



Left Ventricular Pressure-Strain-Volume Loops for the Noninvasive Assessment of Volume Overload-Induced Myocardial Dysfunction

Global longitudinal strain (GLS) by speckle tracking echocardiography (STE) is a sensitive marker of left ventricular (LV) dysfunction, and it has a well-established prognostic value in a variety of cardiovascular diseases. However, several studies have demonstrated that GLS is significantly influenced by loading conditions and chamber geometry (1). Recently, our research group showed that GLS reflects ventriculoarterial coupling rather than mere contractility, using rat models of pressure overload-induced and volume overload (VO)-induced LV dysfunction (2). Thus, GLS may not be perceived as a reliable marker of LV contractility in a considerable subset of patients in whom increased preload and/or afterload are the drivers of LV dysfunction. To mitigate the afterload dependency of GLS, the calculation of myocardial work (by adjusting ventricular deformation to instantaneous LV pressure) was proposed as a promising new concept, and it subsequently entered the clinical arena (3). Nevertheless, changes in preload and LV geometry are still neglected in this method, which could be a substantial shortcoming under pathological conditions accompanied by VO.

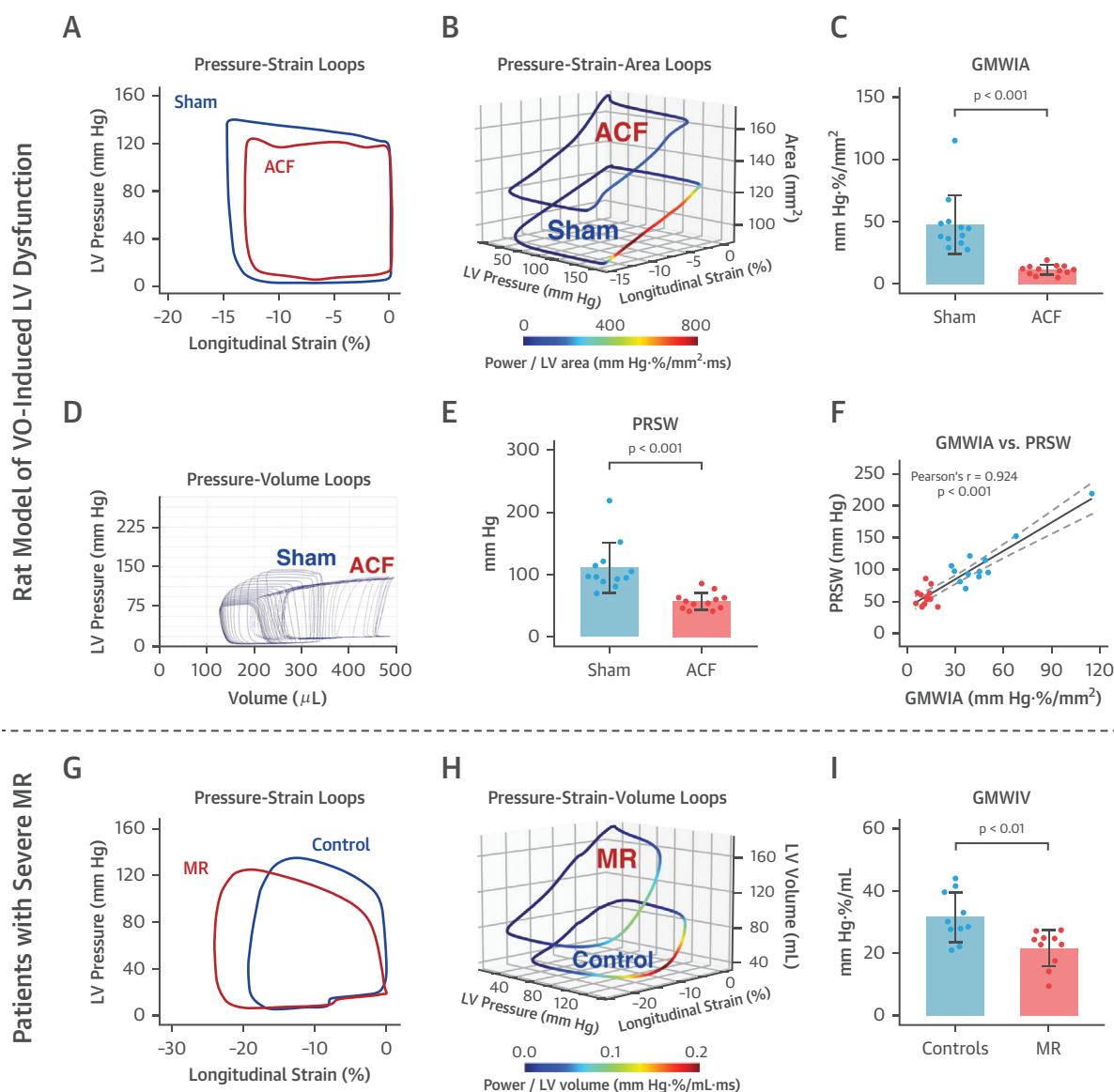
Accordingly, we hypothesized that, by incorporating instantaneous LV size into myocardial work calculation, we can formulate a parameter that: 1) correlates robustly with LV contractility in a rodent model of VO-induced LV dysfunction; and 2) is capable of detecting myocardial dysfunction in patients with severe mitral regurgitation (MR), despite preserved myocardial work. The study protocol was approved by the Ethical Committee for Animal Experimentation (Semmelweis University, Budapest, approval Number PEI/001/2374-4/2015) and the Regional and Institutional Committee of Science and Research Ethics (approval Number 2016/175).

