexpression of transferrin receptor 1, which constitutes evidence of an increased intracellular iron demand [31]. What is more, the overexpressed transferrin receptor 1 was related to an increased apoptosis of cardiomyocytes [31,32]. In human cardiomyocytes, a decreased iron content impairs the mitochondrial respiration, leading to both contractile and relaxation dysfunction [11]. Myocardial iron deficiency is closely linked to left ventricular dilation and fibrosis, resulting in cardiomyopathy and heart failure [12,40].

Furthermore, relationships between iron deficiency and an impairment of antioxidative defense have been postulated [42]. Iron constitutes a metal cofactor for mitochondrial enzymes, responsible for antioxidative processes. Several studies have demonstrated the development of mitochondrial dysfunction under iron-depleted conditions [11,42]. Moreover, the most vulnerable to iron restriction are the cells of high mitogenic potential (i.e., immune cells) or of high energy demand (i.e., cardiomyocytes) [16]. Hence, there are premises to consider iron metabolism to be an important contributor to the complex pathophysiology of MCD.

Iron metabolism plays an important role in the pathogenesis of inflammation [26]. Both ferritin and hepcidin are known positive acute-phase proteins, which means that their plasma concentrations increase during an inflammatory process, and our analyses have confirmed high serum hepcidin and ferritin levels in the patients with acute MCD [20–22,25]. The aim of the alterations in iron status during the inflammation is to limit iron availability to microorganisms in the course of infection. The crucial mechanism, involving iron metabolism into inflammation, seems to be the upregulation of hepcidin, a hormone synthesized predominantly by hepatocytes, by released inflammatory cytokines [26,27]. The circulating hepcidin, via a specific receptor (ferroportin), downregulates the expression of proteins responsible for the import of iron into enterocytes and, by internalizing ferroportin, also disables further export of the intracellular iron to the circulating transferrin [25–27]. As a consequence, it decreases the iron absorption by enterocytes, and additionally reduces the export of the intracellular iron, trapped mainly in hepatocytes and macrophages as iron-rich ferritin, leading to a reduction in the concentration of serum iron [26,27]. On the other hand, iron-poor ferritin is secreted by macrophages into circulation, resulting in high serum ferritin levels [26]. Although the abundant store of intracellular iron results in downregulation of transferrin production and in lowering total iron binding capacity, the extensive decrease in serum iron prevails over this mechanism, leading to a lowering of TSAT [26,27].

Our study has demonstrated an association of lower serum iron and TSAT with greater in-hospital neurohormonal activation and with a subtle deterioration of left ventricular function after six weeks of observation. Considering the aforementioned mechanisms of the pathophysiology of inflammation, our finding may be explained by the fact that the decrease in TSAT and in serum iron concentration may reflect an enhanced myocardial inflammation and a more extensive affection of the myocardium. Furthermore, functional iron deficiency, expressed by low TSAT, can derange myocardial energetics. In consequence, it may adversely affect the processes of healing the damaged myocardial tissue, and thus impair recovery from acute MCD. What is of note, CRP—a biomarker of inflammation routinely used in clinical practice—was related neither to the in-hospital neurohormonal activation nor to the subtle persistent left ventricular dysfunction. The reason for the difference between CRP and TSAT, or serum iron concentration, may be the fact that, in contrast to CRP, the analyzed iron parameters express cumulatively both the intensity of the inflammation and the disturbed myocardial energetics, and thus, they better manifest

the defected recovery process. These indices of iron status may reflect multiple negative mechanisms during the recovery, not only those concerning the inflammatory response.

Further studies and longer periods of observation are required to determine the relationships between the iron metabolism during acute MCD and the risk of an unfavorable progression to post-myocarditis non-ischemic cardiomyopathy. However, the assessment of circulating biomarkers of iron status may become a valuable tool in risk stratification and the evaluation of recovery after acute MCD. Moreover, the treatment of iron deficiency in MCD patients could constitute an interesting area for the future clinical trials.

Limitations of the Study

The current study has certain limitations, which should be punctuated. Firstly, although the recruitment was conducted in two cardiology centers, and consecutive patients hospitalized for acute MCD were enrolled, the final study group comprised a relatively small number of subjects, and thus only basic statistical analyses were performed. However, it needs to be acknowledged that the previous research into MCD has mainly comprised studies of small-scale populations, above all, due to the relatively low incidence of this disease. Therefore, extensive multicenter trials in larger populations are greatly needed. Secondly, we assessed indices of peripheral blood iron status, and we have no data on the myocardial iron status, which may be crucial for a better recognition of the role of iron in the pathobiology of myocardial inflammation. Eventually, to evaluate the inflammatory reactions, we utilized only C-reactive protein concentrations, while a complex assessment of inflammatory indices, including concentrations of pro-inflammatory interleukins, would give a superior insight into the contribution of the immune response, its relationships with iron metabolism, and its associations with recovery from acute MCD.

5. Conclusions

Patients hospitalized for acute MCD have comparable red blood cell indices, but altered indices of iron status, compared with healthy controls. The deranged iron status normalizes within six weeks of recovery. Lower serum iron and TSAT (indicators of iron deficiency other than acute phase reactants) correlate with a greater in-hospital neurohormonal activation and a subtle persistent left ventricular dysfunction.

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

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: M.T. reports personal fees from V-Wave Ltd., Eidos Therapeutics, Cytokinetics, Impulse Dynamics, Alnylam Pharmaceuticals and Takeda, outside the submitted work. E.A.J. reports grants and personal fees from Vifor Pharma, personal fees from Bayer, Novartis, Abbott, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cardiac Dimensions, Takeda, Gedeon Richter, Respicardia, outside the submitted work. P.F., A.K., K.K.-Ł., K.A.K., M.K., A.S., J.J. and P.P. have nothing to disclose.

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8.3. PUBLIKACJA 3

Iron status and myocardial injury while recovering from acute myocarditis.

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Iron status and myocardial injury while recovering from acute myocarditis

Stan gospodarki żelazowej a uszkodzenie miokardium w ostrym zapaleniu mięśnia sercowego

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Abstract

Introduction. The pathophysiology of acute myocarditis (MCD) and subsequent recovery involves complex interplay between the virulence of pathogen, host immunity with possible genetic-based immune dysregulation, comorbidities and environmental factors. Precise identification of patients with increased risk of subsequent post-inflammatory cardiomyopathy is challenging. Abnormal iron status not only is a hallmark of immune activation but also

plays a role in the development of cardiomyopathy, hence we investigated whether iron indices relate to myocardial injury in patients with acute MCD.
Material and methods. Consecutive patients hospitalized for acute MCD in two cardiology centers were prospectively enrolled. We analyzed clinical characteristics, cardiac magnetic resonance (CMR) findings and biomarkers of myocardial necrosis, neurohormonal activation, inflammation, and comprehensive systemic iron status from index hospitalization and an ambulatory control visit after 6 months. Healthy volunteers were control group.
Results. We enrolled 40 patients hospitalized for acute myocarditis (age: 32 ± 9 years, male gender: 98%). In-hospital serum ferritin correlated with CMR late gadolinium enhancement (LGE) mass ($r = 0.537$, $p < 0.001$) and global T2 ratio ($r = 0.360$, $p = 0.03$). LGE, regional abnormalities in myocardial T1 relaxation time and elevated extracellular volume persisted after 6 months of recovery in comparison to healthy controls. Persistent LGE mass correlated with lower transferrin saturation and serum iron at the ambulatory visit ($r = –0.520$, $p = 0.03$; and $r = –0.465$, $p = 0.04$; respectively).
Conclusions. Acute-phase reactant ferritin relates to myocardial injury in the acute phase of MCD, whereas in the recovery phase residual fibrosis is greater in subjects with more profound functional iron deficiency, the latter reflecting, to some extent, systemic low-grade inflammation.
Key words: myocarditis, iron status, inflammation, cardiac magnetic resonance, late gadolinium enhancement

Introduction

The pathophysiology of acute myocarditis (MCD) and subsequent recovery involves complex interplay between the virulence of pathogen, host immunity with possible genetic-based immune dysregulation, comorbidities and eventually environmental factors [1–4]. However, patients at higher risk of progression to post-inflammatory cardiomyopathy are still difficult to identify [1, 2, 5–7]. Although numerous laboratory parameters, including biomarkers of cardiac necrosis, inflammatory or neurohormonal activation, are altered in MCD, no significant indicator for poor outcome in acute MCD has been found yet [4, 5, 8–11].

Iron constitutes an exceptional micronutrient with its position at the crossroads of critical cellular processes, such as: anti-infectious mechanisms, immune reaction, cellular energetics and anti-inflammatory processes [12–15]. Therefore, there are premises to consider iron metabolism as a significant modulator of complex pathophysiology of MCD.

