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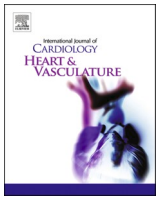

Editorial

The inflammatory and nutritional status in patients with dilated cardiomyopathy: Different impact for distinct phenogroups?

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This editorial refers to 'Prognostic value of preoperative high-sensitivity C-reactive protein to albumin ratio in patients with dilated cardiomyopathy receiving pacemaker therapy: A retrospective two-center study in China', by Pan et al [1].

Dilated cardiomyopathy (DCM) is the most common non-ischemic cardiomyopathy and the most frequent cause of heart failure in patients under 40 years of age [2]. While clinical presentation and aetiological landscape of DCM is manifold, current treatment options focus on general heart failure management only. The first *European Society of Cardiology* guidelines for the management of cardiomyopathies were published in 2023 and provide specific diagnostic definitions in DCM, further including the new 'non-dilated left ventricular cardiomyopathy' (NDLVC) phenotype [3]. While an individualized treatment approach is forwarded, current pharmacological and device-based treatment recommendations for DCM still align with the general heart failure recommendations, mainly guided on left ventricular ejection fraction (LVEF) [4]. Recommendations still fail to consider genetics, epigenetics, inflammation, haematopoiesis and extended functional parameters including diastolic heterogeneity, amongst others. An adequate consideration of the underlying pathophysiological heterogeneity in DCM would require novel diagnostic frameworks, targeted research and adapted treatment approaches to bridge the gap in individualized care. Thus, there remains a vast, yet untapped potential for advancing both therapeutic and diagnostic strategies for DCM patients.

Recently, a two-hit hypothesis proposed that DCM develops due to the coexistence of an underlying genetic abnormality and additional driving factors (e.g., myocarditis, clonal haematopoiesis and others) rather than by monogenetic variants alone (Fig. 1) [2,5]. Various driving factors have been identified that, often in conjunction with a pathogenic background, culminate in clinically manifest DCM. However, the complex genotype-phenotype patterns are still incompletely understood. Currently pragmatic and non-individualized treatment regimens are used in routine clinical practice.

More than 50 genes are considered pathogenic (P) or likely pathogenic (LP) for DCM development. The *Lamin A/C* gene encoding for cardiac sarcomeres and *truncating titin gene variants* (*TTNtv*) are prominent examples, with current evidence showing a penetrance of these genes in up to 40 % of DCM cases [6]. Until now, no clinically implemented gene-based treatment options exist, but initial approaches showed promising results regarding utilisation of microRNA-based therapies (NCT04045405) [7]. Clonal haematopoiesis (CH), which is defined as clonal expansion of somatic mutations in small circulating clones of hematopoietic stem cells, negatively influence the development and time course of various cardiovascular diseases including DCM [8]. CH is an under-reported disease modifier, affecting the clinical course of individuals of all age, which could have a potential and significant impact on anti-inflammatory treatment regimes in selected patient cohorts [8]. There is evidence that diastolic dysfunction could pose a high risk of an adverse clinical outcome independently of systolic function in DCM [9].

Recently, first efforts were made to cluster individual DCM patients based on pathophysiological similarities, instead solely by clinical functional characteristics, with the ultimate goal to compensate for pathophysiological differences and to allow an individualized therapy [10]. This led to the identification of four distinct phenogroups (PGs; PG1: Mild-systolic dysfunction, PG2: autoimmune, PG3: cardiac arrhythmias, PG4: severe systolic dysfunction), which share common metabolic and transcriptomic pathways [10]. This PGs could be replicated in different DCM cohorts across Europe, leading to a dedicated decision tree for routine clinical practice [10].

In a recent issue of this journal, Pan and colleagues provided new evidence on the importance of inflammatory markers and nutritional status in patients with DCM undergoing device therapy [1]. Elevated high-sensitivity C-reactive protein (hs-CRP) levels and low body mass

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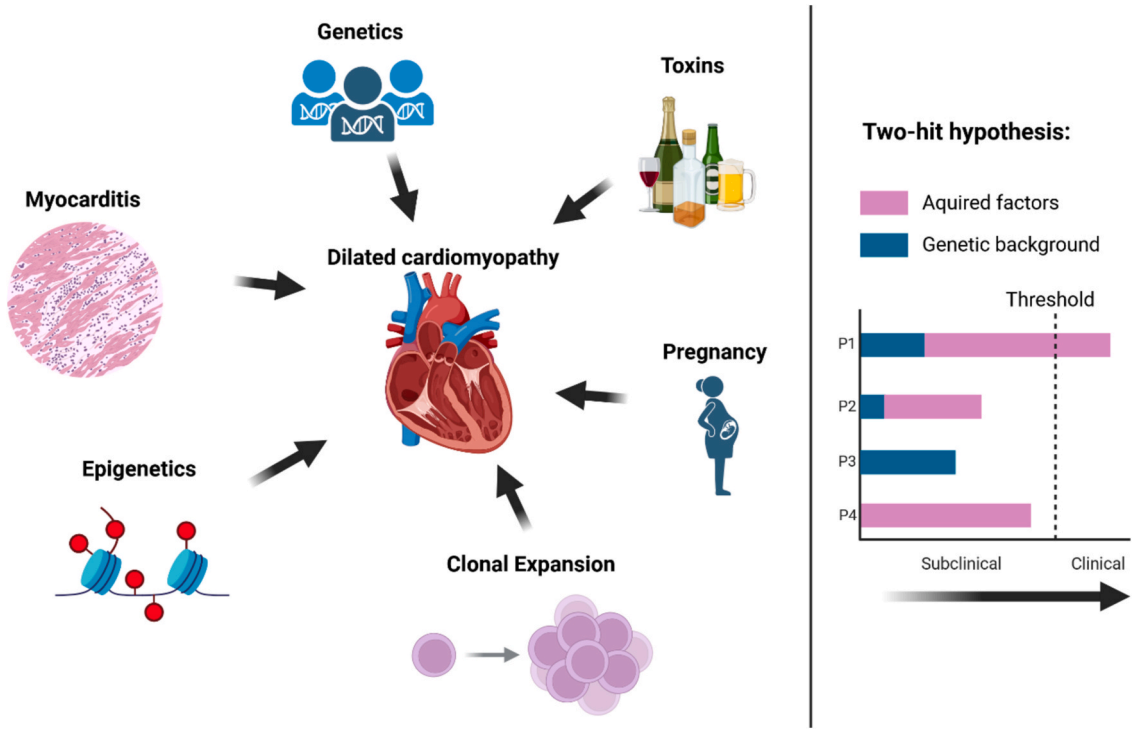

