Pulmonary hypertension, sarcoidosis, and inflammatory and dilated cardiomyopathy: new light shed on prevalence, mechanisms, and treatment

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This is a Focus Issue on heart failure and cardiomyopathies. The issue opens with a Clinical Research article on pulmonary embolism (PE).¹ In this article entitled ‘Chronic thrombo-embolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study’, Luca Valerio from the University Medical Center of the Johannes Gutenberg University in Mainz, Germany, and colleagues⁶ sought to systematically assess late outcomes of acute PE and to investigate the clinical implications of post-PE impairment (PPEI) fulfilling prospectively defined criteria. A prospective multicentre observational cohort study was conducted in 17 large-volume centres across Germany. Consecutive adult patients with confirmed acute symptomatic PE were followed with a standardized assessment plan and pre-defined visits at 3, 12, and 24 months. The co-primary outcomes were (i) a diagnosis of chronic thrombo-embolic pulmonary hypertension (CTEPH) and (ii) PPEI, a combination of persistent or worsening clinical, functional, biochemical, and imaging parameters during follow-up. A total of 1017 patients (45% women, median age 64 years) were included in the primary analysis. They were followed for a median duration of 732 days after PE diagnosis. CTEPH was diagnosed in 16 (1.6%) patients, after a median of 129 days; the estimated 2-year cumulative incidence was 2.3% (1.2–4.4%). Overall, 880 patients were evaluable for PPEI; the 2-year cumulative incidence was 16.0% (95% confidence interval 12.8–20.8%). The PPEI helped to identify 15 of the 16 patients diagnosed with CTEPH during follow-up [hazard ratio (HR) for CTEPH vs. no CTEPH 393]. Patients with PPEI had a higher risk of re-hospitalization and death as well as worse quality of life compared with those without PPEI.

The authors conclude that the cumulative 2-year incidence of CTEPH is 2.3%, but PPEI diagnosed by standardized criteria is frequent. These findings support systematic follow-up of patients after acute PE and may help to optimize guideline recommendations and algorithms for post-PE care. The contribution is accompanied by an Editorial by Irene M. Lang and Tyler Artner from the Medical University of Vienna in Austria.⁷ The authors highlight three issues. First, FOCUS confirms the study of Pengo et al. suggesting that higher risk PE (sPESI >0) carries a higher likelihood of becoming CTEPH. Consequently, a FOCUS-style clinical follow-up of elderly, intermediate to high risk PE serves as a model follow-up and should be recommended. Second, a comprehensive clinical follow-up is needed rather than a single test such as echocardiography or cardiopulmonary exercise testing (CPET) alone. Third, the FOCUS BioSeq substudy was initiated with prospective standardized pre-processing of plasma, serum, and urine with short-term storage at −80°C. Shipped, indexed, and quality-controlled biomaterials (proteins, DNA, and RNA) from ~350 unselected patients have been stored long term in a centralized, 2-D barcoded, and mirrored biobank at −80°C, which represents an invaluable biological resource that has not been collected ever before.

Pulmonary hypertension (PH) is a complex disease with multiple causes, a variable, but frequently poor prognosis, and limited forms of treatment.⁸–¹⁰ The presence of PH severely aggravates the clinical course of heart failure with preserved ejection fraction (HFpEF). In a Clinical Research article entitled ‘Riociguat in pulmonary hypertension and heart failure with preserved ejection fraction: the haemoDYNAMIC trial’, Theresa-Marie Dachs from the Medical University of Vienna in Austria, and colleagues note that to date, neither established heart failure therapies nor pulmonary vasodilators proved beneficial in this setting. This phase IIb, randomized, double-blind, placebo-controlled, parallel-group trial investigated the efficacy of chronic treatment with the oral soluble guanylate cyclase (sGC) stimulator riociguat in patients with PH-HFpEF.¹¹ Key eligibility criteria were mean pulmonary artery pressure ≥25 mmHg, pulmonary...
arterial wedge pressure >15 mmHg, and left ventricular ejection fraction (LVEF) ≥50%. Patients were randomized to oral treatment with riociguat or placebo (1:1). Patients started at 0.5 mg three times daily (t.i.d.) and were up-titrated to 1.5 mg t.i.d. The primary efficacy endpoint was change from baseline to week 26 in cardiac output (CO) at rest, measured by right heart catheterization. Primary efficacy analyses were performed on the full analysis set. Fifty-eight patients received riociguat and 56 patients placebo. After 26 weeks, CO increased by 0.37 ± 1.263 L/min in the riociguat group and decreased by 0.11 ± 0.921 L/min in the placebo group (least-squares mean difference: 0.54 L/min; \(P = 0.0142\)) (Figure 1). Five patients dropped out due to riociguat-related adverse events, but no riociguat-related serious adverse event or death occurred.