Whereas invasive endomyocardial biopsy is limited to experienced centers and severe cases when decision on immunomodulatory therapy needs to be urgently established, cardiac

magnetic resonance (CMR) is becoming an increasingly crucial tool in common diagnosis of MCD and monitoring the process of recovery [1, 16]. Moreover, CMR findings — presence and persistence of late gadolinium enhancement (LGE) — were found to indicate poor prognosis in patients with MCD [7, 17–19].

The objective of the current study was to investigate whether iron indices relate to myocardial injury in patients with acute MCD.

Material and methods

Patients population

We analyzed data from prospective registry of patients hospitalized for acute MCD in years 2014–2019 in two tertiary referral cardiology centers: Cardiology Department of Centre for Heart Diseases in 4th Military Hospital in Wroclaw and Department of Cardiology of Tadeusz Marciniak Lower Silesia Specialist Hospital-Emergency Medicine Center in Wroclaw. Acute MCD was diagnosed based on the following criteria:

1) new onset of symptoms suggestive of myocarditis (chest pain, shortness of breath, exercise intolerance, fatigue, or palpitations);
2) elevated level of high sensitivity cardiac troponin I (hs-cTnI);
3) diagnosis of acute myocarditis in cardiac magnetic resonance;
4) exclusion of obstructive coronary artery disease in coronary angiography or coronary computed tomographic angiography;
5) age ≥ 18 years.

The control group comprised healthy adult age- and gender-matched volunteers. The study protocol was approved by the local ethics committee (Bioethics Committee, Wroclaw Medical University) and the study was conducted in accordance with the Declaration of Helsinki. All enrollees gave written informed consent to participate in the study.

Study scheme

Complex assessment (basic clinical evaluation, laboratory parameters and transthoracic echocardiography) during hospitalization was performed 3 ± 1 days after admission to the cardiology department. CMR was conducted within 10 days after admission. For consecutive patients hospitalized during 2017–2019, a control ambulatory visit was scheduled 6 ± 1 months after discharge.

Laboratory parameters

Laboratory assessment at the cardiology department and at the ambulatory visit included:
— biomarkers of neurohormonal activation, cardiomyocyte necrosis and inflammation: N-terminal pro-B-type natriuretic peptide (NT-proBNP), hs-cTnI, C-reactive protein (CRP) (all measured directly in fresh venous blood);

— indices of iron status: serum ferritin, iron, soluble transferrin receptor and unsaturated iron-binding capacity (fresh venous blood), serum hepcidin (assessed by enzyme-linked immunosorbent assay utilizing frozen serum).

Total iron-binding capacity (TIBC) was automatically assessed using serum iron and unsaturated iron-binding capacity. Transferrin saturation (TSAT) was calculated by dividing the serum iron concentration and TIBC, and expressed as a percentage.

Cardiac magnetic resonance

During hospitalization and at control ambulatory visit CMR was performed on a 1.5-Tesla scanner Magnetom Aera (Siemens Healthcare, Forchheim, Germany). An electrocardiography-gated breath-hold protocol was used.

CMR images were analyzed by two experienced analysts in a blinded fashion and using the Medis Suite MR software (Medis, Leiden, The Netherlands).

In our study we analyzed CMR indices which constitute Lake Louise Criteria II.

For assessment of edema both T2w-STIR sequences and T2 mapping were used.

In search for hyperemia T1 mapping was acquired before and 20 minutes after gadobutrol injection. We identified native T1, T2 and post-contrast T1 values and calculated (using hematocrit value acquired within 24 hours before CMR) extracellular volume (ECV) for each left ventricular segment (according to myocardial segmentation of American Heart Association).

To quantitatively evaluate the myocardial fibrosis, we analyzed the LGE images. According to the current recommendations, for native T1- and T2-mapping, local reference ranges were used [20]. They were generated from data sets of 15 healthy subjects that were acquired, processed, and analyzed in the same way as the intended application, with the upper and lower range of normal defined by the mean ± 2 SD of the normal data. Reference ranges for global and regional (for each left ventricular segment) T1, T2 relaxation times and ECV were calculated. Global native T1 mapping was identified as pathological with values of more than 1056 ms, native T2 mapping — more than 53 ms and ECV — more than 28%.

Statistical analyses

The variables with normal distribution were expressed as mean ± SD, while the variables with skewed distribution (NT-proBNP, hs-cTnI, serum hepcidin, ECV, quantity of segments with edema, high ECV, native T1 or T2) were expressed as median with lower and upper quartiles (interquartile range). The variables with skewed distribution were log-transformed (a natural logarithm, ln) before the inclusion in further analyses. The intergroup differences between patients with acute myocarditis and healthy controls were tested using the t-test for unpaired samples. Categorized variables were expressed as numbers (with percentages) and the intergroup differences were tested using the Chi-square test. The associations between iron

status indices and CMR parameters were tested using Pearson's correlatory coefficients (for baseline study cohort, r_p) or Spearman's rank correlatory coefficients (for follow-up study cohort, r_s). The changes in CMR parameters between hospitalization and ambulatory visit were tested using t-test for paired samples. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the Statistica 13 data analysis software (TIBCO Software Inc., Palo Alto, CA, US).

Results

Patients characteristics

40 patients met the inclusion criteria of our study (Figure 1). Their mean age was 33 ± 11 years, BMI — 26 ± 4 kg/m^2 and they were mainly males — 39 (98%). Regarding iron status mean serum ferritin was 253 ± 159 μg/L, serum iron 72 ± 31 μg/dL, TSAT — 21 ± 9%, sTfR — 1.3 ± 0.3 nmol/L and serum hepcidin 62 ± 50 μg/L.

Out of 21 consecutive patients hospitalized in years 2017–2019 and assessed at control ambulatory visit after 6 months of recovery, in our analysis we excluded 1 patient who was hospitalized and treated (percutaneous coronary intervention) for ST-segment elevation myocardial infarction 4 months after MCD and presented a massive ischemic scar in the follow-up CMR.

The control group of healthy age- and gender-matched volunteers included 15 subjects.

Abnormalities in cardiac magnetic resonance indices

All CMR parameters reflecting Lake Louis II criteria were abnormal in patients hospitalized for acute MCD and all of them significantly changed within 6-month observation. However, indices of LGE, regional increase in native T1 myocardial relaxation time and regional ECV persisted altered in comparison to healthy controls (Table 1).

In-hospital cardiac magnetic resonance

The relationships between in-hospital biomarkers reflecting neurohormonal activation, cardiomyocyte necrosis, inflammation and iron status and cardiac magnetic resonance indices are presented in Table 2. Serum ferritin concentration correlated with analyzed CMR indices of edema (number of segments and T2 ratio) and fibrosis (LGE). NT-proBNP and LVEF in echocardiography ($r_p = –0.385$; $p = 0.02$) correlated with LGE — mass.

Follow-up cardiac magnetic resonance

The relationships of the aforementioned biomarkers assessed at follow-up ambulatory visit with follow-up CMR indices are presented in Table 3. Low serum iron and TSAT correlated with high indices of persistent LGE extent and regional increase in ECV. Regarding in-

hospital iron indices, no relationships with follow-up CMR parameters of post-MCD myocardial injury were found.

Discussion

Our research investigated for the first time the relationships between iron status and CMR abnormalities in acute myocarditis. The major findings arising from the current study are: 1) in patients hospitalized for acute MCD concentration of serum ferritin related to myocardial injury in CMR — correlated with the expanse of edema and, strongly, with LGE extent, 2) after 6 months of recovery from acute MCD, indices of functional iron deficiency (low TSAT and serum iron) correlated with the extent of persistent LGE and regional increase in ECV, 3) high indices of LGE, regional abnormalities in T1 relaxation time or ECV persisted after 6 months of recovery in comparison to healthy controls.

In recent years, a development of new imaging techniques, not included in Lake Louise Criteria I, resulted in numerous studies demonstrating important clinical value of new CMR parameters [16, 20–22]. Therefore, new criteria (Lake Louise Criteria II) were formulated in order to improve the diagnostic accuracy of CMR in search for myocardial inflammation [23].

In our study we comprehensively investigated indices of myocardial injury included in the current criteria and related it to circulating biomarkers of iron status, together with laboratory indicators of neurohormonal activation, cardiomyocyte necrosis or inflammation.

Despite apparent progress in the diagnostic process, the risk stratification in MCD remains exceptionally challenging [1, 2, 5–7]. Recovery from acute MCD is highly diverse [1–3]. Recently, multiple studies explored the relationships between various biomarkers and outcome in heterogeneous population of MCD patients [4, 5, 8–11]. However, out of all comprehensively studied markers, only very high levels of NT-proBNP (≥ 4.245 pg/mL) manifested predictive value for poor outcome [4, 5, 8–11]. Hence, there is still an urgent need for identifying simple laboratory parameters which are associated with the pathobiology of MCD and thus may reflect prognosis.

