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February 2023 at a glance: focus on pathophysiology and treatment

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Pathophysiology

Sympathetic activity

Autonomic nervous system is a main target on novel interventions.[1–4] Badrov *et al.*[5] investigated determinants of augmented muscle sympathetic nerve activity (MSNA) in 177 heart failure (HF) patients and 658 healthy volunteers. MSNA was higher among HF patients, especially in men, with ischaemic cardiomyopathy and among those with sleep apnoea. Burst frequency was inversely associated with stroke volume, cardiac output, and peak oxygen consumption, and directly associated with norepinephrine and peripheral vascular resistance.

Inflammation

Inflammation plays a pivotal role in the progression of HF, though its role remains uncertain.[6–10] Mohebi *et al.*[7] investigated the association between inflammation and HF events. Overall, 1231 patients undergoing diagnostic coronary and/or peripheral angiography from the CASABLANCA study were stratified according to the Universal Definition of HF as stage A (at risk), stage B (pre-HF), and stages C or D (HF and end-stage HF).[11] Twenty-four inflammatory biomarkers were collected and categorized into low, medium and high level of inflammation. Patients with high inflammation levels were at increased adjusted risk of HF events across all the stages of HF confirming the role of inflammation as a marker, if not a cause, of HF severity.[7]

Metabolic syndrome is common in patients with HF. Biomarker expression was compared among HF patients with and without metabolic syndrome. Leptin, fatty acid-binding protein 4, interleukin-1 receptor antagonist, tumour necrosis factor receptor superfamily member 11 and proto-oncogene tyrosine-protein kinase receptor Ret were the most elevated in patients with metabolic syndrome, showing the involvement of inflammatory activation.[12] Michou *et al.*[13] quantified systemic inflammation using a novel interleukin-6 immunoassay in 2042 unselected patients presenting at the emergency department with acute dyspnoea. Half of these patients had a diagnosis of acute HF and presented higher levels of interleukin-6 compared to patients with other causes of dyspnoea. Interleukin-6 was also a strong predictor of 1-year mortality.

Haemodynamic changes during exercise

The pathophysiological, clinical and prognostic significance of invasive haemodynamic and exercise testing in patients with HF and preserved ejection fraction (EF) have been shown.[14–16] Omote *et al.*[17] investigated the prognostic significance of increased pulmonary artery wedge pressure (PAWP) during exercise. Among 764 patients with exertional dyspnoea and EF ≥50% undergoing invasive exercise testing, 384 (50%) showed elevated PAWP at rest (≥15 mmHg) and 187 (24%) had normal resting PAWP and increased PAWP during exercise (≥25 mmHg). Patients with elevated exercise PAWP had a larger than two-fold increased risk of events compared to those with normal PAWP during exercise; patients with elevated resting PAWP showed an even higher risk (*Figure 1*). In a multivariable-adjusted Cox model, each 1 standard deviation (SD) increase in exercise PAWP was associated with a 41% greater hazard of events and each 1 SD decrease in exercise cardiac output was associated with a 37% increased risk.[17]

Clinical assessment

Patient-reported outcomes

New York Heart Association (NYHA) functional classification is traditionally used to estimate health status in patients with HF.[11,18,19] Patient-reported outcomes (PROs), differently from clinician-reported outcomes, switch traditional care to a more patient-centred approach. However, their use remains limited in clinical practice. Savarese *et al.*[20] reviewed their characteristics, methodology and use in randomized trials and clinical trials, to date, aiming for their more extensive application.

