Adaptive anti-myocardial immune response following hospitalization for acute heart failure

Caroline Morbach1,2*, Niklas Beyersdorf3, Thomas Kerkau3, Gustavo Ramos1,2, Floran Sahiti1,2, Judith Albert1,2, Roland Jahns4, Georg Ertl1, Christiane E. Angermann1, Stefan Frantz1,2, Ulrich Hofmann1,2 and Stefan Störk1,2

1Comprehensive Heart Failure Center, University and University Hospital Würzburg, Am Schwarzenberg15, Würzburg, D-97078, Germany; 2Department of Medicine I, University Hospital Würzburg, Würzburg, Germany; 3Institute for Virology and Immunobiology, University of Würzburg, Würzburg, Germany; and 4Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw), University Hospital Würzburg, Würzburg, Germany

Abstract

Aims It has been hypothesized that cardiac decompensation accompanying acute heart failure (AHF) episodes generates a pro-inflammatory environment boosting an adaptive immune response against myocardial antigens, thus contributing to progression of heart failure (HF) and poor prognosis. We assessed the prevalence of anti-myocardial autoantibodies (AMyA) as biomarkers reflecting adaptive immune responses in patients admitted to the hospital for AHF, followed the change in AMyA titres for 6 months after discharge, and evaluated their prognostic utility.

Methods and results AMyA were determined in n = 47 patients, median age 71 (quartiles 60; 80) years, 23 (49%) female, and 24 (51%) with HF with preserved ejection fraction, from blood collected at baseline (time point of hospitalization) and at 6 month follow-up (visit F6). Patients were followed for 18 months (visit F18). The prevalence of AMyA increased from baseline (n = 21, 45%) to F6 (n = 36, 77%; P < 0.001). At F6, the prevalence of AMyA was higher in patients with HF with preserved ejection fraction (n = 21, 88%) compared with patients with reduced ejection fraction (n = 14, 61%; P = 0.036). During the subsequent 12 months after F6, that is up to F18, patients with newly developed AMyA at F6 had a higher risk for the combined endpoint of death or rehospitalization for HF (hazard ratio 4.79, 95% confidence interval 1.13–20.21; P = 0.033) compared with patients with persistent or without AMyA at F6.

Conclusions Our results support the hypothesis that AHF may induce patterns of adaptive immune responses. More studies in larger populations and well-defined patient subgroups are needed to further clarify the role of the adaptive immune system in HF progression.

Keywords Adaptive immune response; Acute heart failure; Anti-myocardial; Autoantibody; Inflammation

Received: 23 December 2020; Revised: 7 March 2021; Accepted: 8 April 2021

*Correspondence to: Caroline Morbach, Comprehensive Heart Failure Center, University and University Hospital Würzburg, Am Schwarzenberg 15, D-97078 Würzburg, Germany. Tel: +49 931 201 46389. Email: morbach_c@ukw.de

Background

Acute decompensation for heart failure (AHF) is a life-threatening condition characterized by acutely impaired cardiac function associated with profound neurohormonal, inflammatory and immune alterations, and poor prognosis.1,2 A systemic inflammatory response3 frequently accompanies AHF that likely primarily reflects the activation of innate immunity, although causality is debated. However, heart-specific adaptive immunity might also be critically involved in these (counter-)regulatory processes.3,5 Circulating heart-reactive autoantibodies (anti-myocardial and anti-intercalated disc autoantibodies) have previously been described in both acute myocarditis/pericarditis and patients suffering from dilated cardiomyopathy at higher frequencies than in normal or non-inflammatory heart failure (HF) controls.3,6 These autoantibodies are directed against multiple antigens. Some are expressed only in the myocardium (organ specific), whereas some anti-myocardial autoantibodies (AMyA) have functional effects on cardiac myocytes...
in vitro as well as in animal models. Depletion of autoantibodies by extracorporeal immunoadsorption is associated with improved ventricular function and reduced cardiac symptoms in some DCM patients, suggesting that AMyA may also have a pathogenetic role in humans. Here, we explored the overarching hypothesis that an acute pro-inflammatory burst triggered by an AHF episode may boost adaptive immune responses against myocardial antigens, which might contribute to the progression of HF and worsened prognosis.

**Aims**

We aimed to assess the prevalence of AMyA in patients admitted to the hospital for AHF, determine the development of AMyA within the 6 months following discharge from the hospital, and estimate their prognostic value in the subsequent year.

