Personalised Medicine For Dilated Cardiomyopathy

Perry M Elliott

University College London

United Kingdom

Key Words: dilated Cardiomyopathy, machine learning, genetic, myocarditis

Word count 1491 (including references)

Address for Correspondence:

Professor Perry Elliott

Institute of Cardiovascular Science

University College London

Paul O'Gorman Building

72 Huntley St.

London WC1E 6AG

United Kingdom

Tel: + 44 (0) 20 7 679 6500

Email: perry.elliott@ucl.ac.uk

Orcid: https://orcid.org/0000-0003-3383-3984

We have to remember that what we observe is not nature in itself, but nature exposed to our method of questioning.

Werner Heisenberg [1]

Healthcare in Western economies is moving rapidly towards systems that aspire to personalised or stratified medicine in which emergent diagnostic technologies, molecular biology, data analysis and real time monitoring are used to better target therapies and thereby improve health, social outcomes and cost efficiency. New scientific disciplines such as genomics, transcriptomics, proteomics and metabolomics are key components of personalised medicine as they provide mechanistic insights that can be used to separate patients into specific groups amenable to tailored therapy at an earlier stage than is currently possible. However, the potential of these sciences to transform human health can only be realised by integrating biological data into disease models that reflect the complex clinical phenotypes seen in patients. This is particularly true for people with genetic diseases of the heart and blood vessels who have diverse and evolving phenotypes throughout their life-course.

In this edition of *The Journal*, Verdonschot and colleagues report a study of 795 patients with dilated cardiomyopathy (DCM) recruited from the Maastricht Cardiomyopathy Registry, in which machine learning was used to analyse multiple data points including clinical, genetic, imaging and histological parameters [2]. The analysis revealed four mutually exclusive clinically distinct 'phenogroups' that were summarised under the following headings: mild systolic dysfunction; auto-immune; genetic and arrhythmia; and severe systolic dysfunction. A subgroup analysis using RNA-sequencing of cardiac samples from 91 patients revealed different transcriptomic profiles for each phenotype cluster with increased pro-inflammatory signalling in the auto-immune group, pro-fibrotic signalling in the genetic and arrhythmic group, and altered metabolic gene expression in the severe systolic failure group. Event-free survival differed among the four phenogroups and decision tree modelling identified four clinical parameters (autoimmune disease, LVEF, atrial fibrillation and kidney function) that could be used to place patients from two independent validation cohorts into one of the four phenogroups. The authors conclude that these data provide a basis for a 'personalised treatment approach'.

Heart failure is a global health challenge affecting millions of people. Over the past 30 years, considerable progress has been made in reducing the morbidity and mortality associated with ventricular dysfunction through the adoption of lifestyle modifications and evidence based therapies. However, despite the success of this approach, cures for heart failure remain elusive.

Heart failure is attributed to idiopathic or non-ischaemic DCM in up to one-third of cases. A substantial proportion of patients with DCM have familial disease, with detectable pathogenic genetic variants in just under 50% of those with a family history and 25% of those with sporadic disease.[3] Myocarditis is reported in up to 40% of cases of chronic DCM and is associated with a worse prognosis.[4]

The paper by Verdonschot et al reassuringly confirms the strong familial component and the role autoimmunity in DCM [5]; the contribution of the third player in DCM–viral persistence–was not assessed. The results show that prognosis in DCM tracks with conventional markers of disease severity such as LVEF and impaired renal function, but also demonstrates that there are individuals–particular those with genetic forms of arrhythmic DCM–that experience adverse events even in the presence of mild to moderate LV systolic impairment. The RNA analysis shows that changes in molecular pathways in the myocardium vary according to aetiology and stage of disease.

Modern physicians are being overwhelmed by mountains of information in various guises, and so it is understandable that techniques such as machine learning are being used to identify and display patterns or relationships in data that are otherwise hidden to human scrutiny. However, the application of machine learning and other aspects of artificial intelligence in clinical practice still requires wisdom and circumspection based on an appreciation of the strengths and limitations of computational analyses and an understanding of clinical methods by those that design them.