On the other hand, recent analyses of CMR indices in patients with acute MCD revealed a relationship between the range of LGE, reflecting reactive interstitial fibrosis, and poor outcome [7, 17–19, 24]. In a large study of consecutive patients with biopsy-proven MCD, representing a broad spectrum of clinical symptoms, the presence of LGE emerged as the best independent indicator of long-term both all-cause and cardiac mortality [7]. Another study of MCD revealed that the presence of LGE is associated with over two-fold increase of death and even over fourteen-fold — of sudden cardiac death [18]. The prognostic value of the presence of LGE in MCD was confirmed by recent meta-analysis [17]. The availability of

CMR imaging in acute conditions remains restricted in numerous cardiology centers. Therefore, biomarkers related to LGE in MCD may offer a valuable clinical benefit and none of such indicators has been established yet. Moreover, the cardiac enzymes and inflammatory parameters (troponin, creatine kinase, myoglobin, NT-proBNP, C-reactive protein, and leukocyte count) investigated so far did not reflect LGE in myocarditis [25].

In our study serum ferritin, an acute phase reactant, was correlated with indices of edema and, strongly, with LGE in baseline CMR performed in patients hospitalized for acute MCD. It may be explained by the fact that more intensified inflammation of myocardial tissue and concurrent derangement of myocardial energetics were expressed by high serum ferritin and represented in CMR by increased features of edema or fibrosis. Further investigation is needed to confirm this finding in a larger cohort before positioning serum ferritin as a simple biomarker of LGE in patients with acute MCD.

The evaluation of iron status and CMR performed 6 months after hospital discharge revealed interesting links between iron metabolism and persistence of CMR abnormalities. Low TSAT and serum iron, which may be considered as markers of functional iron deficiency, were related to persistence of LGE and abnormal regional ECV, both reflecting the scale of myocardial fibrosis. The aforementioned findings indicated links between the hallmark of incomplete recovery from acute myocarditis and functional iron deficiency, which may reflect, to some extent, systemic low-grade inflammation. Our mid-term observation requires further studies comprising more subjects and longer follow-up to validate these associations.

Limitations of the study

Certain limitations of our study should be accentuated. First of all, although the enrollment included two cardiology centers, the study group consisted of a relatively small number of subjects, and particularly the follow-up visit was performed in only half of them. Therefore, we performed only basic statistical analyses. However, it must also be admitted that the previous studies on MCD evaluated mainly small populations. In addition, in our study we assessed circulating biomarkers and parameters of peripheral blood iron status without insight into myocardial iron status.

Conclusions

This is the first study reporting relationships between abnormal iron status and CMR findings in patients with acute MCD. In the acute phase of MCD serum ferritin relates to the myocardial injury. In the recovery phase the extent of residual fibrosis correlates with indices of functional iron deficiency.

Article information and declarations

Data availability statement

The data that support the findings of this study are available from the corresponding author, P.F., upon reasonable request.

Ethics statement

The study protocol was approved by the local ethics committee (Bioethics Committee, Wroclaw Medical University) and the study was conducted in accordance with the Declaration of Helsinki.

Author contributions

Conceptualization and methodology — P.F., K.K.-Ł., P.P. and E.A.J.; enrolment of patients, study execution — P.F., M.T., A.K., K.K.-Ł. and A.S.; specialized laboratory tests/imaging analyses — J.M.S., P.G., K.A.K. and M.K.; database management and statistical analyses — P.F., M.T., A.K., K.K.-Ł. and A.S.; manuscript preparation and revisions — P.F., J.M.S., M.T. and E.A.J.; critical revision of the manuscript for important intellectual content — P.G., A.K., K.K.-Ł., K.A.K., M.K., A.S., J.J., P.P. and E.A.J.; supervision — J.J., P.P. and E.A.J. All authors have read and agreed to the published version of the manuscript.

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None.

Conflict of interest

M.T. reports personal fees from V-Wave Ltd., Eidos Therapeutics, Cytokinetics, Impulse Dynamics, Alnylam Pharmaceuticals and Takeda, outside the submitted work. E.A.J. reports grants and personal fees from Vifor Pharma, personal fees from Bayer, Novartis, Abbott, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cardiac Dimensions, Takeda, Gedeon Richter, Respicardia, outside the submitted work. P.F., J.M.S., P.G., A.K., K.K.-Ł.,A.K., K.A.K., M.K., A.S., J.J. and P.P. have nothing to disclose.

Streszczenie

Wstęp. Patofizjologia ostrego zapalenia mięśnia sercowego, jak i następczego procesu zdrowienia, opiera się o skomplikowane zależności pomiędzy zjadliwością patogenu, odpowiedzią immunologiczną, uwarunkowaniami genetycznymi, współchorobowością oraz czynnikami środowiskowymi. Identyfikacja pacjentów o zwiększonym ryzyku rozwoju następczej kardiomiopatii pozostaje wyzwaniem. Zaburzenia w gospodarce żelazowej

wpływają niekorzystnie na aktywację immunologiczną, oraz, co więcej, uczestniczą w rozwoju kardiomiopatii. Celem naszej pracy było ustalenie związków pomiędzy wskaźnikami żelazowymi a uszkodzeniem miokardium w ostrym zapaleniu mięśnia sercowego.

Materiał i metody. Do badania włączono kolejnych pacjentów hospitalizowanych w dwóch centrach kardiologicznych z powodu zapalenia mięśnia sercowego. Analizie poddano charakterystykę kliniczną pacjentów, wyniki rezonansu magnetycznego oraz parametry laboratoryjne odzwierciedlające: martwicę kardiomiocytów, aktywację neurohormonalną, nasilenie stanu zapalnego, szczegółowy stan gospodarki żelazowej (podczas hospitalizacji oraz kontrolnej wizyty ambulatoryjnej po 6 miesiącach). Grupę kontrolną stanowili zdrowi ochotnicy.

Wyniki. Do badania włączono 40 pacjentów z rozpoznaniem ostrego zapalenia mięśnia sercowego (wiek: 32 ± 9 lat, płeć męska: 98%). Podczas hospitalizacji stężenie ferrytyny korelowało z masą ognisk późnego wzmocnienia pokontrastowego LGE ($r = 0.537$, $p < 0.001$) i globalnym T2 ratio ($r = 0.360$, $p = 0.03$). LGE, regionalne nieprawidłowości w czasach relaksacji T1 i podwyższenie objętości pozakomórkowej utrzymywało się po 6 miesiącach, w porównaniu ze zdrowymi ochotnikami. Masa przetrwałych ognisk LGE korelowała z niższą saturacją transferyny i niższym stężeniem żelaza podczas wizyty ambulatoryjnej ($r = –0.520$, $p = 0.03$; and $r = –0.465$, $p = 0.04$; odpowiednio).

Wnioski. Stężenie ferrytyny, będącej białkiem ostrej fazy, ma związek z uszkodzeniem miokardium w ostrej fazie zapalenia mięśnia sercowego. Natomiast w fazie zdrowienia, rezydualne włóknienie jest bardziej nasilone u pacjentów z funkcjonalnym niedoborem żelaza, który może częściowo odzwierciedlać utrzymywanie się stanu zapalnego w organizmie.

Słowa kluczowe: zapalenie mięśnia sercowego, stan gospodarki żelazowej, zapalenie, rezonans magnetyczny serca, późne wzmocnienie pokontrastowe

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Table 1. Demographic and clinical characteristics, biomarkers of cardiomyocyte necrosis, neurohormal activation or inflammation and cardiac magnetic resonance indices in patients hospitalized for acute myocarditis and at ambulatory follow-up visit 6 months after discharge in comparison with healthy controls

Variables, units	A Patients with acute MCD during hospitalization (n = 40)	B Patients with acute MCD at follow-up visit (n = 20)	C Healthy controls (n = 15)	p-value (A vs. B)	p-value (A vs. C)	p-value (B vs. C)
Age, year	32 ± 9	34 ± 9	31 ± 5	0.07	0.73	0.22
Male gender, yes	39 (98%)	19 (95%)	13 (87%)	0.98	0.38	0.57
BMI [kg/m^2]	26 ± 4	26 ± 4	23 ± 2	0.70	0.04	0.02
Biomarkers of neurohormal activation, cardiomyocyte necrosis or inflammation						
Hs-cTnI, [*μ*g/L]	2.18 (0.53–6.32)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	< 0.001	< 0.001	0.38
NT-proBNP [pg/mL]	290 (185–594)	28 (16–44)	31 (18–46)	< 0.001	< 0.001	0.56