**Methods**

From a larger registry that prospectively identifies patients admitted to our tertiary care hospital for AHF, we retrospectively selected a stratified sample consisting of 48 patients. Strata were male vs. female, chronic vs. de novo manifestation of AHF, and reduced left ventricular ejection fraction (LVEF < 40%, HFrEF) vs. preserved LVEF (LVEF ≥ 50%, HFpEF). Stratification yielded eight groups of

**Figure 1** Study flow. N = 47 patients hospitalized for acute heart failure were analysed for the presence of anti-myocardial antibodies (AMyA). The red drop symbol indicates the time points of venous blood sampling. Twenty patients provided pairs of venous samples at index hospitalization (i.e. baseline). Out of those, n = 12 were AMyA negative at Day 3; none of these patients exhibited altered AMyA titres during the index hospitalization. However, 15 patients who had been AMyA negative at baseline had generated new AMyA titres 6 months later (F6). All patients were followed for 18 months (F18) to collect endpoint information. The lower part of the figure illustrates the qualitative course of AMyA (positive +; negative —) from baseline to F6 in the total study population.

**Figure 2** Status of expression of anti-myocardial antibodies at baseline (BL) and at the 6 month follow-up visit (F6) in patients with acute heart failure and reduced (HFrEF, n = 23) vs. preserved (HFpEF, n = 24) left ventricular ejection fraction. +/+, anti-myocardial antibodies (AMyA) titre positive at BL and F6; —/—, AMyA titre negative at BL and F6; —/+, AMyA titre newly developed between BL and F6.
Table 1. Baseline characteristics and laboratory parameters assessed during index hospitalization in the total sample and in subgroups according to the presence of anti-myocardial autoantibodies (AMyA) at baseline (BL) and 6 month follow-up visit (F6), respectively.