The authors conclude that the vasodilator riociguat improves haemodynamics in PH-HFpEF. Riociguat is safe in most patients but leads to more dropouts as compared with placebo. The contribution is accompanied by an Editorial by Johann Bauersachs and Karen M. Olsson from the Hanover Medical School in Germany. 12 Bauersachs and Olsson confirm that all in all, DYNAMIC does not suggest that riociguat will be a panacea for patients with PH-HFpEF. Nevertheless, further studies exploring the safety and efficacy of sGC stimulators may be warranted, particularly in patients with combined post- and pre-capillary pulmonary hypertension (Cpc-PH) PH-HFpEF. As there are no established surrogate endpoints for this condition, phase II studies will provide limited information, and larger phase III studies focusing on patient-endpoints seem more appropriate. Otherwise, the development of treatments for PH-HFpEF will continue to be more static than DYNAMIC.

PH and pulmonary vascular disease (PVD) are common and associated with adverse outcomes in left heart disease (LHD). In a Clinical Research article entitled 'Pulmonary vascular disease in pulmonary hypertension due to left heart disease: pathophysiological implications', Kazunori Omote from the Mayo Clinic and Foundation in Rochester, MN, USA, and colleagues sought to characterize the pathophysiology of PVD across the spectrum of PH in LHD. 13 Patients with PH-LHD [mean pulmonary artery (PA) pressure >20 mmHg and PA wedge pressure (PAWP) ≥15 mmHg] and controls free of PH or LHD underwent invasive haemodynamic exercise testing with simultaneous echocardiography, expired air and blood gas analysis, and lung ultrasound in a prospective study. Patients with PH-LHD were divided into isolated post-capillary PH (Ipc-PH) and Cpc-PH based upon pulmonary vascular resistance \([pulmonary\ vascular\ resistance\ (PVR)\ <3.0\ or\ ≥3.0\ Wood\ units\ (WU)]\). As compared with controls (n = 69) and Ipc-PH-LHD (n = 55), participants with Cpc-PH-LHD (n = 40) displayed poorer left atrial function and more severe right ventricular (RV) dysfunction at rest. With exercise, patients with Cpc-PH-LHD developed more severe lung congestion compared with both Ipc-PH-LHD and controls, which was associated with lower arterial O2 tension, reduced alveolar ventilation, decreased pulmonary O2 diffusion, and greater ventilation-perfusion mismatch.

The authors conclude that pulmonary vascular disease in LHD is associated with a distinct pathophysiological signature marked by greater exercise-induced lung congestion, arterial hypoxaemia, RV–PA
uncoupling, ventricular interdependence, and impairment in O2 delivery, impairing aerobic capacity. The contribution is accompanied by an Editorial by Marius M. Hoepner from the Hannover Medical School in Mainz, Germany and Stephan Rosenkranz from the Cologne Cardiovascular Research Center (CCRC), Germany. The authors note that in a seminal paper published in 1952, Paul Wood wrote in the section on mitral stenosis that ‘the increased resistance on the arterial side protected the pulmonary venous system from developing unduly high pressures on exertion and excitement; thus symptoms due to pulmonary venous congestion were far less evident in this group. The protection afforded by this type of pulmonary hypertension is at the expense of a diminished cardiac output and excessive strain on the right ventricle. Thus patients complained about fatigue and tended to develop functional tricuspid incompetence and congestive heart failure’. Wood continued stating that ‘clinically, active or protective pulmonary hypertension of this sort could be recognized in cases of mitral stenosis by the following features: (i) cessation of pulmonary congestive symptoms including … pulmonary oedema’. Hoepner and Rosenkranz conclude that the pathophysiology of HF is complex, especially during exercise, and, even 70 years after Paul Wood published his observations, we still do not fully understand it. Thanks to advanced technologies and clinical researchers capable of using and interpreting them, we are making further progress.

