Editorial

Parvovirus B19 in Dilated Cardiomyopathy: There Is More Than Meets the Eye

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Dilated cardiomyopathy (DCM) can be seen as a final phenotype resulting from environmental and endogenous triggers on a genetically susceptible heart.[1] Myocarditis (MC) is one cause of DCM. MC consists of an acute or chronic inflammatory response of the heart to infectious or noninfectious environmental triggers.[2] Viruses have been posited as a potential cause of acute and chronic MC leading to DCM. Parvovirus B19 (B19V) is now the predominant cardiotropic virus found in DCM hearts with chronic MC. Despite this common detection of B19V in endomyocardial biopsy specimens from DCM hearts, causality remains controversial because B19V is also detected in healthy nondiseased hearts.[3]

The study by Hjalmarsson et al in this issue addresses the clinical relevance of B19V presence in DCM hearts.[4] The authors detected B19V genome in 73% of the heart biopsies from 40 hospitalized patients with DCM. The authors followed patients for a mean time of 112 months, which is the longest follow-up time in any study of B19V cardiomyopathy. They found a similar 55% prevalence of B19V in 20 healthy donor hearts. The authors concluded that B19V presence in DCM is likely to be incidental, without pathogenic or prognostic relevance.

This study should be interpreted with caution because relevant factors that influence the pathogenicity of B19V in DCM were not assessed. These include the genetic background of a patient, viral load, cellular localization and activity, coinfection, and associated cellular inflammation (Fig. 1).[3] Foremost, the viral load is essential in determining B19V relevance. Current literature suggests a cutoff value of 200−500 copies/μg DNA.[5,6] However, prospective studies systematically determining the influence of viral load on prognosis have not yet been published. Overall, B19V presence with a viral load of <200 copies/μg DNA should be considered as not clinically relevant. Results about the viral load in healthy and diseased hearts vary, indicating that the viral load is likely not the best method to assess pathogenicity of B19V in DCM.[3,7] The viral load of B19V can be influenced by a coinfection with human herpesvirus 6.[8] Future studies should report relevant coinfections, with an aim to determine a prognostic role for coinfections in MC and DCM. Assessing the replicative status of the virus may be the most accurate way to determine B19V activity in the heart. However, the methodology to reliably detect transcript intermediates of viral replication is not yet validated or widely available. The few published reports on mRNA intermediates suggest that mRNA intermediates are only present in diseased (MC and DCM) and not in control hearts.[8]

Thus, the presence of B19V genome in the heart itself can indicate a latent virus without replicative activity. Future research should focus on the development of a clinically feasible test to determine virus activity. In the present paper, data on cardiac inflammation are also lacking. Active B19V would be expected to cause cardiac inflammation, damage, and dysfunction. Therefore, linking cardiac inflammation to viral load and activity is needed to more accurately determine the pathogenic and prognostic relevance of B19V presence in DCM.[9] Whether B19V genomes provide incremental prognostic information or a valuable target for antiviral therapy remains unknown in part because of limited technology to measure B19V activity. Besides the virus, multiple microRNAs are associated with viral replication and cardiac inflammation.[2,10] Modulating these epigenetic regulators of virus activity and inflammation also provides an extra dimension of therapeutic possibilities.

As the data regarding B19V in DCM and control cohorts grow, the arguments regarding a possible pathogenic role for B19V persist, raising questions about the clinical utility of B19V genome analysis. One important missing piece in the puzzle is an intervention study to eliminate the virus. A pilot study suggested improvement of cardiac function after eradication or reduction of B19V.[11] A prospective, double-blinded,