| Baseline values | Total cohort | AMyA (BL/F6) –/+ | AMyA (BL/F6) –/- | AMyA (BL/F6) +/- |
|----------------|-------------|-----------------|-----------------|----------------|
| Age, median (Q1; Q3) | 71 (60; 80) | 70 (63; 80) | 77 (45; 80) | 71 (60; 78) |
| Female sex, n (%) | 23 (49) | 6 (40) | 5 (45) | 12 (57) |
| HFpEF, n (%) | 23 (49) | 6 (40) | 8 (73) | 9 (43) |
| HFrEF, n (%) | 24 (51) | 9 (60) | 3 (27) | 12 (57) |
| De novo heart failure, n (%) | 23 (49) | 6 (40) | 6 (55) | 11 (52) |
| History of coronary disease, n (%) | 16 (34) | 8 (53) | 2 (18) | 6 (29) |
| History of diabetes mellitus, n (%) | 25 (53) | 11 (73) | 6 (55) | 8 (38) |
| History of hypertension, n (%) | 45 (96) | 15 (100) | 11 (100) | 19 (90) |
| Duration of index hospitalization (days), median (Q1; Q3) | 9 (7; 15) | 10 (7; 23) | 8 (7; 13) | 9 (7; 12) |
| Main cause of AHF | | | | |
| Myocarditis, n (%) | 1 (2) | 0 | 0 | 1 (5) |
| Acute coronary syndrome, n (%) | 6 (13) | 1 (7) | 3 (27) | 2 (10) |
| Hypertension, n (%) | 4 (9) | 3 (20) | 0 | 1 (5) |
| Rhythm disorder, n (%) | 10 (21) | 6 (40) | 1 (9) | 3 (14) |
| Infectious disease, n (%) | 1 (2) | 0 | 0 | 1 (5) |
| Cardiomyopathy, n (%) | 8 (17) | 0 | 2 (18) | 6 (29) |
| Valvular disease, n (%) | 7 (15) | 1 (7) | 0 | 6 (29) |
| Renal failure, n (%) | 4 (9) | 2 (13) | 1 (9) | 1 (5) |
| Other, n (%) | 6 (13) | 2 (13) | 4 (36) | 0 |
| Admission | | | | |
| Haemoglobin (g/dL), median (Q1; Q3) | 12.8 (11.4; 14.3) | 13.0 (11.4; 13.8) | 12.6 (12.0; 14.1) | 12.8 (10.7; 14.5) |
| Leucocytes (× 1000/μL, median (Q1; Q3) | 8.4 (7.2; 9.9) | 8.1 (7.0; 10.4) | 8.9 (7.0; 9.7) | 8.4 (7.4; 9.6) |
| Creatinine (mg/dL, median (Q1; Q3) | 1.3 (1.1; 1.6) | 1.3 (1.1; 1.7) | 1.2 (1.1; 1.5) | 1.2 (0.9; 1.6) |
| eGFR (mL/min/1.73 m²), median (Q1; Q3) | 55 (47; 66) | 52 (43; 64) | 54 (49; 71) | 56 (39; 74) |
| CRP (mg/dL, median (Q1; Q3) | 0.9 (0.3; 2.5) | 1.0 (0.6; 1.9) | 0.5 (0.3; 3.0) | 0.0 (0.3; 3.0) |
| NT-proBNP (pg/mL, median (Q1; Q3) | 4513 (2729; 8255) | 3995 (2159; 6618) | 4243 (3316; 6152) | 4233 (3136; 6152) |
| CK (U/L, median (Q1; Q3) | 78 (51; 120) | 69 (48; 109) | 80 (43; 109) | 96 (54; 168) |
| Discharge | | | | |
| Haemoglobin (g/dL, median (Q1; Q3) | 12.8 (11.7; 14.0) | 12.1 (11.3; 14.0) | 12.8 (11.7; 13.8) | 12.9 (11.7; 14.3) |
| Leucocytes (× 1000/μL, median (Q1; Q3) | 8.0 (6.8; 9.3) | 7.8 (6.3; 10.4) | 7.4 (6.7; 8.7) | 8.3 (7.0; 9.4) |
| Creatinine (mg/dL, median (Q1; Q3) | 1.2 (1.0; 1.5) | 1.4 (1.0; 1.6) | 1.3 (0.9; 1.5) | 1.2 (1.0; 1.5) |
| eGFR (mL/min/1.73 m²), median (Q1; Q3) | 54 (48; 69) | 51.7 (41.5; 66.5) | 60 (51; 69) | 53 (45; 71) |
| CRP (mg/dL, median (Q1; Q3) | 0.5 (0.3; 0.9) | 0.6 (0.4; 0.9) | 0.4 (0.3; 0.7) | 0.5 (0.3; 1.0) |
| NT-proBNP (pg/mL, median (Q1; Q3) | 1447 (740; 2274) | 1113 (740; 1730) | 1058 (824; 2445) | 1492 (580; 2685) |
| CK (U/L, median (Q1; Q3) | 75 (61; 100) | 64 (51; 100) | 76 (64; 102) | 78 (64; 109) |
| Echocardiography* | | | | |
| Baseline | | | | |
| LVEDD (mm), median (Q1; Q3) | 54 (50; 61) | 53 (50; 56) | 56 (53; 60) | 53 (48; 63) |
| LVF (%) | 34 (24; 61) | 52 (27; 61) | 26 (21; 51) | 55 (24; 64) |
| 6 month follow-up | | | | |
| LVEDD (mm), median (Q1; Q3) | 55 (47; 65) | 57 (46; 65) | 58 (48; 65) | 55 (47; 67) |
| Change from BL (mm), median (Q1; Q3) | +3 (–12; +15) | +11 (–11; +16) | +3 (–13; +12) | +0.1 (–0.5; +17) |
| LVF (%) | 43 (29; 55) | 45 (30; 62) | 45 (37; 53) | 37 (28; 51) |
| Change from BL (%) | +1 (–20; +24) | –13 (–25; +37) | +22 (–3; +24) | +0 (–20; +19) |

AHF, acute heart failure; AMyA, anti-myocardial autoantibodies; BL, baseline; CK, creatine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide. Results are displayed as median (Q1; Q3) or n (%) in the respective (sub)group.

*Echocardiography was available in n = 46 patients at BL and in n = 42 patients at F6.

six patients each. In addition, all patients had undergone a 6 month follow-up visit (F6) in our outpatient department and had complete information regarding hospitalization(s) or death for a follow-up period of 18 months after discharge from index hospitalization (F18). The study complies with the Declaration of Helsinki and was approved by the local ethics committee; patients provided informed consent regarding study participation. AMyA were determined in prospectively collected blood samples taken at baseline and visit F6 employing ‘NOVA Lite’ Heart (Primate) IFA slides’ together with anti-human IgG-FITC and standard positive and negative controls (Inova Diagnostics, San Diego, CA, USA). Serum dilutions of 1:20 were used for screening, and individual AMyA titres were determined by limiting dilution (two-fold dilution steps: 1:20, 1:40 etc.; highest titre: 1:1280). All slides were independently assessed by three observers for fluorescence of myofibrils. Titres of ≥1:20 were classified as positive. Statistical analyses were performed using SPSS® (IBM, Armonk, NY, USA) Version 26. Continuous variables are reported as median

