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Letters

TO THE EDITOR

Risk Stratification in Dilated Cardiomyopathy

Is the Arrhythmogenic Substrate Stable Over Time?

David Heinzmann, MD
Meinrad Gawaz, MD
***Peter Seizer, MD**
*Medizinische Klinik
Innere Medizin III
Kardiologie und Kreislauferkrankungen
Universitaetsklinikum Tuebingen
Otfried-Mueller-Strasse 10
72076 Tuebingen
Germany
E-mail: peter.seizer@med.uni-tuebingen.de

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We congratulate Di Marco et al. (1) for their excellent meta-analysis, shedding light into the "darkness" of risk stratification in dilated cardiomyopathy (DCM). As suggested in the editorial comment, a polyparametric approach including late gadolinium enhancement could prove to be helpful (2). In this context, we suggest including results from endomyocardial biopsy in this polyparametric approach, because the clinical diagnosis of DCM often includes a variety of underlying causes. Although the predictive value of programmed ventricular stimulation in ischemic cardiomyopathy is quite good, it has unfortunately proven to be a weak predictor of arrhythmogenic events in patients with DCM (1,3). In our opinion, a better understanding of the arrhythmogenic substrate in patients with DCM could dramatically improve therapeutic and prophylactic approaches.

Our data indicate that ongoing inflammation, as detected by endomyocardial biopsy, may lead to further remodeling and may generate and enhance arrhythmogenic substrates (3). In contrast, the arrhythmogenic substrate in post-embolic cardiomyopathy is quite stable and therefore the prediction of arrhythmogenic events is more feasible than in diseases with ongoing remodeling, such as DCM (4). Because implantable cardioverter-defibrillator implantation is a major decision for life, the assessment of the arrhythmogenic risk at a certain point of time should take into account ongoing remodeling with possible subsequent risk modification. It is also still unclear whether patients with DCM could be more vulnerable to suffer from re-entry tachycardia, enhanced focal autonomy, or vulnerability for ventricular fibrillation induced by ventricular premature beats.

In our opinion, endomyocardial biopsy may be a possibility to analyze parameters of active ventricular remodeling, which might help to find suitable short- and long-term strategies in this patient collective.

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REPLY: Risk Stratification in Dilated Cardiomyopathy: Is the Arrhythmogenic Substrate Stable Over Time?

We thank Dr. Heinzmann and colleagues for their interest in our meta-analysis and their useful comments. We agree that improved risk stratification in nonischemic dilated cardiomyopathy (DCM) will require a multipronged approach, and we share their interest in the role of myocardial inflammation as a driver of adverse remodeling in some subgroups of DCM (1). Although endomyocardial biopsy (EMB) is an invaluable diagnostic tool in selected clinical scenarios, we feel that its invasiveness and shortcomings with respect to sampling error will prevent it from gaining widespread application as a surveillance tool. Indeed, we anticipate that other emerging techniques, including the application of ultra-small iron oxide particles as well as other nano- and nuclear tracers in combination with positron emission

tomography or cardiac magnetic resonance (CMR), may find wider spread clinical application.

Cardiac fibrosis is recognized as the major substrate for ventricular arrhythmias and the assessment of fibrosis is likely to become central to risk stratification for sudden death in DCM. Combining late gadolinium enhancement (LGE) and T1 mapping with extracellular volume (ECV) quantification, CMR can provide a comprehensive, noninvasive evaluation of the substrate, in terms of both localized and diffuse fibrosis. Both LGE and ECV have been validated histologically against EMB (2,3). Moreover, LGE has shown a strong association with outcomes in DCM, and recent evidences suggest that T1 mapping may add useful prognostic information (4). In consideration of this evidence, CMR might be considered the new gold standard for substrate assessment in patients with chronic heart failure.

Other variables, such as myocardial strain and circulating biomarkers of collagen turnover or galectin 3, have also been associated with myocardial fibrosis. Nowadays, CMR might be used instead of EMB to probe these other markers of fibrosis.

Interestingly, it seems that the LGE status of DCM patients (LGE+ or LGE−) does not change during follow-up (5), thus, continuous reassessment of the fibrotic substrate might be redundant, especially in patients without LGE. This observation, together with the marked differences in prognosis between LGE+ and LGE− patients, may suggest that the presence or absence of LGE identify separate clinical entities within the DCM spectrum.

*Andrea Di Marco, MD
Matthias Schmitt, MD, PhD
Ignasi Anguera, MD, PhD
*Arrhythmia Unit
Heart Institute
Department of Cardiology
Bellvitge University Hospital
Carrer feixa llarga
08907, Barcelona
Spain
E-mail: ayfanciu@hotmail.com

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Observational Versus Randomized

Sliding Toward Nonevidence-Based Medicine

We welcome the provision of additional data in the field of atrial fibrillation (AF) and heart failure (HF), a combination of conditions that results in difficult management decisions and worse outcomes, both for patients with reduced and preserved left ventricular ejection fraction. However, it remains important to adhere to some fundamental aspects of evidence-based medicine. Recent years have seen an abundance of subgroup analyses attempting to answer questions related to treatment effects in nonrandomized studies. These analyses, often using propensity matching or other statistical adjustments, have become commonplace and are often mistakenly considered to be as important as randomized controlled trials (RCTs). Regardless of analysis method, observational data should only be used to generate hypotheses about treatment effects (1,2), and we should resist the temptation to analyze datasets simply because of availability. Ignoring the weaknesses of such studies, and incorrect interpretation, can subsequently lead to confounded conclusions.

In the case of the paper by Cadrin-Tourigny et al. (3), the patients were not randomized to receive beta-blockers, and hence there was confounding at both the patient and physician level that hampers external validity. Physicians typically give beta-blockers to patients at lower risk, confirmed in this study as being younger in age, with more nonischemic cardiomyopathy, less time in AF, and higher use of anticoagulation and defibrillator therapy (all factors associated with lower mortality). Although a propensity-matched analysis can be useful to mitigate minor differences in demographic characteristics, it was not designed to account for different patient populations or for exposures that interact with the outcome. The limitations of propensity-matched analysis have been demonstrated for digoxin therapy