Fig. 1. Genetic and acquired aetiological causes potentially leading to (sub-)clinical manifest dilated cardiomyopathy (DCM). The illustration showing the specific disease thresholds is based on the two-hit hypothesis for DCM manifestation and was modified according to the original presentation by Verdonschot et al. [2]. P1-4: exemplary patients 1–4. Created with BioRender.com.

index (BMI), indicative of a pro-inflammatory state and impaired nutritional status, were associated with adverse outcomes in DCM patients [10]. Low BMI and high hs-BNP also link DCM patients to the autoimmunity phenogroup, which consistently exhibited the poorest prognosis among phenogroups with shared transcriptomic features [10]. Notably, hs-CRP and BMI emerged as pivotal factors distinguishing the autoimmunity phenogroup from others, including the phenogroup associated with severe systolic dysfunction, which demonstrated the second-worst outcomes [10].

While hs-CRP-guided anti-inflammatory therapy was proposed recently for atherosclerotic disease [11], routine assessment of hs-CRP to serum albumin ratio (CAR) is currently not used in clinical practice for risk assessment in patients with DCM. Here, the authors provided evidence on the potential role of hs-CRP as a surrogate of cardiac inflammasome activity [1]. The authors were able to determine a relevant cut-off value to characterize patients with elevated CAR into high- or low-CAR groups. Primary outcomes including major cardiovascular adverse events were associated with high-CAR. To address the yet unknown implications of a pro-inflammatory state on left ventricular reverse remodelling, Pan et al. [1] linked an elevated CAR with adverse remodelling. This sheds new light on the potential roles cardiac- and vascular inflammasomes in patients with DCM or other types of heart failure.

In the context of DCM, autoimmunity and myocarditis are known and extensively discussed drivers for increased hs-CRP levels. Autoimmunity was investigated as potential causative factor in animal models, but remains highly controversial due to high heterogeneity of the DCM phenotypes [5,12]. Cardiac autoantigens could be of interest for further research in selected patients within the same transcriptomic phenogroup. Besides autoimmunity, myocarditis is proven to induce acute and chronic inflammatory reactions in DCM. Clinically manifested myocarditis *per se* is a disease with a heterogenous clinical phenotype due to various aetiologies including viral infection, autoimmune disorders and cancer immunotherapy [13]. Adenoviruses, enteroviruses, erythroparvoviruses, human herpes viruses and influenza viruses are the most common cardiotropic viral infections in DCM [14]. At present, antiviral therapies and anti-inflammatory treatment regimens are not generally recommended but can be considered depending on the state of inflammation, the causative aetiology, the type of virus and number of viral copies [15].

Despite current guideline recommendations, many patients experience poor outcomes including malignant arrythmias and structural change following CRT or ICD implantation [1,3,4]. Pan and colleagues [1] now propose that a stricter adherence to heart failure medication could pave patients' way to more favourable clinical outcomes and that an interdisciplinary approach including nutritionists, cardiologists, and immunologists could aid in a more patient-centered treatment approach. In addition, integrating the expertise of a human geneticist could provide valuable insights into the genetic predispositions influencing patients' response to heart failure therapies, further personalizing treatment strategies. Arguably, an interdisciplinary assessment including more frequent follow-up investigations of left ventricular reverse remodelling and better nutritional states preoperatively will lead to substantial long-term strategies.

To provide a more holistic understanding of CAR for clinical DCM therapy, phenotyping and inclusion into previously reported, transcriptome-based PGs would have been more feasible. CAR could serve as novel biomarker for the prognostic assessment of patients with DCM undergoing device therapy, however inflammatory and nutritional status are still not yet proven to be a prognostic marker for all-commers with DCM. Finally, it remains elusive whether monitoring of inflammatory markers or nutritional state may serve as risk factor for all patients with DCM undergoing device therapy, or if the use of CAR should be restricted to dedicated patients exhibiting shared transcriptomic characteristics. Undoubtedly, further research is needed to refine the currently used "one-size-fits-all" approach regarding DCM therapy and risk assessment. Specifically, the role of individualized transcriptomic signatures must be explored to unravel new therapeutic strategies and address the intricate mechanisms underpinning heart failure in DCM patients.

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CRediT authorship contribution statement

Tobias Lerchner: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft. **Anke Fender:** Conceptualization, Data curation, Investigation, Software, Writing – review & editing. **Dobromir Dobrev:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Tienush Rassaf:** Conceptualization, Project administration, Resources, Software, Supervision, Writing – review & editing. **Lars Michel:** Conceptualization, Project administration, Software, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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