In figure 1, I attempt to show how an enhanced clinical workflow can better inform diagnosis and treatment without recourse to a computer algorithm. The process is based on a relatively brief interview with a patient coupled with a few readily available tests,

but the description of aetiology and phenotype is deliberately 'multiparametric' (using an approach to classification proposed by Eloisa Arbustini and colleagues in 2015 [6]). The complete 'data-set' generated by a systematic clinical enquiry is linked to a personalised treatment plan and supporting evidence where available. The potential of artificial intelligence in this context is to refine already detailed clinical phenotypes and to link them with biological insights that suggest new therapeutic targets.

The opening quote in this editorial is a reference to the description of atomic events, but it is a useful reminder of the limits of human perception and the importance of a complete contextual analysis. Most heart failure therapies are based on an implicit assumption that all participants have the same phenotype, usually defined by a single variable of interest (LV ejection fraction). This simplification is useful for trial design as results can be described in terms of an average change in preselected groups, but it also obscures the full range of individual responses. This paper provides further inspiration to those advocating more personalised approaches to the diagnosis and treatment of cardiovascular diseases.

References

1. *Heisenberg, Werner (1958). Physics and philosophy: the revolution in modern science. Harper. p. 58.*

2. Verdonschot et al. EHJ 2020 xxxx

3. Haas J, Frese KS, Peil B, Kloos W, Keller A, Nietsch R, Feng Z, Müller S, Kayvanpour E, Vogel B, Sedaghat-Hamedani F, Lim WK, Zhao X, Fradkin D, Köhler D, Fischer S, Franke J, Marquart S, Barb I, Li DT, Amr A, Ehlermann P, Mereles D, Weis T, Hassel S, Kremer A, King V, Wirsz E, Isnard R, Komajda M, Serio A, Grasso M, Syrris P, Wicks E, Plagnol V, Lopes L, Gadgaard T, Eiskjær H, Jørgensen M, Garcia-Giustiniani D, Ortiz-Genga M, Crespo-Leiro MG, Deprez RH, Christiaans I, van Rijsingen IA, Wilde AA, Waldenstrom A, Bolognesi M, Bellazzi R, Mörner S, Bermejo JL, Monserrat L, Villard E, Mogensen J, Pinto YM, Charron P, Elliott P, Arbustini E, Katus HA, Meder B.

Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J. 2015;36:1123-35a.

4. Caforio, A. L. P. et al. 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;4:2636–2648

5. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, Duboc D, Gimeno J, de Groote P, Imazio M, Heymans S, Klingel K, Komajda M, Limongelli G, Linhart A, Mogensen J, Moon J, Pieper PG, Seferovic PM, Schueler S, Zamorano JL, Caforio AL, Charron P. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J. 2016;37(23):1850-8.

6. Arbustini E, Narula N, Dec GW, Reddy KS, Greenberg B, Kushwaha S, Marwick T, Pinney S, Bellazzi R, Favalli V, Kramer C, Roberts R, Zoghbi WA, Bonow R, Tavazzi L, Fuster V, Narula J. The MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathy: endorsed by the World Heart Federation. J Am Coll Cardiol. 2013;62(22):2046-72.

Conflicts of Interest

Consultancies and speaker fees from Pfizer, MyoKardia, Sanofi Genzyme, Alnylam.