Medical therapy

Early start of the four pillars of guideline-directed medical therapies (GDMT) in patients with HF and reduced EF (HFrEF) is strongly suggested.[19,21–24] A survey involving 615 cardiologists worldwide showed that the historical sequential approach (angiotensin-converting enzyme inhibitors or angiotensin receptor–neprilysin inhibitors first, beta-blockers second, mineralocorticoid receptor antagonists third, and sodium–glucose

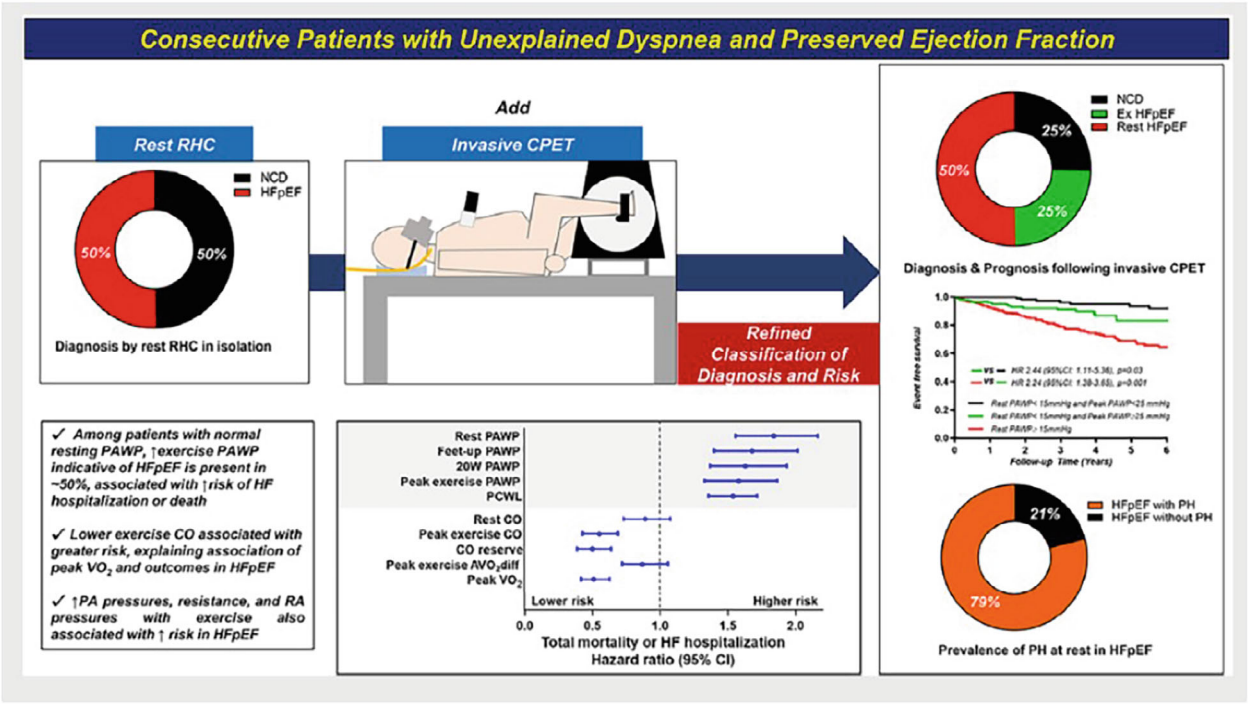

Figure 1 Prognostic role of exercise haemodynamics in patients with heart failure with preserved ejection fraction. AVO_2diff, arterial–venous oxygen content difference; CO, cardiac output; CPET, cardiopulmonary exercise testing; Ex, exercise; iCPET, invasive cardiopulmonary exercise testing; NCD, non-cardiac dyspnoea; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PCWL, workload-adjusted pulmonary artery wedge pressure; PH, pulmonary hypertension; RA, right atrial; RHC, right heart catheterization; VO_2, oxygen consumption. From Omote *et al.*[17]

cotransporter 2 inhibitors [SGLT2i] fourth) remains the most chosen among specialists, despite recent recommendations and the ongoing increase in the use of SGLT2i.[22–26] A cost-effectiveness analysis showed that immediate versus 12-month delayed initiation of dapagliflozin is associated with almost 10% additional quality-adjusted life year gain and greater clinical benefits.[27]