It is well recognized that sodium–glucose co-transporter 2 (SGLT-2) inhibitors improve the outcomes of HF. Empagliflozin is known to reduce serum uric acid (SUA), but the relevance of this effect in patients with HF is unclear. In a Clinical Research article entitled ‘Uric acid and sodium–glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial’, Wolfram Doehner from the Charité Universitätsmedizin in Berlin, Germany, and colleagues aimed to investigate the effect of empagliflozin on SUA levels and the therapeutic efficacy of empagliflozin in relation to SUA. The association between SUA and the composite primary outcome of cardiovascular death or hospitalization for worsening HF, its components, and all-cause mortality was investigated in 3676 patients of the EMPEROR-Reduced trial (98.6% of the study cohort). The treatment effect of empagliflozin was studied in relation to SUA as the continuous variable, to clinical hyperuricaemia (SUA >5.7 mg/dL for women, >7.0 mg/dL for men), and in subgroups of patients of tertiles of SUA. Hyperuricaemia was prevalent in 53% of patients, with no sex differences. Elevated SUA (highest tertile, mean SUA 9.38 ± 1.49 mg/dL) was associated with advanced severity of HF and with the worst outcomes (composite outcome, HR 1.64; cardiovascular mortality, HR 1.98; all-cause mortality, HR 1.8, all P < 0.001) in multivariate adjusted analyses, as compared with the lowest tertile. SUA was reduced following treatment with empagliflozin at 4 weeks (vs. placebo: −1.12 ± 0.04 mg/dL, P < 0.0001) and remained lower throughout follow-up, with a similar reduction in all pre-specified subgroups. Empagliflozin reduced events of clinically relevant hyperuricaemia (acute gout, gouty arthritis, or initiation of anti-gout therapy) by 32% (HR 0.68, P = 0.004). The beneficial effect of empagliflozin on the primary endpoint was independent of baseline SUA (HR 0.76, P < 0.001) and of the change in SUA at 4 weeks (HR 0.81, P = 0.012). As a hypothesis-generating finding, an interaction between SUA and treatment effect suggested a benefit of empagliflozin on mortality (cardiovascular and all-cause mortality) in patients with elevated SUA (P for interaction = 0.005 and = 0.011, respectively).

The authors conclude that hyperuricaemia is common in HF and is an independent predictor of advanced disease severity and increased mortality. Empagliflozin induces a rapid and sustained reduction of SUA levels and of clinical events related to hyperuricaemia. The benefit of empagliflozin on the primary outcome is observed independently of SUA. The manuscript is accompanied by an Editorial by Isla S. Mackenzie and Thomas M. MacDonald from the University of Dundee in the UK. The authors conclude that the place of empagliflozin or dapagliflozin therapy in patients already treated for gout but without HF could also be explored further. Perhaps future studies should investigate whether these SGLT-2 inhibitors improve outcomes in patients with treated gout and high cardiovascular risk. Added to best gout prophylaxis therapy, SGLT-2 inhibitors may improve gout outcomes in the most common inflammatory arthritis in men. Might they also improve cardiovascular outcomes?