C-reactive protein [mg/L]	55 ± 54	3 ± 1	3 ± 0	< 0.001	< 0.001	0.29
Cardiac magnetic resonance parameters						
LVEF (%)	58 ± 9	57 ± 6	61 ± 5	0.95	0.20	0.06
RVEF (%)	59 ± 9	61 ± 8	60 ± 7	0.47	0.75	0.64
Edema — number of segments (n)	3 (0–5)	0 (0–0)	0 (0–0)	< 0.001	< 0.001	
T2 ratio	2.1 ± 0.6	1.5 ± 0.1	1.5 ± 0.2	< 0.001	< 0.001	0.67
LGE — mass (g)	7 ± 6	3 ± 3	0 ± 0	0.003	< 0.001	0.003
LGE — % (%)	6 ± 5	4 ± 4	0 ± 0	< 0.001	< 0.001	0.003
LGE — number of segments, n	5 ± 2	3 ± 2	0 ± 0	< 0.001	< 0.001	< 0.001
LGE — area of major focus [cm^2]	1.4 ± 1.0	1.0 ± 0.8	0 ± 0	< 0.001	< 0.001	< 0.001
Native T1 (global) (ms)	1058 ± 60	1010 ± 30	1010 ± 23	0.02	0.006	0.78
ECV (global) (%)	29 (27–32)	27 (25–29)	25 (24–26)	0.04	0.02	0.18
Native T2 (global) (ms)	51 ± 4	46 ± 3	48 ± 3	< 0.001	0.02	0.06
High native T1 — number of segments (n)	4 (2–6)	1 (0–2)	0 (0–0)	0.002	< 0.001	0.03
High ECV — number of segments (n)	4 (2–8)	2 (0–5)	0 (0–0)	0.04	0.001	0.04
High native T2 — number of segments (n)	2 (1–6)	0 (0–1)	0 (0–0)	0.002	0.003	0.43

Data are presented as mean value ± standard deviation or median (with interquartile range) for continuous variables and counts (percentages) for nominal variables

ECV — extracellular volume; hs-cTnI — high-sensitivity cardiac troponin I; LGE — late gadolinium enhancement; LVEF — left ventricular ejection fraction; MCD — myocarditis;

NT-proBNP — N-terminal pro B-type natriuretic peptide; RVEF — right ventricular ejection fraction

Table 2. The relationships between baseline indices of iron status, cardiomyocyte necrosis, neurohormal activation or inflammation and in-hospital cardiac magnetic resonance parameters in patients hospitalized for acute myocarditis (n = 40)

Variables, units	**LVEF (%)**	**RVEF (%)**	**Edema — number of segments, ln**	**T2 ratio**	**LGE — mass [g]**	**LGE — number of segments (n)**	**LGE — area of major focus, (cm^2)**
Biomarkers of neurohormal activation, cardiomyocyte necrosis or inflammation							
Hs-TnI, ln [*μ*g/L]	0.053	0.164	0.291	0.376 *	0.249	0.101	0.217
NT-proBNP, ln [pg/mL]	–0.267	–0.149	0.284	0.236	0.336 *	0.111	0.223
C–reactive protein [mg/L]	–0.066	–0.252	0.021	0.117	0.232	0.054	–0.004
Iron status indices							
Serum iron [μg/dL]	0.204	0.190	–0.076	–0.457 *	–0.100	0.173	–0.023
Serum ferritin [*μ*g/L]	–0.029	–0.212	0.439 **	0.360 *	0.537 ***	0.430 **	0.344 *
Transferrin saturation (%)	0.182	0.222	0.001	–0.371 *	–0.042	0.199	0.009
Serum soluble transferrin receptor	0.121	0.091	0.104	0.057	–0.120	0.030	0.007

[nmol/L]							
Serum hepcidin, ln [μg/L]	–0.035	–0.166	0.116	0.259	0.079	–0.004	0.117

Data are presented as Pearson's correlation coefficient

*p–value < 0.05, **p–value < 0.01, ***p–value < 0.001

Abbreviations: see Table 1

Table 3. The relationships between indices of iron status, cardiomyocyte necrosis, neurohormal activation or inflammation and cardiac magnetic resonance parameters assessed after 6 months of recovery in patients with acute myocarditis (n = 20)

Variables, units	**LVEF (%)**	**RVEF (%)**	**LGE – mass [g]**	**High native T1 — number of segments, ln**	**High ECV — number of segments, ln**	**High native T2 — number of segments, ln**
NT–proBNP, ln [pg/mL]	–0.392	0.334	–0.101	–0.003	–0.134	–0.023
Hs–TnI, ln [μg/L]	0.043	0.301	–0.420	–0.271	–0.285	–0.121
C–reactive protein, [mg/L]	0.449	–0.381	0.238	–0.009	0.363	–0.221
Serum iron, [μg/dL]	0.103	0.315	–0.465 *	0.137	–0.454 *	–0.138
Serum ferritin, [μg/L]	–0.280	–0.125	–0.056	–0.024	–0.028	0.277

Transferrin saturation (%)	0.021	0.417	–0.520 *	0.080	–0.509 *	–0.086
Serum soluble transferrin receptor, nmol/L	–0.011	–0.303	–0.297	0.207	0.212	0.244
Serum hepcidin, ln *μ*g/L	0.100	0.082	–0.150	–0.111	–0.240	–0.352

Data are presented as Spearman's correlation coefficient

*p–value < 0.05, **p–value < 0.01, ***p–value < 0.001

Abbreviations: see Table 1

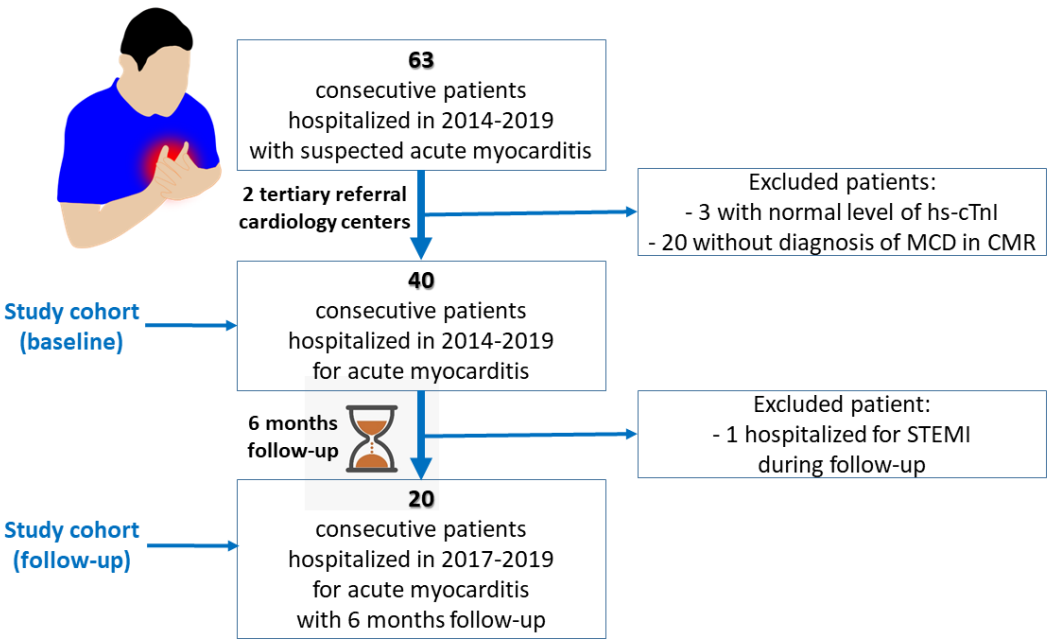

Figure 1. Enrollment and follow-up — flowchart of the study
CMR — cardiac magnetic resonance; hs-cTnI — high-sensitivity cardiac troponin I; MCD — myocarditis; STEMI — ST-segment elevation myocardial infarction

9. PODSUMOWANIE I WNIOSKI

Na podstawie badań przedstawionych w powyższych publikacjach, opisano zaburzenia stanu gospodarki żelaza, do których dochodzi w trakcie ostrego zapalenia mięśnia sercowego, oraz wykazano związki pomiędzy ich nasileniem a przebiegiem choroby i następczego procesu zdrowienia.

W pracy przeglądowej pt. "*Cardiovascular Complications of Viral Respiratory Infections and COVID-19*" zostały przedstawione sercowo-naczyniowe powikłania oddechowych infekcji wirusowych. Do najważniejszych z nich zalicza się niedokrwienie miokardium, incydenty zakrzepowo-zatorowe, choroby osierdzia, arytmie, a także właśnie zapalenie mięśnia sercowego i kardiomiopatię pozapalną [39,40]. Wirusy oddechowe są uważane za główną przyczynę zapalenia mięśnia sercowego, a do najczęściej identyfikowanych patogenów zalicza się: adenowirusy, enterowirusy, wirus grypy i koronawirusy [10]. W publikacji podkreślono wagę dalszych badań nad przyczynami rozwoju zapalenia mięśnia sercowego w trakcie infekcji oddechowych. Tematyka powyższej pracy przeglądowej wydaje się być szczególnie ważna i aktualna współcześnie, kiedy pandemia COVID-19 i następcze powikłania tej choroby odcisnęły piętno na profilu obciążeń pacjentów [40].