A consistent increase in haematocrit has been observed following the initiation of SGLT2i.[9,28,29] A post hoc analysis of the Empire HF trial assessed the early effects of empagliflozin on erythropoiesis and iron metabolism in HFrEF patients. Overall, 190 patients were randomized 1:1 to empagliflozin or placebo for 12 weeks. Increased erythropoietin and reduced hepcidin were reported in the treated group, consistent with an anti-inflammatory effect, while no changes in erythroferrone were observed.[30]

The efficacy of the selective cardiac myosin activator omecamtiv mecarbil seems to be greater in patients with more severe systolic HF.[31–34] A pre-specified analysis of GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in HF) trial investigated the effect of treatment according to baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations (≤ median, > median), excluding individuals with atrial fibrillation/flutter. There was an interaction between treatment effects and NT-proBNP levels, examined as a continuous variable, with greater effect of omecamtiv mecarbil on the primary outcome in patients with a higher baseline NT-proBNP.[35]

Hypertrophic cardiomyopathy

Mavacamten, a selective allosteric inhibitor of cardiac myosin ATPase, improved exercise capacity and symptoms in patients with obstructive hypertrophic cardiomyopathy (oHCM).[36] Subgroup analyses by beta-blocker use were performed in patients with oHCM from the EXPLORER-HCM. Among patients enrolled, 75.3% were treated with beta-blockers. Mavacamten effectively improved symptoms, functional capacity and biomarker concentrations regardless of beta-blocker use. Beta-blockers affected chronotropic incompetence, influencing peak oxygen consumption and other heart rate-dependent measures.[37]

Devices

His-bundle pacing

The impact of His-bundle pacing on HF symptoms and exercise capacity was evaluated in the HOPE-HF (His Optimized Pacing Evaluated for Heart Failure) randomized, double-blind, cross-over trial. Patients with HFrEF, PR interval ≥200 ms and either QRS

≤140 ms or right bundle branch block had atrial and His-bundle leads implanted and were randomized to 6 months of pacing and 6 months of no-pacing. Pacing did not improve peak oxygen uptake but improved quality of life and symptoms, without adverse effects.[38]

Left ventricular assist device and aortic regurgitation

Uriel *et al.* reported the incidence, predictors and clinical correlates of *de-novo* aortic regurgitation (AR) in patients undergoing left ventricular assist device (LVAD) implantation using data from the MOMENTUM 3 trial portfolio (n = 918; HeartMate 3 [HM3], n = 465; HeartMate II [HMII], n = 453). At 2 years the rate of *de-novo* AR was lower with HM3 compared to the previous HMII. *De-novo* AR did not affect prognosis.[39,40]

Vaccination

The fear of adverse reactions often leads to vaccine hesitancy. Peikert *et al.*[41] examined the correlation between influenza vaccination-related adverse events and morbidity and mortality in patients with elevated cardiovascular (CV) risk. Compared to those without adverse events, patients experiencing mild to moderate adverse reactions presented a lower risk of CV hospitalization and all-cause mortality. Conversely, severe adverse reactions increased CV risk.

The administration of COVID-19 vaccination is recommended in HF patients.[42] Although generally safe, post-vaccine myocarditis was observed.[43,44] In a prospective study including 324 health workers receiving the fourth dose of the Pfizer-BioNTech vaccine, pain at injection site and fatigue were the most common adverse events. Vaccine-related myocardial injury, as assessed with high-sensitivity cardiac troponin during vaccine administration and 2–4 days afterward, was only found in 2 patients (0.62%), of whom one presented mild symptoms and the other was asymptomatic.[45]