Sarcoidosis is a systemic granulomatous disease of unknown cause with various clinical presentations that can affect any organ. Cardiac sarcoidosis (CS) is considered to be clinically apparent in only 5% of patients with systemic sarcoidosis; however, cardiac granulomas are found more often at autopsy. Indeed, recent advances in cardiac imaging techniques, such as cardiac magnetic resonance (CMR) imaging and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), have shown high accuracy for detecting CS. According to the studies using CMR and FDG-PET, cardiac involvement is more common than indicated in previous reports, with a rate as high as 30%. Although contemporary data suggest that survival may not be as poor as previously thought, patients with CS are known to have a poorer prognosis than patients with sarcoidosis without cardiac involvement. However, the characteristics and prognosis of patients with CS have yet to be clarified, as there are few multicentre studies, with a limited number of patients in each study. In a Clinical Research article entitled ‘Risk stratification of patients with cardiac sarcoidosis: the ILLUMINATE-CS registry’, Takeru Nabeta from the Kitasato University School of Medicine in Sagamihara, Japan and colleagues evaluated the prognosis and its predictors of cardiac CS. Patients from a retrospective multicentre registry, diagnosed with CS between 2001 and 2017 based on the 2016 Japanese Circulation Society or 2014 Heart Rhythm Society criteria, were included. The primary endpoint was a composite of all-cause death, hospitalization for HF, and documented fatal ventricular arrhythmia events (FVAE), each constituting exploratory endpoints. Among 512 registered patients, 148 combined events (56 HF hospitalizations, 99 documented FVAE, and 49 all-cause deaths) were observed during a median follow-up of 1042 days. The 10-year estimated event rates for the primary endpoint, all-cause death, HF hospitalizations, and FVAE were 48, 18, 21, and 32%, respectively. On multivariable Cox regression, a history of ventricular tachycardia (VT) or fibrillation (HR 2.53, P < 0.001), log-transformed brain natriuretic peptide (BNP) levels (HR 1.28, P = 0.008), LVEF (HR 0.94 per 5% increase, P = 0.046), and post-diagnosis radiofrequency ablation for VT (HR 2.65, P = 0.045) independently predicted the primary endpoint.

The authors conclude that although mortality is relatively low in CS, adverse events are common, mainly due to FVAE. Patients with low LVEF, with high BNP levels, with VT/fibrillation history, and requiring ablation to treat VT are at higher risk. The contribution is accompanied by an Editorial by Benjamin Meder and Jan Koelemen from the University of Heidelberg in Germany. The authors conclude that no prospective, randomized, and controlled clinical trial has hitherto been published for CS. Recently some trials comparing different immunosuppressive therapy regimes have been initiated, with results to be awaited with great excitement in the coming years.

In a Clinical Research article entitled ‘Immunosuppressive therapy in virus-negative inflammatory cardiomyopathy:...
20-year follow-up of the TIMIC trial, Cristina Chimenti from the Sapienza University of Rome, Italy and colleagues evaluated long-term results of the Tailored Immunosuppression in virus-negative Inflammatory Cardiomyopathy (TIMIC) trial. Eighty-five patients with endomyocardial biopsy-proven virus-negative chronic inflammatory cardiomyopathy were enrolled in the randomized, double-blind, placebo-controlled TIMIC trial and received prednisone and azathioprine (n = 43) or placebo (n = 42) for 6 months. Immunosuppressive treatment promoted an improvement in cardiac function in 88% of the cases compared with none of the patients in the placebo group, which were switched to a 6-month immunosuppressive therapy at the end of the 6-month study period. Long-term (up to 20 years) clinical outcomes of the whole cohort of 85 patients originally enrolled in the TIMIC trial (Group A) were compared with those of a 1:2 propensity score-matched control cohort of patients untreated with the TIMIC protocol (Group B) and followed for a comparable period of time. The primary outcome was a composite of cardiovascular death and heart transplantation. At long-term follow-up, the risks of cardiovascular death (HR 6.77) and heart transplantation (HR 7.92) were significantly higher in Group B patients. Group A showed a persistent improvement in the LVEF compared with Group B (HR 7.24). A higher number of Group B patients underwent implantable cardioverter defibrillator implantation. The incidence of recurrent myocarditis was similar between groups, and patients with evidence of a recurrent cardiac inflammatory process promptly responded to a TIMIC protocol application.

