Folia Cardiologica 2024, 19
DOI: 10.5603/fc.96888
Copyright © 2024 Via Medica
ISSN 2353–7752
e-ISSN 2353–7760

Iron status and myocardial injury while recovering from acute myocarditis

Stan gospodarki żelazowej a uszkodzenie miokardium w ostrym zapaleniu mięśnia sercowego

Paweł Franczuk[1, 2], Justyna Maria Sokolska[1, 2], Michał Tkaczyszyn[1, 2], Paweł Gać[3, 4], Aneta Kosiorek[1], Katarzyna Kulej-Łyko[2], Kamil Aleksander Kobak[5], Monika Kasztura[6], Alicja Sołtowska[7, 8], Joanna Jaroch[7, 8], Piotr Ponikowski[1, 2], Ewa Anita Jankowska[1, 2]

[1]Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland
[2]Institute of Heart Diseases, University Hospital, Wroclaw, Poland
[3]Division of Environmental Health and Occupational Medicine, Department of Population Health, Wroclaw Medical University, Wroclaw, Poland
[4]Centre of Diagnostic Imaging, 4th Military Hospital, Wroclaw, Poland
[5]Aging and Metabolism Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, United States
[6]Department of Food Hygiene and Consumer Health Protection, Faculty of Veterinary Medicine, Wroclaw University of Environmental and Life Sciences, Wroclaw, Poland
[7]Department of Cardiology, Tadeusz Marciniak Lower Silesia Specialist Hospital-Emergency Medicine Center, Wroclaw, Poland
[8]Division of Internal Medicine Nursing, Faculty of Health Science, Wroclaw Medical University, Wroclaw, Poland

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.

Address for correspondence: Paweł Franczuk MD, Institute of Heart Diseases, Wroclaw Medical University, ul. Borowska 213, 50–556 Wroclaw, Poland, e-mail: lekarz.pawelfranczuk@gmail.com, phone: +48 71 733 11 12

Received: 10.08.2023 Accepted: 20.08.2023 Early publication date: 30.08.2023

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

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

Folia Cardiologica 2024; 19: 16–24

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:

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

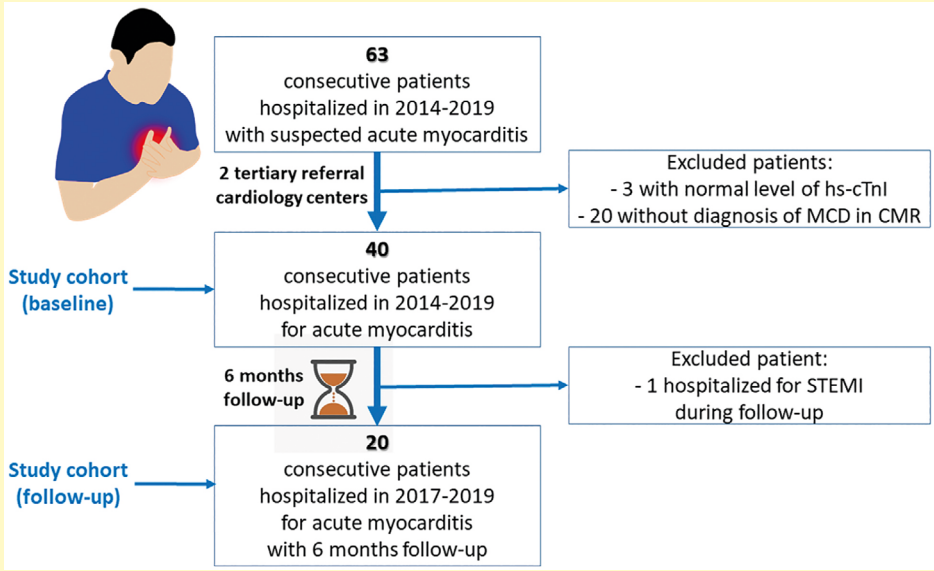

Figure 1. Enrollment and follow-up — flowchart of the study. CMR — cardiac magnetic resonance; hs-cTnI — high-sensitivity cardiac troponin I; MCD — myocarditis; STEMI — ST-segment elevation myocardial infarction

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

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, [µg/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

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

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 [µg/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 [µg/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 [nmol/L]	0.121	0.091	0.104	0.057	–0.120	0.030	0.007
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 µg/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

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.

Funding

This research was financially supported by subsidy no. SUBZ.A460.23.005 for the Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland.