References

1. Malek F, Gajewski P, Zymlinski R, Janczak D, Chabowski M, Fudim M, et al. Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial. *Eur J Heart Fail.* 2021;**23**:1134–43.
2. Riccardi M, Sammartino AM, Piepoli M, Adamo M, Pagnesi M, Rosano G, et al. Heart failure: an update from the last years and a look at the near future. *ESC Heart Fail.* 2022;**9**:3667–93.
3. Fudim M, Ponikowski PP, Burkhoff D, Dunlap ME, Sobotka PA, Molinger J, et al. Splanchnic nerve modulation in heart failure: mechanistic overview, initial clinical experience, and safety considerations. *Eur J Heart Fail.* 2021;**23**:1076–84.
4. Coats AJS, Abraham WT, Zile MR, Lindenfeld JA, Weaver FA, Fudim M, et al. Baroreflex activation therapy with the Barostim device in patients with heart failure with reduced ejection fraction: a patient level meta-analysis of randomized controlled trials. *Eur J Heart Fail.* 2022;**24**:1665–73.
5. Badrov MB, Keir DA, Tomlinson G, Notarius CF, Millar PJ, Kimmerly DS, et al. Normal and excessive muscle sympathetic nerve activity in heart failure: implications for future trials of therapeutic autonomic modulation. *Eur J Heart Fail.* 2023;**25**:201–10.
6. Bayes-Genis A, Aimo A, Jhund P, Richards M, de Boer RA, Arfsten H, et al. Biomarkers in heart failure clinical trials. A review from the Biomarkers Working Group of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2022;**24**:1767–77.
7. Mohebi R, Liu Y, van Kimmenade R, Gaggin HK, Murphy SP, Januzzi JL Jr. Inflammation across universal definition of heart failure stages: the CASABLANCA study. *Eur J Heart Fail.* 2023;**25**:152–60.
8. Nunez J, de la Espriella R, Minana G, Santas E, Llacer P, Nunez E, et al. Antigen carbohydrate 125 as a biomarker in heart failure: a narrative review. *Eur J Heart Fail.* 2021;**23**:1445–57.
9. Packer M. How can sodium-glucose cotransporter 2 inhibitors stimulate erythrocytosis in patients who are iron-deficient? Implications for understanding iron homeostasis in heart failure. *Eur J Heart Fail.* 2022;**24**:2287–96.
10. van Woerden G, van Veldhuisen DJ, Westenbrink BD, de Boer RA, Rienstra M, Gorter TM. Connecting epicardial adipose tissue and heart failure with preserved ejection fraction: mechanisms, management and modern perspectives. *Eur J Heart Fail.* 2022;**24**:2238–50.
11. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail.* 2021;**23**:352–80.
12. van der Hoef CCS, Boorsma EM, Emmens JE, van Essen BJ, Metra M, Ng LL, et al. Biomarker signature and pathophysiological pathways in patients with chronic heart failure and metabolic syndrome. *Eur J Heart Fail.* 2023;**25**:163–73.
13. Michou E, Wussler D, Belkin M, Simmen C, Strebel I, Nowak A, et al. Quantifying inflammation using interleukin-6 for improved phenotyping and risk stratification in acute heart failure. *Eur J Heart Fail.* 2023;**25**:174–84.