W ramach analiz opisanych w publikacji pt. "*Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study*" potwierdzono, że stan gospodarki żelaza u pacjentów hospitalizowanych z powodu ostrego zapalenia mięśnia sercowego jest zaburzony. Wśród tych chorych, mimo porównywalnych wartości parametrów czerwonokrwinkowych, obserwowano wyższe stężenie ferrytyny i hepcydny oraz niższe stężenie żelaza i saturację transferyny w porównaniu do osób zdrowych. Normalizacja wskaźników żelazowych następowała w ciągu sześciu tygodni obserwacji. Niskie stężenie żelaza i saturacja transferyny, stanowiące wskaźniki niedoboru żelaza nienależące do białek ostrej fazy, korelowały z bardziej nasiloną aktywacją neurohormonalną (ocenianą przez stężenie NT-proBNP) oraz z utrzymującą się po sześciu tygodniach od zakończenia hospitalizacji łagodną dysfunkcją lewej komory w ocenie echokardiograficznej (wyrażoną poprzez niższą frakcję wyrzutową lewej komory oraz bardziej zaburzone globalne odkształcenie podłużne lewej komory).

W publikacji pt. "*Iron status and myocardial injury while recovering from acute myocarditis*" przedstawiono analizę szczegółowych parametrów rezonansu magnetycznego u

pacjentów z ostrym zapaleniem mięśnia sercowego. Do zidentyfikowanych nieprawidłowości w stosunku do grupy kontrolnej należały: globalne podwyższenie czasów relaksacji T1, T2 oraz objętości pozakomórkowej, obecność ognisk LGE, obrzęku i regionalnych nieprawidłowości w zakresie czasów relaksacji T1, T2 oraz objętości pozakomórkowej. W porównaniu ze zdrowymi ochotnikami, u chorych sześć miesięcy po zapaleniu mięśnia sercowego utrzymywały się ogniska LGE, regionalne nieprawidłowości w czasach relaksacji T1 i podwyższenie objętości pozakomórkowej. U pacjentów hospitalizowanych z powodu ostrego zapalenia mięśnia sercowego stężenie ferrytyny korelowało z nasileniem obrzęku oraz rozległością ognisk LGE. Ponadto, po sześciu miesiącach od zakończenia hospitalizacji, wskaźniki czynnościowego niedoboru żelaza (niska saturacja transferyny oraz niskie stężenie żelaza) były związane z rozległością utrzymujących się ognisk LGE oraz z miejscowymi nieprawidłowościami w postaci podwyższonej objętości pozakomórkowej.

Wyniki powyższych prac dostarczają dowodów na udział gospodarki żelaza w patofizjologii zapalenia mięśnia sercowego oraz następczego zdrowienia. Znajduje to uzasadnienie w patogenezie procesu zapalnego, który ściśle łączy się z metabolizmem żelaza [21]. Ferrytyna i hepcydyna to białka ostrej fazy, a więc ich stężenie we krwi wzrasta podczas procesów zapalnych, co potwierdziły również wyniki powyższych badań [21-26]. Cytokiny zapalne zwiększają produkcję i stężenie hepcydyny, która po połączeniu ze swoistym receptorem (ferroportyną), zmniejsza ekspresję białek odpowiedzialnych za wchłanianie żelaza z jelit oraz uwalnianie wewnątrzkomórkowego żelaza do krwiobiegu [21,42,43]. Wskutek tego, stężenie żelaza w surowicy zmniejsza się [21,42]. Do krwi uwalniana jest uboga w żelazo ferrytyna, podczas gdy w hepatocytach i makrofagach gromadzona jest ferrytyna bogata w żelazo [21,42,43]. Celem powyższych procesów jest ograniczenie biodostępności kluczowego mikroelementu dla mikroorganizmów odpowiedzialnych za infekcję [21,42].

Wyniki omawianych analiz sugerują związek czynnościowego niedoboru żelaza u pacjentów z ostrym zapaleniem mięśnia sercowego z cechami uszkodzenia miokardium podczas zdrowienia po ostrej fazie choroby. Optymalny stan gospodarki żelaza jest konieczny dla zapewnienia prawidłowego funkcjonowania procesów energetycznych komórki [27,28]. Negatywny wpływ niedoboru żelaza na mięsień sercowy jest powszechnie znany, a liczne badania eksperymentalne dostarczyły dowodów na jego wielopłaszczyznowy charakter [30,31,33,35]. U zwierząt doświadczalnych systemowy niedobór żelaza (uzyskiwany przez indukowane krwawienie lub ubogożelazową dietę) prowadził do dysfunkcji mitochondriów, zaburzeń wewnątrzkomórkowego metabolizmu oraz destrukcji i/lub apoptozy kardiomiocytów

[44-48]. Konsekwencją wyżej wymienionych zmian była progresja do kardiomiopatii z dysfunkcją skurczową miokardium oraz rozwój objawowej niewydolności serca [48-50]. W hodowlach komórkowych ludzkich kardiomiocytów spadek stężenia żelaza wiązał się z dysfunkcją mitochondrialnego łańcucha oddechowego, skutkującą pogorszeniem ich kurczliwości i relaksacji [51]. Z kolei ostatnie modele eksperymentalne dowiodły, iż szkodliwy wpływ niedoboru żelaza na mięsień sercowy może być odwrócony wskutek suplementacji żelaza [51-53]. Dodatkowo, duże randomizowane badania kliniczne FAIR-HF i CONFIRM-HF wykazały korzystny wpływ suplementacji żelaza u pacjentów z jego niedoborem oraz przewlekłą niewydolnością serca z obniżoną frakcją wyrzutową lewej komory – u poddawanych dożylnemu leczeniu żelazem chorych obserwowano regresję objawów niewydolności serca, poprawę wydolności wysiłkowej oraz jakości życia [54,55]. Metaanaliza obejmująca powyższe badania dowiodła również poprawy rokowania podczas stosowanego leczenia [56]. Ponadto ostatnio, w randomizowanym badaniu klinicznym AFFIRM-HF oceniano efekty suplementacji żelaza u pacjentów po epizodzie ostrej niewydolności serca – w tym scenariuszu klinicznym leczenie żelazem skutkowało istotną redukcją kolejnych hospitalizacji [57].

Wykazany w obu publikacjach związek wskaźników czynnościowego niedoboru żelaza (niskiego stężenia żelaza i niskiej saturacji transferyny) z uszkodzeniem miokardium, uchwyconym w wykonanych badaniach obrazowych, można uzasadnić rolą, jaką żelazo odgrywa w patofizjologii zapalenia i w homeostazie procesów energetycznych komórki [21-30]. Większe nasilenie procesu zapalnego miało odzwierciedlenie w bardziej zaawansowanym przesunięciu równowagi żelazowej w kierunku niedoboru. Niedobór ten, poprzez negatywny wpływ na energetykę kardiomiocytów, mógł skutkować upośledzeniem procesów naprawczych i tym samym utrzymywaniem się rezydualnego uszkodzenia miokardium.

Wartym podkreślenia znaleziskiem omawianych analiz jest również wykazany związek między wysokim stężeniem ferrytyny i większą rozległością ognisk LGE, które odzwierciedlają obszary reaktywnego włóknienia śródmiąższowego [58]. Zaawansowanie ognisk LGE jest unikalnym udowodnionym czynnikiem predykcyjnym złego rokowania w zapaleniu mięśnia sercowego [13,18-20]. Obecność ognisk LGE, ich rozległość oraz brak regresji w czasie, wiązały się w długoterminowej obserwacji z większą śmiertelnością ogólną, większą śmiertelnością z przyczyn sercowo-naczyniowych i wyższym odsetkiem nagłych zgonów sercowych w kilku prospektywnych badaniach oraz następczej metaanalizie [13,18-20]. Niewątpliwie, prosty i łatwo dostępny parametr laboratoryjny, który wiązałby się z rokowaniem

w tej grupie chorych, byłby wartościowym uzupełnieniem procesu diagnostycznego. Dlatego dalsze badania nad znaczeniem prognostycznym ferrytyny, obejmujące wieloletnią obserwację pacjentów, wydają się być uzasadnione.

Podsumowując, zebrane w niniejszej rozprawie doktorskiej publikacje dostarczają nowych danych na temat udziału gospodarki żelaza w patofizjologii ostrego zapalenia mięśnia sercowego. W powyższych analizach przedstawiono dowody na związek metabolizmu żelaza z przebiegiem choroby oraz jej następstwami w postaci rezydualnego uszkodzenia miokardium. Dlatego rola żelaza w rozwoju zapalenia mięśnia sercowego i kardiomiopatii pozapalnej stanowi obiecujący kierunek dla dalszych badań w celu poprawy możliwości diagnostyczno-terapeutycznych w tej populacji pacjentów.