Acknowledgements

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

Folia Cardiologica 2024; 19: 16–24

References

1. Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nat Rev Cardiol. 2021; 18(3): 169–193, doi: 10.1038/s41569-020-00435-x, indexed in Pubmed: 33046850.
2. Sagar S, Liu PP, Cooper LT. Myocarditis. Lancet. 2012; 379(9817): 738–747, doi: 10.1016/S0140-6736(11)60648-X, indexed in Pubmed: 22185868.
3. Caforio ALP, Pankuweit S, Arbustini E, et al. European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013; 34(33): 2636–48, 2648a, doi: 10.1093/eurheartj/eht210, indexed in Pubmed: 23824828.
4. Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. J Am Coll Cardiol. 2012; 59(9): 779–792, doi: 10.1016/j.jacc.2011.09.074, indexed in Pubmed: 22361396.
5. Piccirillo F, Watanabe M, Di Sciascio G. Diagnosis, treatment and predictors of prognosis of myocarditis. A narrative review. Cardiovasc Pathol. 2021; 54: 107362, doi: 10.1016/j.carpath.2021.107362, indexed in Pubmed: 34192559.
6. Anzini M, Merlo M, Sabbadini G, et al. Long-term evolution and prognostic stratification of biopsy-proven active myocarditis. Circulation. 2013; 128(22): 2384–2394, doi: 10.1161/CIRCULATIONAHA.113.003092, indexed in Pubmed: 24084750.
7. Grün S, Schumm J, Greulich S, et al. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. J Am Coll Cardiol. 2012; 59(18): 1604–1615, doi: 10.1016/j.jacc.2012.01.007, indexed in Pubmed: 22365425.
8. Ammann P, Naegeli B, Schuiki E, et al. Long-term outcome of acute myocarditis is independent of cardiac enzyme release. Int J Cardiol. 2003; 89(2-3): 217–222, doi: 10.1016/s0167-5273(02)00478-3, indexed in Pubmed: 12767545.
9. Imazio M, Brucato A, Barbieri A, et al. Good prognosis for pericarditis with and without myocardial involvement: results from a multicenter, prospective cohort study. Circulation. 2013; 128(1): 42–49, doi: 10.1161/CIRCULATIONAHA.113.001531, indexed in Pubmed: 23709669.
10. Gilotra NA, Minkove N, Bennett MK, et al. Lack of relationship between serum cardiac troponin i level and giant cell myocarditis diagnosis and outcomes. J Card Fail. 2016; 22(7): 583–585, doi: 10.1016/j.cardfail.2015.12.022, indexed in Pubmed: 26768222.
11. Ukena C, Kindermann M, Mahfoud F, et al. Diagnostic and prognostic validity of different biomarkers in patients with suspected myocarditis. Clin Res Cardiol. 2014; 103(9): 743–751, doi: 10.1007/s00392-014-0709-z, indexed in Pubmed: 24781421.
12. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr. 2001; 131(2S-2): 568S–579S; discussion 580S, doi: 10.1093/jn/131.2.568S, indexed in Pubmed: 11160590.
13. Mu Q, Chen L, Gao X, et al. The role of iron homeostasis in remodeling immune function and regulating inflammatory disease. Sci Bull (Beijing). 2021; 66(17): 1806–1816, doi: 10.1016/j.scib.2021.02.010, indexed in Pubmed: 36654387.
14. Ni S, Yuan Y, Kuang Y, et al. Iron metabolism and immune regulation. Front Immunol. 2022; 13: 816282, doi: 10.3389/fimmu.2022.816282, indexed in Pubmed: 35401569.
15. Tkaczyszyn M, Górniak KM, Lis WH, et al. Iron deficiency and deranged myocardial energetics in heart failure. Int J Environ Res Public Health. 2022; 19(24), doi: 10.3390/ijerph192417000, indexed in Pubmed: 36554881.
16. Luetkens JA, Homsi R, Sprinkart AM, et al. Incremental value of quantitative CMR including parametric mapping for the diagnosis of acute myocarditis. Eur Heart J Cardiovasc Imaging. 2016; 17(2): 154–161, doi: 10.1093/ehjci/jev246, indexed in Pubmed: 26476398.
17. Georgiopoulos G, Figliozzi S, Sanguineti F, et al. Prognostic impact of late gadolinium enhancement by cardiovascular magnetic resonance in myocarditis: a systematic review and meta-analysis. Circ Cardiovasc Imaging. 2021; 14(1): e011492, doi: 10.1161/CIRCIMAGING.120.011492, indexed in Pubmed: 33441003.
18. Greulich S, Seitz A, Müller KAL, et al. Predictors of mortality in patients with biopsy-proven viral myocarditis: 10-year outcome data. J Am Heart Assoc. 2020; 9(16): e015351, doi: 10.1161/JAHA.119.015351, indexed in Pubmed: 32787653.
19. Barone-Rochette G, Augier C, Rodière M, et al. Potentially simple score of late gadolinium enhancement cardiac MR in acute myocarditis outcome. J Magn Reson Imaging. 2014; 40(6): 1347–1354, doi: 10.1002/jmri.24504, indexed in Pubmed: 24293405.
20. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson. 2017; 19(1): 75, doi: 10.1186/s12968-017-0389-8, indexed in Pubmed: 28992817.
21. Lurz P, Luecke C, Eitel I, et al. Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: the myoracer-trial. J Am Coll Cardiol. 2016; 67(15): 1800–1811, doi: 10.1016/j.jacc.2016.02.013, indexed in Pubmed: 27081020.
22. von Knobelsdorff-Brenkenhoff F, Schüler J, Dogangüzel S, et al. Detection and monitoring of acute myocarditis applying quantitative cardiovascular magnetic resonance. Circ Cardiovasc Imaging. 2017;

10(2), doi: 10.1161/CIRCIMAGING.116.005242, indexed in Pubmed: 28213448.
23. Cundari G, Galea N, De Rubeis G, et al. Use of the New Lake Louise Criteria improves CMR detection of atypical forms of acute myocarditis. Int J Cardiovasc Imaging. 2021; 37(4): 1395–1404, doi: 10.1007/s10554-020-02097-9, indexed in Pubmed: 33190198.
24. Mewton N, Liu CY, Croisille P, et al. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol. 2011; 57(8): 891–903, doi: 10.1016/j.jacc.2010.11.013, indexed in Pubmed: 21329834.
25. Berg J, Kottwitz J, Baltensperger N, et al. Cardiac magnetic resonance imaging in myocarditis reveals persistent disease activity despite normalization of cardiac enzymes and inflammatory parameters at 3-month follow-up. Circ Heart Fail. 2017; 10(11), doi: 10.1161/CIRCHEARTFAILURE.117.004262, indexed in Pubmed: 29158437.