14. Guazzi M, Wilhelm M, Halle M, Van Craenenbroeck E, Kemps H, de Boer RA, et al. Exercise testing in heart failure with preserved ejection fraction: an appraisal through diagnosis, pathophysiology and therapy – A clinical consensus statement of the Heart Failure Association and European Association of Preventive Cardiology of the European Society of Cardiology. *Eur J Heart Fail.* 2022;**24**:1327–45.
15. Reddy YNV, Stewart GM, Obokata M, Koepp KE, Borlaug BA. Peripheral and pulmonary effects of inorganic nitrite during exercise in heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2021;**23**:814–23.
16. Sugumar H, Nanayakkara S, Vizi D, Wright L, Chieng D, Leet A, et al. A prospective STudy using invAsive haemodynamic measurements foLLowing catheter ablation for AF and early HFpEF: STALL AF-HFpEF. *Eur J Heart Fail.* 2021;**23**:785–96.
17. Omote K, Verbrugge FH, Sorimachi H, Omar M, Popovic D, Obokata M, et al. Central haemodynamic abnormalities and outcome in patients with unexplained dyspnoea. *Eur J Heart Fail.* 2023;**25**:185–96.
18. Lindberg F, Lund LH, Benson L, Dahlstrom U, Karlstrom P, Linde C, et al. Trajectories in New York Heart Association functional class in heart failure across the ejection fraction spectrum: data from the Swedish Heart Failure Registry. *Eur J Heart Fail.* 2022;**24**:2093–104.
19. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2022;**24**:4–131.
20. Savarese G, Lindenfeld J, Stolfo D, Adams K, Ahmad T, Desai NR, et al. Use of patient-reported outcomes in heart failure: from clinical trials to routine practice. *Eur J Heart Fail.* 2023;**25**:139–51.
21. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. *Eur J Heart Fail.* 2021;**23**:882–94.
22. Rosano GMC, Moura B, Metra M, Bohm M, Bauersachs J, Ben Gal T, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2021;**23**:872–81.
23. Tomasoni D, Fonarow GC, Adamo M, Anker SD, Butler J, Coats AJS, et al. Sodium-glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail.* 2022;**24**:431–41.
24. Seferovic PM, Polovina M, Adlbrecht C, Belohlavek J, Chioncel O, Goncalvesova E, et al. Navigating between Scylla and Charybdis: challenges and strategies for implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. *Eur J Heart Fail.* 2021;**23**:1999–2007.
25. Fauvel C, Bonnet G, Mullens W, Giraldo CIS, Meznar AZ, Barasa A, et al. Sequencing and titrating approach of therapy in heart failure with reduced ejection fraction following the 2021 European Society of Cardiology guidelines: an international cardiology survey. *Eur J Heart Fail.* 2023;**25**:213–22.
26. Becher PM, Schrage B, Ferrannini G, Benson L, Butler J, Carrero JJ, et al. Use of sodium-glucose co-transporter 2 inhibitors in patients with heart failure and type 2 diabetes mellitus: data from the Swedish Heart Failure Registry. *Eur J Heart Fail.* 2021;**23**:1012–22.