The authors conclude that virus-negative inflammatory cardiomyopathy benefits from immunosuppressive therapy even after long-term follow-up. Recurrence appears to respond to a new TIMIC protocol application. The contribution is accompanied by an Editorial by Heinz-Peter Schultheiss from the Department of Cardiology Institute of Cardiac Diagnostics and Therapy and Felicitas Escher from the Charité-Universitätsmedizin Berlin in Germany. The authors highlight the two most important lessons learned from the TIMIC study. First, a specific and causal treatment adapted to endomyocardial biopsy (EMB)-based pathophysiological characterized cardiomyopathy forms leads to a significant clinical improvement and a better prognosis of the patients. Secondly, an individual and more differentiated selection of therapeutic candidates is required in this setting. The path to disease-specific, causal, and personalized treatment requires in-depth clinical, immunological, and virological phenotyping, including differential immune response testing with accurate immune cell typing, and identification of novel biomarkers (e.g. TLR3/TLR4, microRNA profiling, cytokine measurements, specific high titre autoantibody types, as well as gene expression profiling). This is the prerequisite for specific individualized immunosuppressive or antiviral treatment, future microRNA-based strategies, or targeted cytokine treatment. To address this clinical need, advanced diagnostics and guidelines are required, to optimize the management of this disease using a personalized treatment strategy.

The issue also contains the Translational Research article ‘Serine biosynthesis as a novel therapeutic target for dilated cardiomyopathy’ by Isaac Perea-Gil from the Stanford University School of Medicine in California, USA, and colleagues. Using patient-specific induced pluripotent stem cell (iPSCs) carrying a pathogenic TNNT2 gene mutation (p.R183W) and CRISPR-based genome editing, a faithful dilated cardiomyopathy (DCM) model was developed in vitro. An unbiased phenotypic screening in TNNT2 mutant iPSC-derived cardiomyocytes (iPSC-CMs) with small molecule kinase inhibitors (SMKIs) was performed to identify novel therapeutic targets. Two SMKIs, Gö 6976 and SB 203580, were discovered whose combinatorial treatment rescued contractile dysfunction in DCM iPSC-CMs carrying gene mutations.
mutations of various ontologies (TNNT2, TTN, LMNA, PLN, TPM1, and LAMA2). The combinatorial SMKI treatment up-regulated the expression of genes that encode serine, glycine, and one-carbon metabolism enzymes, and significantly increased the intracellular levels of glucose-derived serine and glycine in DCM iPSC-CMs. Furthermore, the treatment rescued the mitochondrial respiration defects and increased the levels of the tricarboxylic acid cycle metabolites and ATP in DCM iPSC-CMs. Finally, the rescue of the DCM phenotypes was mediated by the activating transcription factor 4 (ATF4) and its downstream effector genes, phosphoglycerate dehydrogenase (PHGDH), which encodes a critical enzyme of the serine bio-synthesis pathway, and Tribbles 3 (TRIB3), a pseudokinase with pleiotropic cellular functions (Figure 2).

The authors conclude that this study establishes a phenotypic screening platform using DCM iPSC-CMs for therapeutic target discovery. A combination of SMKIs ameliorates contractile and metabolic dysfunction in DCM iPSC-CMs mediated via the ATF4-dependent serine biosynthesis pathway. Together, these findings suggest that modulation of serine biosynthesis signalling may represent a novel genotype-agnostic therapeutic strategy for genetic DCM. The contribution is accompanied by an Editorial by Thomas Eschenhagen from the University Medical Center Hamburg Eppendorf in Germany.29 Eschenhagen notes that the present study is an excellent example of how to harness the potential of human iPSC technology, it provides exciting evidence for a novel therapeutic target that, even if it will not be the exact combination of kinase inhibitors, could be directly addressed by small molecule inhibitors.

The issue is also complemented by a two Discussion Forum contributions. In an article entitled ‘Atrial functional assessment at rest and during exercise stress in left ventricular diastolic dysfunction’, Sören Backhaus and Andreas Schuster from the University Medical Center Hamburg Eppendorf in Germany comment on the previous publication entitled ‘Cardiac magnetic resonance identifies raised left ventricular filling pressure: prognostic implications’ by Pankaj Garg from the The University of Sheffield in the UK.30,31 Pankaj Garg et al. respond in a separate comment.32 The editors hope that this issue of the European Heart Journal will be of interest to its readers.

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