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EDITORIAL COMMENT

# DNA Damage Prediction Tool in Dilated Cardiomyopathy

## Don't Go Breaking My Heart*

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Dilated nonischemic cardiomyopathy (DCM) is the most common indication for heart transplantation (1). DCM is characterized by systolic dysfunction and enlargement of 1 or both ventricles. The causes of DCM vary widely and include idiopathic, genetic, pregnancy, toxin, infectious, metabolic/endocrine, inflammatory/infiltrative/autoimmune, and neuromuscular disease mechanisms (2). There are additional mechanisms that can lead to cardiomyopathy which overlap phenotypically with DCM, including ischemic cardiomyopathy, hypertensive heart disease, and athlete's heart. The wide-ranging phenotypic overlap and diverse mechanisms which can result in DCM make the management challenging, especially with respect to predicting which individual patients will undergo left ventricular reverse remodeling (LVRR) in response to therapy. Although treatment includes removing the stressor, such as discontinuing alcohol for alcoholic DCM patients or starting methimazole for thyrotoxicosis, standard guideline-directed medical treatment (GDMT) also requires beta-blocker and renin-angiotensin-aldosterone system inhibitor therapy to promote reverse remodeling and recovery of systolic function. Unfortunately, despite our best efforts, many DCM patients do not recover cardiac function and subsequently progress to end-stage heart failure requiring advanced heart failure therapies (3).

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Evaluation for DCM often begins upon incidentally finding cardiomegaly on chest radiography; and typically, a careful history, physical examination, and echocardiography study yields clues to the cause. Additional work-up often requires cardiac magnetic resonance to evaluate for late gadolinium enhancement and, in many cases, an endomyocardial biopsy for histological analysis. Prior animal studies performed by Ko et al. (4) in this issue of *JACC: Basic to Translational Science* demonstrated that unrepaired DNA damage increases expression of inflammatory and DNA damage response signaling that play a causative role in the pathogenesis of heart failure (5). Ko et al. (4) hypothesized that DNA damage in DCM patients can be assessed from endomyocardial biopsy results and that these markers of DNA damage may be useful in predicting LVRR in response to GDMT. Specifically, the study evaluated 2 major markers of DNA damage, poly (ADP-ribose) (PAR) and γ-H2A.X, by using immunohistochemical analysis of endomyocardial samples from 58 DCM patients prior to initiating 12 months of optimal GDMT. A total of 43% of these patients demonstrated LVRR, defined in the study as an absolute increase in LV ejection fraction ≥10% to a final value of >35% with a concomitant decrease in LV end-diastolic diameter ≥10%, whereas 57% of patients did not have LVRR in response to GDMT (i.e., they were LVRR-negative). PAR and γ-H2A.X nuclear staining was significantly reduced in LVRR-positive patients, and propensity score analysis demonstrated that the proportions of PAR (%PAR) and %γ-H2A.X staining

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were significant and independent risk factors for DCM as well as independent predictors of LVRR. Finally, receiver-operating characteristic analysis demonstrated the incremental prognostic power of %PAR staining with a sensitivity of 78% and a specificity of 87% to predict LVRR. An exciting finding was that markers of DNA damage could be used retrospectively to predict LVRR and patient clinical outcomes in DCM patients. If it is possible to predict which patients are unlikely to recover cardiac function, then advanced heart failure therapies can be deployed earlier.

A strength of this study is the bench-to-bedside approach used by the team, whereby findings of DNA damage in animal models of heart failure were translated to a novel prediction tool for patients with DCM. One pertinent question this study raises is what was the mechanism underlying the differential response observed in DCM patients with less DNA damage who underwent LVRR? One possibility is that the patients with LVRR had accumulated less DNA damage overall, as represented by lower %PAR-stained nuclei. Was this, perhaps, due to having had DCM for a shorter period of time? Because we know that "time is muscle" in the setting of acute myocardial infarction, does a similar prediction model hold true in nonischemic DCM with respect to LVRR? A potential future follow-up study could measure DNA damage in serial biopsies over time after removal of the stressor and/or GDMT to correlate these DNA damage markers with the level of cardiac recovery. To this end, it would also be interesting to evaluate patients who have undergone LVRR and subsequently have had recurrence of LV systolic dysfunction, as is often seen clinically and as reported in the TRED-HF trial (6). Of note, prior preclinical studies using a pressure-overload heart failure model demonstrated that, after the stressor was removed (i.e., debanding), there was incomplete reversal of transcriptional changes despite recovery of LV systolic function (7). This "memory" of a prior injury suggests a potential epigenetic basis. Given that 1 of the markers used in this study, γ-H2A.X, is a histone variant, these markers may herald a molecular signature of epigenetic changes that have reached a "point of no return" and progress to irreversible LVRR. Therefore, this study raises interesting directions for further elucidation of downstream bench research.

Although there are several study limitations related to sample size and selection bias for primarily end-stage heart failure patients as described by the authors, a second major strength is that DNA damage was an independent prognostic marker in all types of DCM. Although the authors did not report the types of DCM encountered, if the ratios were similar to previously studied cohorts, evaluation of DNA damage in all DCM patients could meet criteria for a screening test (8). With a larger, prospective study cohort, a subgroup analysis of the types of DCM may uncover that the patients without LVRR will fall primarily into certain types of DCM, further allowing targeted therapies and model validation. This point was partially illustrated in this study, given that familial DCM patients were primarily in the LVRR-negative group (4). Because the prevalence of DCM in Japan is estimated to be 14/100,000 compared to the US prevalence of 36.5/100,000, it is imperative to determine if the findings of this study can be applied globally and across the various types of DCM (9,10).

In conclusion, the findings by Ko et al. (4) validated a novel prognostic tool to determine LVRR in DCM patients. By assessing DNA damage by using PAR-stained cardiomyocyte nuclei from an endomyocardial biopsy, it may be possible to predict the clinical prognosis of DCM patients, with adequate sensitivity and specificity. A future prospective study is warranted to determine whether this can be used to dictate future clinical care.

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