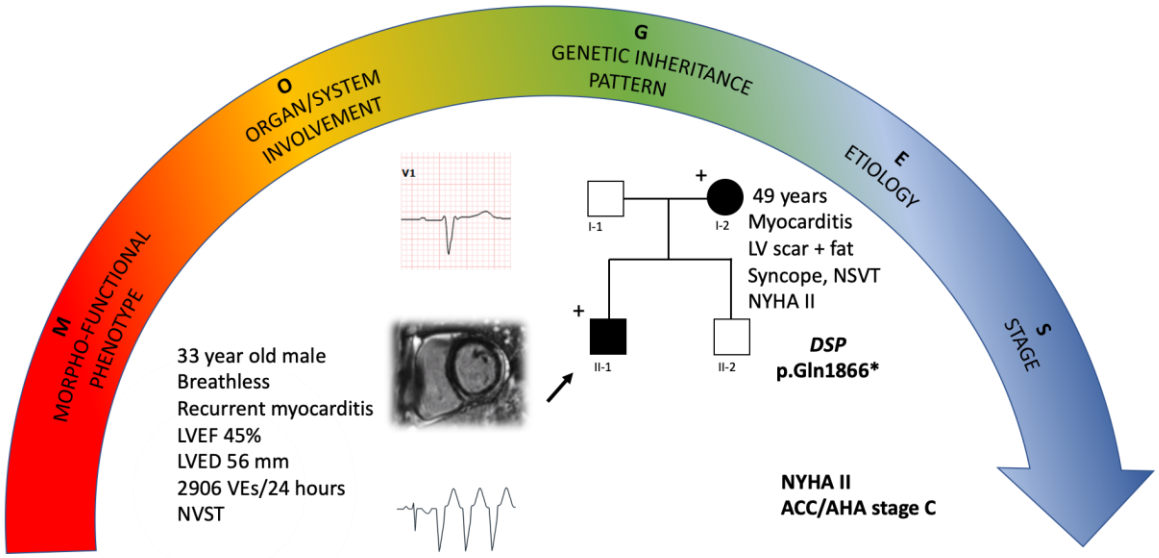
Acknowledgements

I am grateful to Drs Akhtar, Protonotarios and Cannie for their assistance in preparing this document.

Figure legend: Enhanced clinical work flow for a patient with dilated cardiomyopathy.

This figure shows how a multiparametric approach to clinical phenotyping linked with targeted diagnostics including genetic testing can be used to create highly specific phenotypes that facilitate personalised treatment plans. The approach to disease description is based on the MOGES system proposed by Arbustini and colleagues in 2015 [6]. MOGES addresses five simple attributes of a cardiomyopathic disorder: morphofunctional characteristic (M), organ involvement (O), genetic or familial inheritance pattern (G), and an explicit etiological annotation (E) with details of genetic defect or underlying disease/cause; information about the functional status (S). In this worked example, the diagnosis transforms from a simplistic categorisation based on symptoms and LV ejection fraction to a complex genetic disorder characterised by myocardial scar and a propensity to ventricular arrhythmia. The approach applies equally to familial and non-familial diseases such as myocarditis.

Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; ASHG=American Society of Human Genetics; DCM=dilated cardiomyopathy; DSP=desmoplakin; EPS=electrophysiological study; HF=heart failure; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction; LVED=left ventricular end-diastolic dimension); NSVT=non sustained ventricular tachycardia; NYHA=New York Heart Association; TAD=terminal activation duration; VE=ventricular ectopics



PHENOTYPE:	LV systolic impairment and dilatation	Prolonged TAD Sub epicardial LV scar Ventricular arrhythmia	Autosomal dominant arrhythmic cardiomyopathy

$M_D\ O_H\ G_{AD}E_{G\text{-}DSP\ p.Gln1866}\text{•}S_{II}$

	FAMILY SCREENING/PREGNANCY/PREIMPLANTATION GENETIC TESTING	LIFESTYLE	RISK OF LIFE THREATENING ARRHYTHMIA	MEDICAL THERAPY/STROKE PREVENTION	DISEASE SPECIFIC THERAPY
Level of Evidence	DSP variant in proband classified as pathogenic by ASHG criteria	Observational studies showing association between intense exercise and disease progression.	Cohort studies indicate high risk in patients with syncope, extensive disease, ventricular arrhythmia	No specific data on drug therapy in DSP mutations so extrapolated from pivotal HF trials. Frequent symptomatic VEs possible detrimental effect on LVEF	No specific treatment
Recommendation	**Offer cascade testing to 1° relatives**	**Avoid competitive /endurance exercise**	**Counsel on ICD implantation.** **S-ICD possible option**	**ß-blocker.** **EPS and ablation for frequent VEs if a dominant morphology** **Conventional prognostic heart failure medication.**	**Provide advice on 'hot-phase' symptoms**