Recurrent asymptomatic acute cellular rejection after heart transplantation: monitoring with speckle-tracking echocardiography

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Although the incidence of acute cellular rejection (ACR) in heart transplant patients has been reduced by the use of potent immunosuppressive agents, it remains an important complication in the early posttransplantation period and elevates the risk of heart failure. Left ventricular ejection fraction (LVEF) and other conventional echocardiographic parameters have limited clinical application to detect ACR after heart transplantation. Despite severe ACR confirmed by the gold standard method, endomyocardial biopsy (EMB), LVEF often remains preserved (>50%), indicating the need for reliable noninvasive alternatives for graft function surveillance prior to the onset of clinical symptoms.[1,2]

We present a case of a 60-year-old female patient who underwent orthotopic heart transplantation in January 2016. The first echocardiography showed normal biventricular systolic function. The patient was treated with standard immunosuppressant therapy including tacrolimus, mycophenolate mofetil, and prednisone. She underwent EMB on the 7th postoperative day, which showed diffuse infiltrate with multifocal myocytolysis and cellular edema recognized as ACR 3a International Society for Heart and Lung Transplantation (ISHLT) grade. At this point, echocardiography revealed normal LVEF and reduced biventricular longitudinal function by speckle-tracking echocardiography (STE): a left ventricular (LV) global longitudinal strain (LV-GLS) of –12.3% (FIGURE 1A and 1B) with substantial LV mechanical dispersion, which was defined as a time interval between the earliest and the latest peak negative strains, and right ventricular free-wall longitudinal strain (RV-FWS) of –15.1% (FIGURE 1C). The patient was treated with methylprednisolone infusion administered parenterally for 3 days. In the echocardiography performed during and after treatment, LVEF was still normal, but longitudinal function of both ventricles was increased: LV-GLS was –17.4% and RV-FWS was –24.3%.

The biopsies performed weekly during the first month after heart transplantation revealed no additional signs of significant rejection (1a, 2, 1a ISHLT grade). Echocardiography performed in the 2nd month after the procedure showed preserved LVEF, but again decreased longitudinal biventricular function: an LV-GLS of 14.4% and an RV-FWS of 18.1%. At this time, concomitant EMB confirmed significant ACR (3a ISHLT grade), which required intravenous methylprednisolone supply for 3 days. Despite therapy, we observed signs of significant rejection on repetead EMB, and longitudinal strain of both ventricles was still decreased. The patient's condition was clinically stable, and, as a consequence, she was again treated with parenteral methylprednisolone. Mycophenolate mofetil was replaced by everolimus. One week after repeated steroid treatment, EMB revealed no significant rejection (1b ISHLT grade). On echocardiography, overall contractility of both ventricles was satisfactory, with improved LV-GLS of –19.9% (FIGURE 1D and 1E) and RV-FWS of –31.5% (FIGURE 1F).

A previous study[3] demonstrated that the combination of both LV and RV longitudinal strains has a potential to exclude ACR in heart transplant patients more accurately than conventional measures, such as diastolic function, which is greatly dependent on donor age, heart rate, loading conditions, and electrical dissociation between the donor's and recipient's atria. As suggested before,[4] during significant ACR, it is longitudinal fiber shortening that is mostly affected, and circumferential fibers demonstrate compensatory