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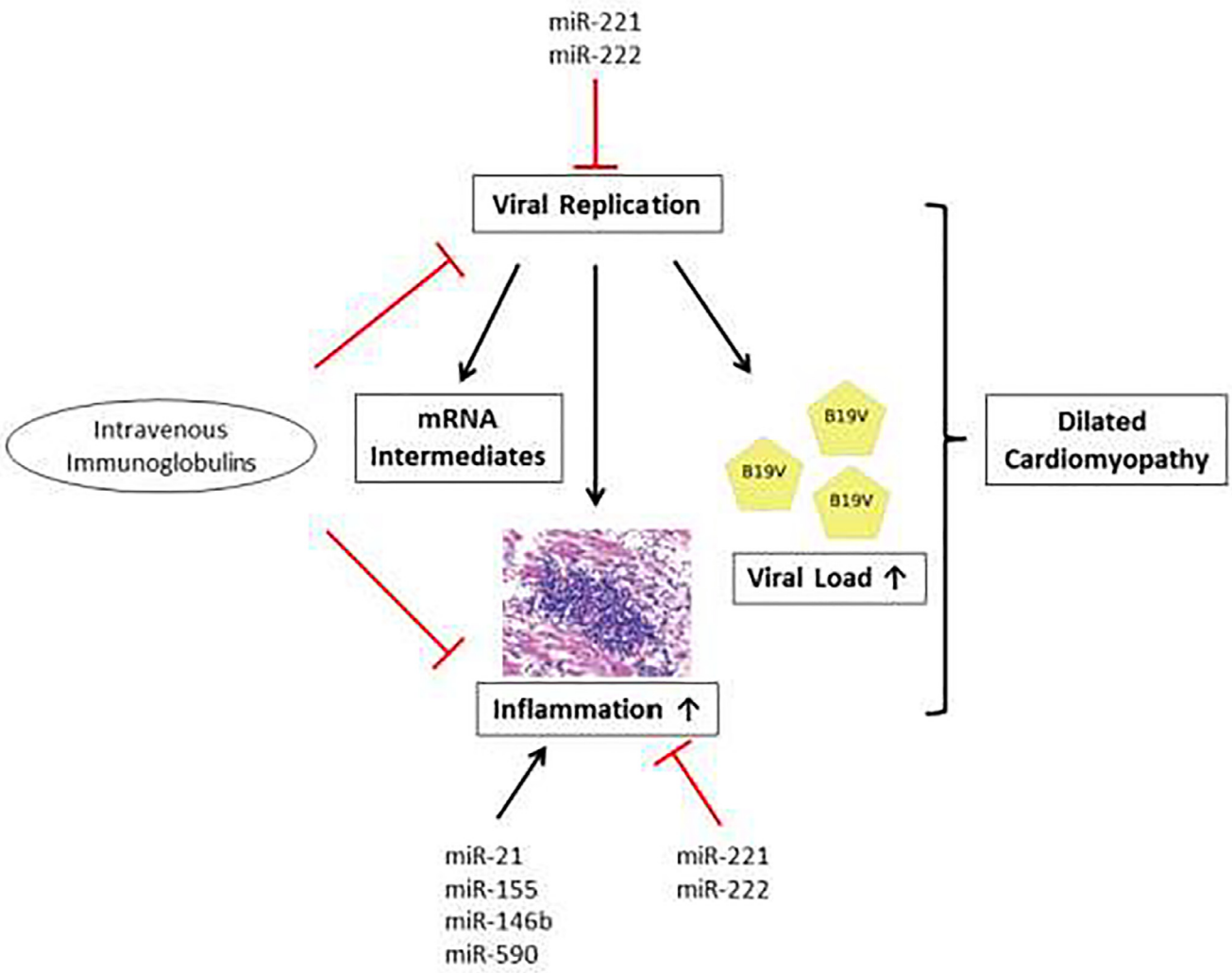

Fig. 1. Many factors play a role in determining the pathogenicity of B19V in the heart. Active replication of the virus is the most important, potentially leading to an increase in mRNA intermediates which can be detected. Virus activity will subsequently lead to an increase in viral load and cardiac inflammation. In genetically susceptible individuals, this can lead to dilated cardiomyopathy. Besides the virus, multiple miRNAs play a role in the pathogenic processes. Administration of intravenous immunoglobulins has the potential to limit disease activity and prevent the onset of disease.

randomized, placebo-controlled clinical trial investigating a role of intravenous immunoglobulin treatment in DCM patients with cardiac B19V >200 copies/μg DNA was finished in June 2018 after the inclusion and follow-up of 50 patients (Clinicaltrials.gov identifier: NCT00892112). Results are expected to be published in 2019. Hopefully, this trial will provide us with additional answers to the remaining question whether elimination of the B19V may hold some therapeutic benefit for cardiac function.

Disclosures

None.

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