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11. ZAŁĄCZNIKI

11.1. DOROBEK NAUKOWY

Wykaz publikacji

Paweł Franczuk

Lp	Opis bibliograficzny	IF	Punkty
1	Rafalska Agnieszka, Franczuk Jolanta, **Franczuk Paweł**, Augustyniak-Bartosik Hanna, Krajewska Magdalena: Stratifying risk for progression in IgA nephropathy: how to predict the future?, Polskie Archiwum Medycyny Wewnętrznej, 2014, vol. 124, nr 7-8, s. 365-372, DOI:10.20452/pamw.2341	2,121	30
2	**Franczuk Paweł**, Kaczorowski Maciej, Kucharska Karolina, Franczuk Jolanta, Josiak Krystian, Zimoch Wojciech, Kosowski Michał, Reczuch Krzysztof, Majda Jacek, Banasiak Waldemar, Ponikowski Piotr, Jankowska Ewa A.: Could an analysis of mean corpuscular volume help to improve risk stratification in non-anemic patients with acute myocardial infarction?, Cardiology Journal, 2015, vol. 22, nr 4, s. 421-427, DOI:10.5603/CJ.a2015.0031	1,13	20
3	Kobak Kamil A., **Franczuk Paweł**, Schubert Justyna, Dzięgała Magdalena, Kasztura Monika, Tkaczyszyn Michał, Drozd Marcin, Kosiorek Aneta, Kiczak Liliana, Bania Jacek, Ponikowski Piotr, Jankowska Ewa A.: Primary human cardiomyocytes and cardiofibroblasts treated with sera from myocarditis patients exhibit an increased iron demand and complex changes in the gene expression, Cells, 2021, vol. 10, nr 4, art.818 [16 s.], DOI:10.3390/cells10040818	7,666	140
4	Sierpiński Radosław, **Franczuk Paweł**, Tkaczyszyn Michał, Suchocki Tomasz, Krekora Jan, Opolski Grzegorz, Maggioni Aldo, Poloński Lech, Ponikowski Piotr, Jankowska Ewa A.: Burden of multimorbidity in a Polish cohort of ambulatory and hospitalized heart failure patients from 2 large European registry programs: prognostic implications, Polskie Archiwum Medycyny Wewnętrznej, 2021, vol. 131, nr 11, art.16101 [9 s.], DOI:10.20452/pamw.16101	5,218	140
5	**Franczuk Paweł**, Tkaczyszyn Michał, Kulak Maria, Domenico Esabel, Ponikowski Piotr, Jankowska Ewa Anita: Cardiovascular complications of viral respiratory infections and COVID-19, Biomedicines, 2023, vol. 11, nr 1, art.71 [12 s.], DOI:10.3390/biomedicines11010071	4,7*	100
6	**Franczuk Paweł**, Tkaczyszyn Michał, Kosiorek Aneta, Kulej-Łyko Katarzyna, Kobak Kamil Aleksander, Kasztura Monika, Sołtowska Alicja, Jaroch Joanna, Ponikowski Piotr, Jankowska Ewa Anita: Iron status and short-term recovery after non-severe acute myocarditis: a prospective observational study, Biomedicines, 2023, vol. 11, nr 8, art.2136 [12 s.], DOI:10.3390/biomedicines11082136	4,7*	100
7	**Franczuk Paweł**, Sokolska Justyna, Tkaczyszyn Michał, Gać Paweł, Kosiorek Aneta, Kulej-Łyko Katarzyna, Kobak Kamil, Kasztura Monika, Sołtowska Alicja, Jaroch Joanna, Ponikowski Piotr, Jankowska Ewa Anita Folia Cardiologica. 2023; Published online: 2023-08-30 doi: 10.5603/fc.96888 Epub ahead of print	-	100
	Podsumowanie	25,535	630

**IF 2022*

2. Abstrakty

Lp	Opis bibliograficzny
1	**Franczuk Paweł**, Tubek Stanisław, Kobak Kamil, Banasiak Waldemar, Ponikowski Piotr, Jankowska Ewa: Characteristics and post-myocardial infarction prognosis in patients with ischaemic heart failure with mid-range ejection fraction, Kardiologia Polska, 2017, vol. 75, nr supl.4, s. 51-52, [XXI Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Katowice, 21-23 września 2017. Streszczenia. Toż s.220-221]

2	Kobak Kamil A., Dzięgała Magdalena, **Franczuk Paweł**, Kasztura Monika, Tkaczyszyn Michał, Drozd Marcin, Josiak Krystian, Sidorowicz N., Gać Paweł, Kiczak L., Bania J., Banasiak W., Ponikowski Piotr, Jankowska Ewa A.: The influence of iron status on the impaired functioning of human cardiofibroblasts and cardiomyocytes in the course of acute phase of myocarditis, European Heart Journal, 2018, vol. 39, nr suppl., 177-178 poz.P920, [European Society of Cardiology Congress 2018. Munich (Germany), 25-29 August 2018], DOI:10.1093/eurheartj/ehy564.P920
3	**Franczuk Paweł**, Kulej-Łyko Katarzyna, Drozd Marcin, Tkaczyszyn Michał, Sidorowicz N., Flinta Irena, Gać Paweł, Banasiak Waldemar, Ponikowski Piotr, Jankowska Ewa Anita: Iron deficiency relates to neurohormonal activation in acute myocarditis, European Journal of Heart Failure, 2018, vol. 20, nr suppl.1, 132 poz.P516, [Heart Failure 2018 and the World Congress on Acute Heart Failure. Vienna, Austria, 26-29 May 2018. Abstracts], DOI:10.1002/ejhf.1197
4	Kobak Kamil A., Dzięgała Magdalena, **Franczuk Paweł**, Kasztura Monika, Tkaczyszyn Michał, Drozd Marcin, Josiak Krystian, Sidorowicz N., Gać Paweł, Kiczak L., Bania J., Banasiak Waldemar, Ponikowski Piotr, Jankowska Ewa A.: Contribution of iron status to malfunctioning of human cardiomyocytes and cardiofibroblasts in the course of myocarditis, European Journal of Heart Failure, 2018, vol. 20, nr suppl.1, 491 poz.P1901, [Heart Failure 2018 and the World Congress on Acute Heart Failure. Vienna, Austria, 26-29 May 2018. Abstracts], DOI:10.1002/ejhf.1197
5	**Franczuk Paweł**, Drozd Marcin, Kulej-Łyko Katarzyna, Tkaczyszyn Michał, Sidorowicz Natalia, Flinta Irena, Gać Paweł, Banasiak Waldemar, Ponikowski Piotr, Jankowska Ewa: Iron deficiency is associated with neurohormonal activation in acute myocarditis, Kardiologia Polska, 2018, vol. 76, nr supl.1, s. 315-316, [XXII Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Kraków, 13-15 września 2018. Streszczenia]
6	**Franczuk Paweł**, Kosiorek Aneta, Tkaczyszyn Michał, Drozd Marcin, Zapolska Anna, Walczak Tomasz, Kulej-Łyko Katarzyna, Sidorowicz N., Sołtowska Alicja, Banasiak Waldemar, Kosmala Wojciech, Przewłocka-Kosmala Monika, Jaroch Joanna, Ponikowski Piotr, Jankowska Ewa A.: Iron status indices (transferrin saturation, serum ferritin) in the course of acute myocarditis: relations with neurohormonal activation, cardiac dysfunction and clinical recovery, European Heart Journal, 2019, vol. 40, nr suppl., 358 poz.P754, [ESC Congress 2019 together with World Congress of Cardiology. Paris (France), 31 August - 4 September 2019], DOI:10.1093/eurheartj/ehz747.0356
7	Kobak Kamil A., Schubert J., Kasztura Monika, **Franczuk Paweł**, Dzięgała Magdalena, Drozd Marcin, Tkaczyszyn Michał, Kulej-Łyko Katarzyna, Bania J., Banasiak W., Ponikowski Piotr, Jankowska Ewa A.: Iron depletion in human cardiomyocytes cultured with sera from myocarditis patients, European Heart Journal, 2019, vol. 40, nr suppl., 3955 poz.P6353, [ESC Congress 2019 together with World Congress of Cardiology. Paris (France), 31 August - 4 September 2019], DOI:10.1093/eurheartj/ehz746.0949
8	Drozd Marcin, Tkaczyszyn Michał, Zapolska Anna, Walczak Tomasz, Tobiszewski J., **Franczuk Paweł**, Kosiorek Aneta, Flinta Irena, Jaroch Joanna, Sołtowska Alicja, Kulej-Łyko Katarzyna, Banasiak Waldemar, Ponikowski Piotr, Jankowska Ewa A.: Depleted iron stores are associated with decreased exercise capacity in patients with non-ischaemic cardiomyopathy, European Journal of Heart Failure, 2019, vol. 21, nr suppl.1, 101 poz.P437, [Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts], DOI:10.1002/ejhf.1488
9	**Franczuk Paweł**, Kosiorek Aneta, Tkaczyszyn Michał, Drozd Marcin, Zapolska Anna, Walczak Tomasz, Kulej-Łyko Katarzyna, Sidorowicz N., Sołtowska Alicja, Banasiak Waldemar, Jaroch Joanna, Ponikowski Piotr, Jankowska Ewa A.: Biomarkers of iron status (transferrin saturation, serum ferritin) in the course of acute myocarditis: relations with neurohormonal activation, cardiac dysfunction and clinical recovery, European Journal of Heart Failure, 2019, vol. 21, nr suppl.1, 279-280 poz.P1143, [Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts], DOI:10.1002/ejhf.1488
10	Kosiorek Aneta, **Franczuk Paweł**, Gać Paweł, Drozd Marcin, Tkaczyszyn Michał, Walczak Tomasz, Zapolska Anna, Kulej-Łyko Katarzyna, Sidorowicz N., Sołtowska Alicja, Banasiak Waldemar, Jaroch Joanna, Ponikowski Piotr, Jankowska Ewa A.: High circulating ferritin predicts oedema and fibrosis assessed in cardiac magnetic resonance in patients with acute myocarditis, European Journal of Heart Failure, 2019, vol. 21, nr suppl.1, 458 poz.P1812, [Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts], DOI:10.1002/ejhf.1488