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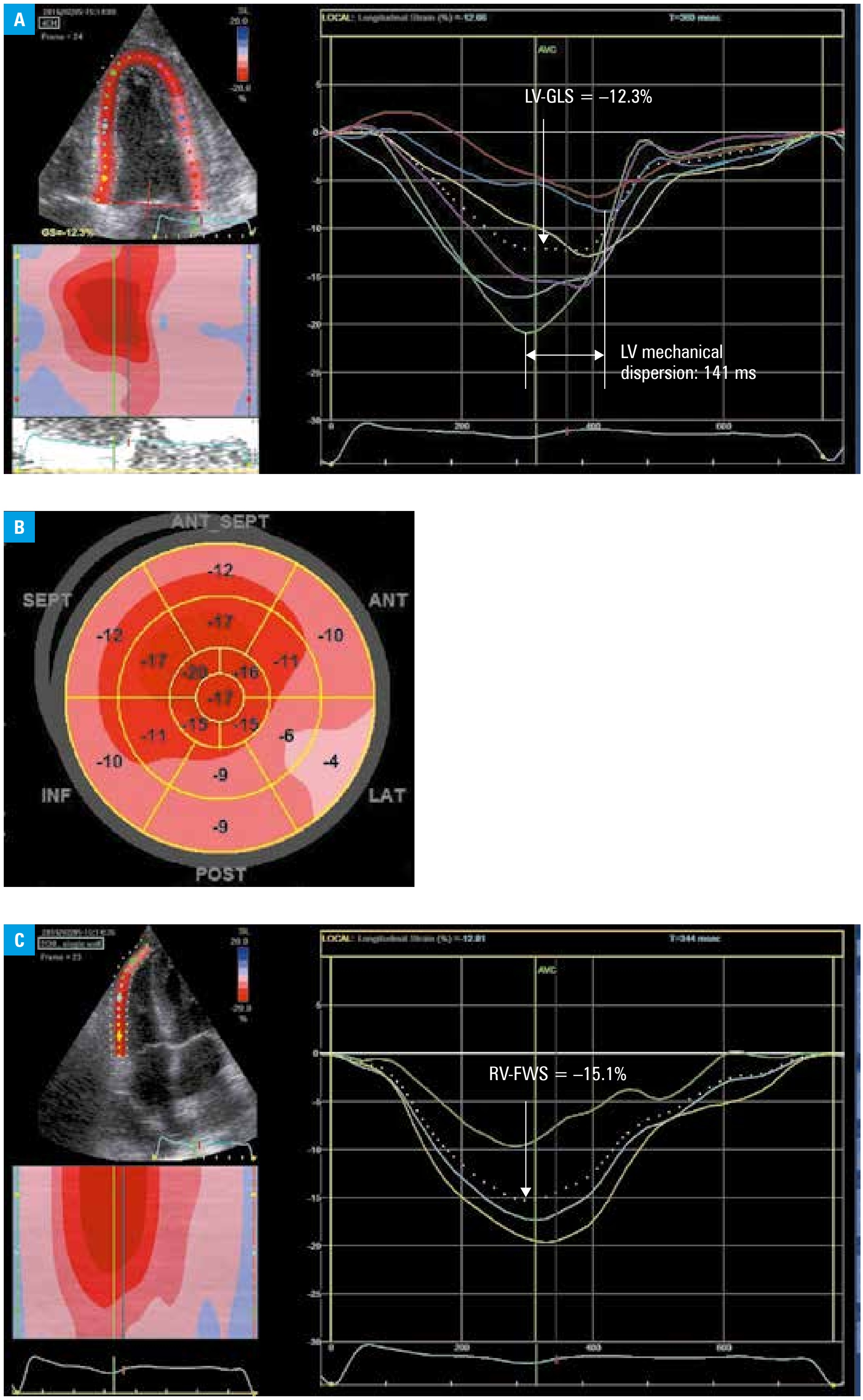

FIGURE 1 **A** – left ventricular (LV) global longitudinal strain (LV-GLS) during the first episode of significant rejection (3a ISHLT grade). Strain curves represent segmental deformation over time, and the dotted white curve stands for global strain. Note the overall reduced peak longitudinal strain and the presence of substantial LV mechanical dispersion. **B** – concomitant bull's-eye map during significant rejection (the color intensity represents the magnitude of LV segmental longitudinal strain). **C** – right ventricular free-wall longitudinal strain (RV-FWS) during significant rejection