DOI: 10.1002/ehf2.13376
(quartiles) and categorical variables as frequency (per cent). Groupwise differences were calculated using $\chi^2$ and Kruskal–Wallis tests, as appropriate. Prognostic information is displayed using Kaplan–Meier survival curves and log-rank test. The prognostic yield of AMyA was assessed using Cox proportional hazard regression analyses, and hazard ratios with 95% confidence intervals are reported.

**Results**

For the present analysis, serum samples of 47 patients hospitalized for AHF (index hospitalization; May 2015–March 2017) and at F6 were analysed (one female patient with de novo HFrEF yielded insufficient blood quality and thus did not enter analyses). Sampling at index hospitalization had been performed on Day 3 ($n = 38$) and on the day of discharge ($n = 29$; Figure 1). The median age of these patients was 71 (60; 80) years, and $n = 23$ (49%) were female. The median duration of index hospitalization was 9 (7; 15) days. Sixteen (34%) patients had known coronary disease, and 14 (30%) patients were in atrial fibrillation. At baseline, 21 (45%) patients exhibited AMyA within a range of 1:20–1:80. There was no difference in the prevalence of AMyA in HFrEF ($n = 9$, 39%) vs. HFrEF ($n = 12$, 50%; $P = 0.454$), in de novo ($n = 11$, 48%) vs. chronic HF ($n = 10$, 42%; $P = 0.671$), and in male ($n = 9$, 38%) vs. female patients ($n = 12$, 52%; $P = 0.312$). In 20 patients with blood samples from both Day 3 and the day of discharge, 12 (60%) were AMyA negative at Day 3 and remained negative until discharge (Figure 1). We found an increase in the prevalence of AMyA from baseline ($n = 21$, 45%) to F6 ($n = 36$, 77%; $P < 0.001$) and a higher prevalence of AMyA in HFrEF ($n = 21$, 88%) than in HFrEF at F6 ($n = 14$, 61%; $P = 0.036$; Figure 2). One male patient, who had an AMyA titre of 1:20 at baseline, was negative at F6 (assuming persistence of AMyA; this patient was considered +/+ for further analyses). All other patients with positive AMyA titres at baseline remained positive at F6. Fifteen (32%) patients newly developed positive AMyA titres, and 11 (23%) patients remained negative. Table 1 illustrates baseline characteristics and laboratory parameters according to the prevalence of AMyA at baseline and F6.

In the 12 months following F6 (i.e. up to Month 18, F18), eight patients reached the combined endpoint death or re-hospitalization for HF [$n = 5$ rehospitalizations for HF (with two subsequent deaths), $n = 3$ deaths]. Five of those (63%) had newly developed AMyA, two patients (25%) had persistent AMyA, and one patient (13%) had been negative for AMyA at baseline and F6. Figure 3 illustrates event-free survival according to AMyA at baseline and F6. Prognosis differed according to AMyA status, and patients with newly developed AMyA at F6 had a significantly worse prognosis compared with the other two groups (hazard ratio 4.79, 95% confidence interval 1.13–20.21; $P = 0.033$).

**Conclusions**

This pilot study analysed prospectively collected serum samples and clinical characteristics of 47 AHF patients and revealed three major findings. First, there was a high prevalence of AMyA in patients hospitalized for AHF, which
appeared independent of sex, HF phenotype, and mode of presentation. Second, an important proportion of AHF patients newly developed AMyA between baseline and the first 6 months following discharge, which was more pronounced in HFrEF compared with HFrEF. Third, we observed a worse prognosis in AHF patients with newly developed AMyA compared with those with persistent or without AMyA at F6.