11	Kobak Kamil Aleksander, Schubert J., Dzięgała Magdalena, Kasztura Monika, **Franczuk Paweł**, Drozd Marcin, Kulej-Łyko Katarzyna, Bania J., Ponikowski Piotr, Jankowska Ewa A.: HFWM: Sera from myocarditis patients caused iron depletion in cultured human cardiomyocytes, European Journal of Heart Failure, 2019, vol. 21, nr suppl.1, 475 poz.P1874, [Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts], DOI:10.1002/ejhf.1488
12	Kosiorek Aneta, **Franczuk Paweł**, Gać Paweł, Drozd Marcin, Tkaczyszyn Michał, Walczak Tomasz, Zapolska Anna, Kulej-Łyko Katarzyna, Sidorowicz Natalia, Sołtowska Alicja, Banasiak Waldemar, Jaroch Joanna, Ponikowski Piotr, Jankowska Ewa: High circulating ferritin reflects myocardial injury assessed in cardiac magnetic resonance in patients with acute myocarditis, Kardiologia Polska, 2019, vol. 77, nr suppl.1, s. 124-125, [The 23rd International Congress of the Polish Cardiac Society. Katowice, Poland, September 26-28, 2019. Abstract proceedings], DOI:10.33963/KP.15080
13	**Franczuk Paweł**, Kosiorek Aneta, Tkaczyszyn Michał, Drozd Marcin, Zapolska Anna, Walczak Tomasz, Kulej-Łyko Katarzyna, Sidorowicz Natalia, Soltowska Alicja, Banasiak Waldemar, Kosmala Wojciech, Przewłocka-Kosmala Monika, Jaroch Joanna, Ponikowski Piotr, Jankowska Ewa: Indicators of iron status (serum ferritin, transferrin saturation) in the course of acute myocarditis: relations with cardiac dysfunction, neurohormonal activation and clinical recovery, Kardiologia Polska, 2019, vol. 77, nr suppl.1, s. 132-133, [The 23rd International Congress of the Polish Cardiac Society. Katowice, Poland, September 26-28, 2019. Abstract proceedings], DOI:10.33963/KP.15080
14	Drozd Marcin, Tkaczyszyn Michał, Walczak Tomasz, Zapolska Anna, Tobiszewski Jan, Lis Weronika, **Franczuk Paweł**, Kosiorek Aneta, Flinta Irena, Jaroch Joanna, Kosmala Wojciech, Przewłocka-Kosmala Monika, Banasiak Waldemar, Ponikowski Piotr, Jankowska Ewa: Iron deficiency predicts decreased exercise capacity in patients with non-ischaemic cardiomyopathy, Kardiologia Polska, 2019, vol. 77, nr suppl.1, s. 135-136, [The 23rd International Congress of the Polish Cardiac Society. Katowice, Poland, September 26-28, 2019. Abstract proceedings], DOI:10.33963/KP.15080

Impact Factor: 25,535

Punkty ministerialne: 630,0

31.08.2023 r. Beata Majewska

11.2. ZGODA KOMISJI BIOETYCZNEJ

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 190/2020

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

prof. dr hab. Jacek Daroszewski (choroby wewnętrzne, endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr Luiza Műller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
prof. dr hab. Leszek Szenborn, (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela (ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Znaczenie gospodarki żelazowej w patofizjologii ostrego zapalenia mięśnia sercowego"

zgłoszonym przez **lek. Pawła Franczuka** uczestnika studiów doktoranckich w Katedrze Chorób Serca Wydziału Nauk o Zdrowiu Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła wyrazić zgodę na przeprowadzenie badania w Samodzielnej Pracowni Badań Układu Krążenia Katedry Chorób Serca Wydziału Nauk o Zdrowiu Uniwersytetu Medycznego we Wrocławiu oraz Centrum Chorób Serca Uniwersyteckiego Szpitala Klinicznego im. Jana Mikulicza-Radeckiego we Wrocławiu pod nadzorem prof. dr hab. Ewy Anity Jankowskiej **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności:

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu

Opinia powyższa dotyczy: projektu badawczego będącego podstawą rozprawy doktorskiej

Wrocław, dnia 8 kwietnia 2020 r.

BW

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kornafel

11.3. OŚWIADCZENIA O WSPÓŁAUTORSTWIE

Paweł Franczuk
Instytut Chorób Serca
Uniwersytecki Szpital Kliniczny we Wrocławiu

Wrocław, 01.09.2023

OŚWIADCZENIE

Oświadczam, że w pracach:

1) **Complications of Viral Respiratory Infections and COVID-19.**
Franczuk P, Tkaczyszyn M, Kulak M, Domenico E, Ponikowski P, Jankowska EA. Biomedicines. 2023. Doi: 10.3390/biomedicines11010071

2) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study.**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Biomedicines. 2023. doi: 10.3390/biomedicines11082136

3) **Iron status and myocardial injury while recovering from acute myocarditis.**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:

- stworzeniu koncepcji pracy,
- przeglądzie danych literaturowych,
- przygotowaniu i redagowaniu treści manuskryptu;

PUBLIKACJA 2:

- stworzeniu koncepcji i projektowaniu badania,
- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych,
- przygotowaniu i redagowaniu treści manuskryptu;

PUBLIKACJA 3:

- stworzeniu koncepcji i projektowaniu badania,
- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych,
- przygotowaniu i redagowaniu treści manuskryptu.

Podpis

Paweł Franczuk

Prof. dr hab. Ewa Anita Jankowska
Instytut Chorób Serca
Uniwersytet Medyczny we Wrocławiu

Wrocław, 04.09.2023

OŚWIADCZENIE

Oświadczam, że w pracach:

1) **Complications of Viral Respiratory Infections and COVID-19.**
Franczuk P, Tkaczyszyn M, Kulak M, Domenico E, Ponikowski P, Jankowska EA. Biomedicines. 2023. Doi: 10.3390/biomedicines11010071

2) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study.**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Biomedicines. 2023. doi: 10.3390/biomedicines11082136

3) **Iron status and myocardial injury while recovering from acute myocarditis.**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:

- stworzeniu koncepcji pracy,
- krytycznej ocenie i redagowaniu treści manuskryptu;

PUBLIKACJA 2:

- stworzeniu koncepcji i projektowaniu badania,
- przygotowaniu treści manuskryptu,
- krytycznej ocenie i redagowaniu treści manuskryptu,
- nadzorze nad prowadzonym badaniem i procesem publikacji;

PUBLIKACJA 3:

- stworzeniu koncepcji i projektowaniu badania,
- przygotowaniu treści manuskryptu,
- krytycznej ocenie i redagowaniu treści manuskryptu,
- nadzorze nad prowadzonym badaniem i procesem publikacji.

Podpis

Dr hab. Joanna Jaroch, prof. UMW
Zakład Pielęgniarstwa Internistycznego
Uniwersytet Medyczny we Wrocławiu

Wrocław, 31.08.2023

OŚWIADCZENIE

Oświadczam, że w pracach:

1) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA.
Biomedicines. 2023. doi: 10.3390/biomedicines11082136

2) **Iron status and myocardial injury while recovering from acute myocarditis**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak K, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA
Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:
- nadzorze nad rekrutacją pacjentów,
- krytycznej ocenie i redagowaniu treści manuskryptu;

PUBLIKACJA 2:
- nadzorze nad rekrutacją pacjentów,
- krytycznej ocenie i redagowaniu treści manuskryptu.

Podpis

Dr hab. Paweł Gać, prof. UMW
Zakład Zdrowia Środowiskowego i Medycyny Pracy
Uniwersytet Medyczny we Wrocławiu

Wrocław, 31.08.2023

OŚWIADCZENIE

Oświadczam, że w pracy:

- Iron status and myocardial injury while recovering from acute myocarditis
Franczuk Paweł, Sokolska Justyna, Tkaczyszyn Michał, Gać Paweł, Kosiorek Aneta, Kulej-Łyko Katarzyna, Kobak Kamil, Kasztura Monika, Sołtowska Alicja, Jaroch Joanna, Ponikowski Piotr, Jankowska Ewa Anita
Folia cardiologica, 2023, doi: 10.5603/fc.96888

Mój udział polegał na:
- przeprowadzeniu specjalistycznych analiz badań obrazowych,
- redagowaniu treści manuskryptu.