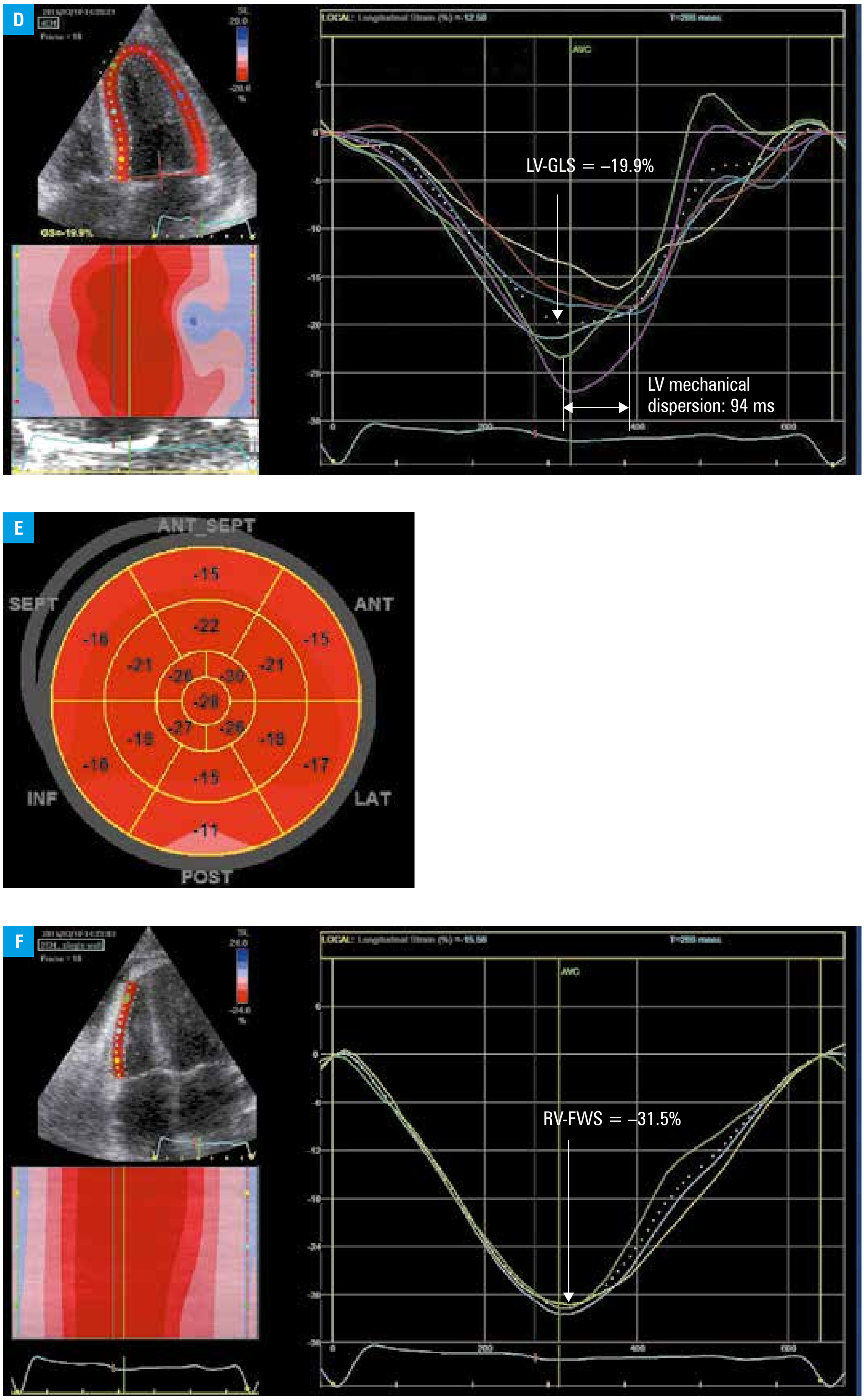

FIGURE 1 **D** – LV-GLS after methyloprednisolone therapy, free from significant rejection (1b ISHLT grade). Note increased overall peak longitudinal strain and diminished LV mechanical dispersion. **E** – concomitant bull's-eye map after treatment; **F** – RV-FWS improvement after resolution of significant rejection

enhanced thickening (radial function). In our case, a decrease in LV global longitudinal strain together with radial strain enhancement showed a strong association with ACR. Conventional and LV strain measurements collected during ACR and after effective treatment are presented in the table (Supplementary material online).

In conclusion, STE may potentially serve as a noninvasive monitoring tool in optimizing the timing of EMB.[5] Whether STE has an ability to replace EMB in the case of longitudinal strain reduction or LV mechanical dispersion enhancement is still to be determined.

Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

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