The data accumulating in recent years demonstrate that elevated markers of inflammation correlate with prognosis both in HFrEF and in HFrEF patients. Markers like pro-inflammatory cytokines, C-reactive protein, or galectin 3 primarily reflect innate immunity. There is solid mechanistic evidence that activation of innate immunity in the myocardium contributes to myocardial fibrosis, adverse remodelling, and finally to HF progression. Nevertheless, therapeutic approaches targeting inflammation in unselected HF patients were not successful in reducing HF events, so far. On the other hand, circulating heart-reactive autoantibodies have been found in both acute inflammatory syndromes of the heart and in chronic HF syndromes. Some of these autoantibodies were shown to elicit functional effects in vitro as well as in animal models. In patients with chronic HF, antibody removal by extracorporeal immunoadsorption was associated with improved LV function and reduced clinical HF symptoms, suggesting that AMyA may also have a functional role in humans. However, there is still an unmet need in defining diagnostic criteria to identify patients potentially benefitting from immunomodulatory therapy. We still lack clinical evidence on the relevance of adaptive immunity for HF progression. Therefore, we studied AMyA as biomarkers reflecting adaptive immune responses against myocardial antigens.

Our results strengthen the hypothesis that AHF, similar to acute cardiac inflammatory syndromes, may induce an adaptive immune response and support further research regarding the role of the adaptive immune system in the progression of HF. However, we recognize the limitations of our approach. First, the reasons for an AMyA positive status at baseline (and, hence, a persistent AMyA positive status at F6) remain unclear. There might be pre-existing AMyA in some patients, either due to a preceding AHF episode in patients with known HF or due to a subclinical, protracted decompensation in patients with nominally ‘de novo’ HF. These AMyA might be less or non-pathogenic AMyA recognizing a different set of antigens. Second, due to our aim to analyse the incidence of new AMyA development following AHF (i.e. focusing on AMyA —/+ AHF patients), we had to select patients with samples drawn at F6, hence patients who survived the first 6 months after hospitalization for acutely decompensated HF. This resulted in the selection of a relatively healthy patient group with lower event rates compared with the current literature.

Larger studies including also sicker patients are needed to closely monitor the course and determinants of AMyA in acute and chronic HF as well as of the association of prevalent/incident AMyA with cardiac dimensions and myocardial function over time. Further research should investigate if AMyA as a biomarker for cardiac inflammatory processes might guide immunomodulatory therapies targeting the adaptive immune system in patients with HFrEF or HFrEF.

**Acknowledgement**

The authors would like to thank Claudia Hahn for expert technical assistance for detecting AMyA by immunofluorescence microscopy.

**Conflict of interest**

C.M. reports research cooperation with the University of Würzburg and TOMTEC Imaging Systems funded by a research grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy, Germany; advisory and speaker honoraria as well as travel grants from Amgen, TOMTEC, Orion Pharma, Alnylam, Akcea, Pfizer, Boehringer Ingelheim, and EBR Systems; principal investigator in trials sponsored by Alnylam and AstraZeneca; and financial support from the interdisciplinary centre for clinical research—IZKF Würzburg (advanced clinician–scientist programme). N.B. declares reception of a travel grant from Roche Diagnostics GmbH. T.K. and G.R. have nothing to disclose. F.S. receives financial support from IZKF Würzburg (MD/PhD programme scholarship). J.A. reports financial support from the interdisciplinary centre for clinical research—IZKF Würzburg (UNION CVD clinician–scientist programme). R.J. reports several research grants from the German Federal Ministry of Education and Research BMBF FKZ 01ES0816 und FKZ 01EY1712, and the Interdisciplinary Centre of Research (IZKF), University Hospital Würzburg (Z-9). G.E. reports significant honoraria for trial leadership from Abbott and Novartis; has been a consultant for Abbott, Boehringer Ingelheim, Novartis, ResMed, and Vifor (modest); and received significant grant support from Boehringer Ingelheim, Thermo Fisher, Siemens Healthineers, Vifor, and German Federal Ministry of Education and Research. C.E.A. reports honoraria for trial leadership from Abbott, Boehringer Ingelheim, and Novartis; has been a consultant for and/or received speaker honoraria from Abbott and Novartis; and received grant support from Boehringer Ingelheim, Thermo Fisher, Siemens Healthineers, Vifor, and German Federal Ministry of Education and Research. S.F. reports advisory and speaker honoraria as well as travel grants from Amgen Europe, AstraZeneca, Bayer Vital, Boehringer Ingelheim, Bristol Meyers Squibb GmbH, Daiichi Sankyo, MSD, Novartis, Pfizer, Sanofi, Servier, and Vifor. U.H. reports advisory and speaker honoraria as well as travel grants from Amgen Europe.
grants from AstraZeneca, Bayer Vital, Boehringer Ingelheim, Bristol Meyers Squibb GmbH, Daiichi Sankyo, MSD, Novartis, Pfizer, and Sanofi. S.S. reports research grants from the German Federal Ministry of Education and Research, European Union, and University Hospital Würzburg; participation in data safety monitoring or event adjudication in studies sponsored by Roche and Medtronic; participation in advisory boards for Novartis, Bayer, Boehringer Ingelheim, Thermo Fisher, and Boston Scientific; principal investigator in trials (co-)sponsored by Boehringer Ingelheim, Novartis, Bayer, and Lundbeck; and speaker honoraria by Boehringer Ingelheim, Servier, Novartis, AstraZeneca, Pfizer, Bayer, and Thermo Fisher.