Podpis

Dr hab. n. med. Paweł Gać
Profesor UMW
lekarz specjalista
radiologii i diagnostyki obrazowej
European Diploma in Radiology
EACVI Cardiac Computed Tomography Exam
EACVI Cardiovascular Magnetic Resonance Exam
PWZ 2590859

Dr n. med. Michał Tkaczyszyn
Instytut Chorób Serca
Uniwersytet Medyczny we Wrocławiu

Wrocław, 04.09.2023

OŚWIADCZENIE

Oświadczam, że w pracach:

1) **Complications of Viral Respiratory Infections and COVID-19.**
Franczuk P, Tkaczyszyn M, Kulak M, Domenico E, Ponikowski P, Jankowska EA. Biomedicines. 2023. Doi: 10.3390/biomedicines11010071

2) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study.**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Biomedicines. 2023. doi: 10.3390/biomedicines11082136

3) **Iron status and myocardial injury while recovering from acute myocarditis.**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:

- stworzeniu koncepcji pracy,
- przeglądzie danych literaturowych,
- przygotowaniu treści manuskryptu,
- krytycznej ocenie i redagowaniu treści manuskryptu;

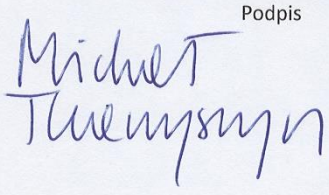
PUBLIKACJA 2:

- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych,
- przygotowaniu i redagowaniu treści manuskryptu;

PUBLIKACJA 3:

- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych,
- przygotowaniu i redagowaniu treści manuskryptu.

Podpis



Dr n. med. Justyna Maria Sokolska
Instytut Chorób Serca
Uniwersytecki Szpital Kliniczny we Wrocławiu

Wrocław, 04.09.2023

OŚWIADCZENIE

Oświadczam, że w pracy:
Iron status and myocardial injury while recovering from acute myocarditis.
Franczuk P, Sokolska JM, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:

- przeprowadzeniu specjalistycznych analiz badań obrazowych,
- przygotowaniu i redagowaniu treści manuskryptu.

Podpis

Justyna Sokolska

Dr Monika Kasztura
Katedra Higieny Żywności i Ochrony Zdrowia Konsumenta
Uniwersytet Przyrodniczy we Wrocławiu

Wrocław, 03.09.2023

OŚWIADCZENIE

Oświadczam, że w pracach:
1) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study.**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Biomedicines. 2023. doi: 10.3390/biomedicines11082136

2) **Iron status and myocardial injury while recovering from acute myocarditis.**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:

- przeprowadzeniu specjalistycznych badań laboratoryjnych,
- krytycznej ocenie i redagowaniu treści manuskryptu;

PUBLIKACJA 2:

- przeprowadzeniu specjalistycznych badań laboratoryjnych,
- krytycznej ocenie i redagowaniu treści manuskryptu.

Podpis

Monika Kasztura

Dr n. med. Kamil Kobak
Aging and Metabolism Program
Oklahoma Medical Research Foundation

Oklahoma City, 04.09.2023

OŚWIADCZENIE

Oświadczam, że w pracach:
1) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study.**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Biomedicines. 2023. doi: 10.3390/biomedicines11082136

2) **Iron status and myocardial injury while recovering from acute myocarditis.**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:

- stworzeniu koncepcji i projektowaniu badania,
- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych,
- krytycznej ocenie i redagowaniu treści manuskryptu;

PUBLIKACJA 2:

- stworzeniu koncepcji i projektowaniu badania,
- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych,
- krytycznej ocenie i redagowaniu treści manuskryptu.

Podpis

Esabel Domenico
Faculty of Medicine
Wroclaw Medical University
50-345 Wroclaw, Poland

Wrocław, 25.08.2023

Co-authorship declaration

I declare that in the preparation of the publication:

- Cardiovascular Complications of Viral Respiratory Infections and COVID-19.
Franczuk P, Tkaczyszyn M, Kulak M, Domenico E, Ponikowski P, Jankowska EA.
Biomedicines. 2023; 11(1):71. doi: 10.3390/biomedicines11010071

I was involved in:
- review of literature,
- writing—original draft preparation.

Signature 

Maria Kulak
Wydział Lekarski
Gdański Uniwersytet Medyczny

Gdańsk, 25.08.2023

OŚWIADCZENIE

Oświadczam, że w pracy:

- Cardiovascular Complications of Viral Respiratory Infections and COVID-19.
Franczuk P, Tkaczyszyn M, Kulak M, Domenico E, Ponikowski P, Jankowska EA.
Biomedicines. 2023; 11(1):71. doi: 10.3390/biomedicines11010071

Mój udział polegał na:
- przeglądzie danych literaturowych,
- przygotowaniu treści manuskryptu.

Maria Kulak
Podpis

Dr n. med. Katarzyna Kulej-Łyko
Instytut Chorób Serca
Uniwersytecki Szpital Kliniczny we Wrocławiu

Wrocław, 04.09.2023

OŚWIADCZENIE

Oświadczam, że w pracach:

1) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study.**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Biomedicines. 2023. doi: 10.3390/biomedicines11082136

2) **Iron status and myocardial injury while recovering from acute myocarditis.**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:

- stworzeniu koncepcji i projektowaniu badania,
- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych,
- krytycznej ocenie i redagowaniu treści manuskryptu;

PUBLIKACJA 2:

- stworzeniu koncepcji i projektowaniu badania,
- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych,
- krytycznej ocenie i redagowaniu treści manuskryptu.

Katarzyna Kulej-Łyko

dr n. med. Katarzyna Kulej-Łyko
lekarz
kardiolog
2531307

Podpis

Aneta Kosiorek
Instytut Chorób Serca
Uniwersytet Medyczny we Wrocławiu

Wrocław, 03.09.2023

OŚWIADCZENIE

Oświadczam, że w pracach:
1) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study.**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Biomedicines. 2023. doi: 10.3390/biomedicines11082136

2) **Iron status and myocardial injury while recovering from acute myocarditis.**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:

- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych;

PUBLIKACJA 2:

- rekrutacji pacjentów,
- przygotowaniu i analizie statystycznej danych.

Aneta Kosiorek

Podpis

Alicja Sołtowska
Zakład Pielęgniarstwa Internistycznego
Uniwersytet Medyczny we Wrocławiu

Wrocław, 31.08.2023

OŚWIADCZENIE

Oświadczam, że w pracach:

1) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA.
Biomedicines. 2023. doi: 10.3390/biomedicines11082136

2) **Iron status and myocardial injury while recovering from acute myocarditis**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak K, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA
Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:
- rekrutacji pacjentów,
- przygotowaniu danych do analiz,
- redagowaniu treści manuskryptu;

PUBLIKACJA 2:
- rekrutacji pacjentów,
- przygotowaniu danych do analiz,
- redagowaniu treści manuskryptu.

Podpis

Alicja Sołtowska

Prof. dr hab. Piotr Ponikowski
Dyrektor Instytutu Chorób Serca
Uniwersytet Medyczny we Wrocławiu

Wrocław, 01.09.2023

OŚWIADCZENIE

Oświadczam, że w pracach:

1) **Complications of Viral Respiratory Infections and COVID-19.**
Franczuk P, Tkaczyszyn M, Kulak M, Domenico E, Ponikowski P, Jankowska EA. Biomedicines. 2023.
Doi: 10.3390/biomedicines11010071

2) **Iron Status and Short-Term Recovery after Non-Severe Acute Myocarditis: A Prospective Observational Study.**
Franczuk P, Tkaczyszyn M, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Biomedicines. 2023. doi: 10.3390/biomedicines11082136

3) **Iron status and myocardial injury while recovering from acute myocarditis.**
Franczuk P, Sokolska J, Tkaczyszyn M, Gać P, Kosiorek A, Kulej-Łyko K, Kobak KA, Kasztura M, Sołtowska A, Jaroch J, Ponikowski P, Jankowska EA. Folia Cardiologica. 2023. doi: 10.5603/fc.96888

Mój udział polegał na:

PUBLIKACJA 1:
- krytycznej ocenie i redagowaniu treści manuskryptu;

PUBLIKACJA 2:
- stworzeniu koncepcji i projektowaniu badania,
- krytycznej ocenie i redagowaniu treści manuskryptu,
- nadzorze nad prowadzonym badaniem i procesem publikacji;

PUBLIKACJA 3:
- stworzeniu koncepcji i projektowaniu badania,
- krytycznej ocenie i redagowaniu treści manuskryptu,
- nadzorze nad prowadzonym badaniem i procesem publikacji.

Podpis

Uniwersytet Medyczny we Wrocławiu
Wydział Lekarski
INSTYTUT CHORÓB SERCA
dyrektor
prof. dr hab. Piotr Ponikowski