27. Miller RJ, Chew DS, Qin L, Fine NM, Chen J, McMurray JJ, et al. Cost-effectiveness of immediate initiation of dapagliflozin in patients with a history of heart failure. *Eur J Heart Fail.* 2023;**25**:238–47.
28. Ferreira JP, Anker SD, Butler J, Filippatos G, Iwata T, Salsali A, et al. Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR-Reduced. *Eur J Heart Fail.* 2022;**24**:708–15.
29. Docherty KF, Curtain JP, Anand IS, Bengtsson O, Inzucchi SE, Kober L, et al. Effect of dapagliflozin on anaemia in DAPA-HF. *Eur J Heart Fail.* 2021;**23**:617–28.
30. Fuchs Andersen C, Omar M, Glenthoj A, El Fassi D, Moller HJ, Lindholm Kurtzhals JA, et al. Effects of empagliflozin on erythropoiesis in heart failure: data from the Empire HF trial. *Eur J Heart Fail.* 2023;**25**:226–34.
31. Felker GM, Solomon SD, Claggett B, Diaz R, McMurray JJV, Metra M, et al. Assessment of omecamtiv mecarbil for the treatment of patients with severe heart failure: a post hoc analysis of data from the GALACTIC-HF randomized clinical trial. *JAMA Cardiol.* 2022;**7**:26–34.
32. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Effect of ejection fraction on clinical outcomes in patients treated with omecamtiv mecarbil in GALACTIC-HF. *J Am Coll Cardiol.* 2021;**78**:97–108.
33. Metra M, Pagnesi M, Claggett BL, Diaz R, Felker GM, McMurray JJV, et al. Effects of omecamtiv mecarbil in heart failure with reduced ejection fraction according to blood pressure: the GALACTIC-HF trial. *Eur Heart J.* 2022;**43**:5006–16.
34. Tomasoni D, Vishram-Nielsen JKK, Pagnesi M, Adamo M, Lombardi CM, Gustafsson F, et al. Advanced heart failure: guideline-directed medical therapy, diuretics, inotropes, and palliative care. *ESC Heart Fail.* 2022;**9**:1507–23.
35. Docherty KF, McMurray JJV, Claggett BL, Miao ZM, Adams KF, Arias-Mendoza A, et al. Efficacy of omecamtiv mecarbil in heart failure with reduced ejection fraction according to N-terminal pro-B-type natriuretic peptide level: insights from the GALACTIC-HF trial. *Eur J Heart Fail.* 2023;**25**:248–59.
36. de Boer RA, Heymans S, Backs J, Carrier L, Coats AJS, Dimmeler S, et al. Targeted therapies in genetic dilated and hypertrophic cardiomyopathies: from molecular mechanisms to therapeutic targets. A position paper from the Heart Failure Association (HFA) and the Working Group on Myocardial Function of the European Society of Cardiology (ESC). *Eur J Heart Fail.* 2022;**24**:406–20.
37. Wheeler MT, Jacoby D, Elliott PM, Saberi S, Hegde SM, Lakdawala NK, et al. Effect of beta-blocker therapy on the response to mavacamten in patients with symptomatic obstructive hypertrophic cardiomyopathy. *Eur J Heart Fail.* 2023;**25**:260–70.
38. Whinnett ZI, Shun-Shin MJ, Tanner M, Foley P, Chandrasekaran B, Moore P, et al. Effects of haemodynamically atrio-ventricular optimized His-pacing on heart failure symptoms and exercise capacity: the His Optimized Pacing Evaluated for Heart Failure (HOPE-HF) randomized, double-blind, cross-over trial. *Eur J Heart Fail.* 2023;**25**:274–83.
39. Uriel N, Milano C, Agarwal R, Lee S, Cleveland J, Goldstein D, et al. Incidence and clinical correlates of de-novo aortic regurgitation with a fully magnetically levitated left ventricular assist device: a MOMENTUM 3 trial portfolio analysis. *Eur J Heart Fail.* 2023;**25**:286–94.
40. Mehra MR, Cleveland JC Jr, Uriel N, Cowger JA, Hall S, Horstmanshof D, et al. Primary results of long-term outcomes in the MOMENTUM 3 pivotal trial and continued access protocol study phase: a study of 2200 HeartMate 3 left ventricular assist device implants. *Eur J Heart Fail.* 2021;**23**:1392–400.
41. Peikert A, Claggett BL, Kim K, Udell JA, Joseph J, Desai AS, et al. Association of post-vaccination adverse reactions after influenza vaccine with mortality and cardiopulmonary outcomes in patients with high-risk cardiovascular disease: the INVESTED trial. *Eur J Heart Fail.* 2023;**25**:299–310.
42. Rosano G, Jankowska EA, Ray R, Metra M, Abdelhamid M, Adamopoulos S, et al. COVID-19 vaccination in patients with heart failure: a position paper of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2021;**23**:1806–18.
43. Hirsch VG, Schallhorn S, Zwadlo C, Diekmann J, Langer F, Jonigk DD, et al. Giant cell myocarditis after first dose of BNT162b2 – a case report. *Eur J Heart Fail.* 2022;**24**:1319–22.
44. Heidecker B, Dagan N, Balicer R, Eriksson U, Rosano G, Coats A, et al. Myocarditis following COVID-19 vaccine: incidence, presentation, diagnosis, pathophysiology, therapy, and outcomes put into perspective. A clinical consensus document supported by the Heart Failure Association of the European Society of Cardiology (ESC) and the ESC Working Group on Myocardial and Pericardial Diseases. *Eur J Heart Fail.* 2022;**24**:2000–18.
45. Levi N, Moravsky G, Weitsman T, Amsalem I, Bar-Sheshet Itach S, Algur N, et al. A prospective study on myocardial injury after BNT162b2 mRNA COVID-19 fourth dose vaccination in healthy persons. *Eur J Heart Fail.* 2023;**25**:313–8.