Funding

This work was supported by the German Federal Ministry of Education and Research within the Comprehensive Heart Failure Center [Bundesministerium für Bildung und Forschung (BMBF) 01EO1004 and 01EO1504]. Further support was provided by an unrestricted grant from Boehringer Ingelheim. This publication was supported by the Open Access Publication Fund of the University of Würzburg (Julius-Maximilians-Universität Würzburg). Open access funding was enabled and organized by Projekt DEAL.

References

1. Sabbah HN. Pathophysiology of acute heart failure syndrome: a knowledge gap. Heart Fail Rev 2017; 22: 621–639.
2. Frantz S, Falcão-Pires I, Balligand JL, Bauersachs J, Brutsaert D, Ciccarelli M, Dawson D, de Windt LJ, Giacca M, Hamdani N, Hilfiker-Kleiner D, Hirsch E, Leite-Moreira A, Mayr M, Thum T, Tocchetti CG, van der Velden J, Varricchi G, Heymans S. The innate immune system in chronic cardiomyopathy: a European Society of Cardiology (ESC) scientific statement from the Working Group on Myocardial Function of the ESC. Eur J Heart Fail 2018; 20: 445–459.
3. Caforio AL, Tona F, Bottaro S, Vinci A, Dequal G, Daliento L, Thiene G, Iliceto S. Clinical implications of anti-heart autoantibodies in myocarditis and dilated cardiomyopathy. Autoimmunity 2008 2008; 41: 35–45.
4. Kaya Z, Leib C, Katus HA. Autoantibodies in heart failure and cardiac dysfunction. Circ Res 2012; 110: 145–158.
5. Keppner L, Heinrichs M, Rieckmann M, Demengeot J, Frantz S, Hofmann U, Ramos G. Antibodies aggravate the development of ischemic heart failure. Am J Physiol Heart Circ Physiol 2018 1; 315: H1358–H1367.
6. Caforio ALP, Brucato A, Doria A, Angelini A, Ghirardello A, Bottaro S, Tonfoni F, Betterle C, Daliento L, Thiene G, Iliceto S. Anti-heart and anti-intercalated disk autoantibodies: evidence for autoimmunity in idiopathic recurrent acute pericarditis. Heart 2010; 96: 779–784.
7. Caforio AL, Angelini A, Blank M, Shani A, Kivity S, Goddard G, Doria A, Scharf A, Testolino M, Bottaro S, Marcolongo R, Thiene G, Iliceto S, Shoenfeld Y. Passive transfer of affinity-purified anti-heart autoantibodies (AHA) from sera of patients with myocarditis induces experimental myocarditis in mice. Int J Cardiol 2015; 20: 166–177.
8. Seferović PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, Felix SB, Arbustini E, Caforio ALP, Farmakis D, Filippatos GS, Gialafos E, Kanjhu V, Krijanač G, Limongelli G, Linhart A, Lyon AR, Maksimović R, Miličić D, Milinković I, Noutsias M, Oto A, Oto Ō, Pavlović SU, Piepoli MF, Ristić AD, Rosano GMC, Seggewiss H, Anšan M, Seferović JP, Rusčitkaja F, Čeļutkienė J, Jaarsma T, Mueller C, Moura B, Hill L, Volterrani M, Lopatin Y, Metra M, Baek J, Mullens W, Chioncel O, de Boer RA, Anker S, Ravezzi C, Coats AJ, Tschope C. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019; 21: 553–576.
9. Deftereos S, Giannopoulos G, Panagopoulos V, Bouras G, Raisakis K, Kossyvakis C, Karageorgiou S, Papadimitriou C, Vastaki M, Krouskas A, Angelidis C, Pagonis S, Pyrgakis V, Alexopoulos D, Manolis AS, Stefanadis C, Clemen MW. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. JACC Heart Fail 2014; 2: 131–137.