First, we sought to investigate whether the pressure-strain-area loop-derived metric exhibits a stronger correlation with LV contractility than GLS and the pressure-strain loop-derived myocardial work in a rodent model of VO-induced LV

dysfunction. VO was established by creating an aortocaval fistula (ACF) in male Wistar rats ($n = 12$; 5 to 6 weeks old; 175 to 200 g) (2). A 24-week follow-up period was applied after the operation to evoke the characteristic features of VO-induced LV dysfunction. Age-matched sham-operated animals served as controls (Sham, $n = 12$). At the end of the follow-up period, STE was performed to assess GLS according to our previously published protocol (4). Instantaneous LV cavity area was measured by tracing the endocardial border in echocardiographic recordings acquired from parasternal long-axis views throughout the cardiac cycle. Following echocardiography, invasive pressure-volume analysis with transient occlusion of the inferior vena cava was performed to compute preload recruitable stroke work (PRSW), which represents a gold standard parameter of cardiac contractility. Global myocardial work index (GMWI) was computed by integrating the instantaneous power (the product of the longitudinal strain rate and the invasively measured LV pressure) from mitral valve closure until mitral valve opening (3). To calculate GMWI adjusted to LV cavity area (GMWIA); power was divided by the instantaneous LV cavity area before integration. For visualization, we created 3-dimensional (3D) pressure-strain-area loops that were color-coded based on the instantaneous power. Group comparisons were performed using unpaired Student *t*-test or Mann-Whitney *U* test, as appropriate. A *p*-value of < 0.05 was considered statistically significant.

LV ejection fraction (LVEF) did not differ significantly between the 2 groups (ACF vs. Sham: $59.0 \pm 3.8\%$ vs. $64.8 \pm 9.6\%$; $p = 0.071$), whereas GLS was slightly decreased in the ACF group ($-13.2 \pm 2.3\%$ vs. $-15.4 \pm 1.9\%$; $p = 0.022$). In contrast, GMWI (Figure 1A), GMWIA (Figures 1B and 1C), and PRSW (Figures 1D and 1E) were considerably reduced in rats with ACF than in controls ($1,383 \pm 382$ mm Hg·%, vs. $1,928 \pm 281$ mm Hg·%; 11.6 ± 3.7 mm Hg·%/mm² vs. 47.9 ± 22.8 mm Hg·%/mm²; 57 ± 13 mm Hg vs. 111 ± 38 mm Hg; all $p < 0.01$). Both GLS and GMWI correlated moderately with PRSW (Pearson $r = -0.550$ and $r = 0.681$; both $p < 0.01$, respectively). A stronger correlation was seen between GMWIA and PRSW (Pearson $r = 0.924$; $p < 0.001$) (Figure 1F).

To test the feasibility of our novel metric in a clinical setting, we performed 3D echocardiography to assess LV volumes and longitudinal strain in 10 patients (9 males, age 57 ± 10 years) with severe primary MR (effective regurgitant orifice area: ≥ 0.4 cm²;

FIGURE 1 Alterations in GLS, GMWI, and GMWIA/GMWIV under Pathological Conditions Accompanied by VO

(A, B, D) Pressure-strain, pressure-strain-area, and pressure-volume loops of representative animals. (C, E) GMWIA and PRSW in rats of the ACF and Sham groups. (F) The correlation between GMWIA and PRSW in our rat model of volume overload-induced LV dysfunction. (G, H) Pressure-strain and pressure-strain-volume loops of a representative patient with severe MR and a healthy control subject. (I) GMWIV in patients with severe MR and healthy controls. ACF = aortocaval fistula; GMWI = global myocardial work index; GMWIA = global myocardial work index adjusted to the instantaneous left ventricular area in rats; GMWIV = global myocardial work index adjusted to the instantaneous 3D left ventricular volume in humans; LV = left ventricular; MR = mitral regurgitation; PRSW = preload recruitable stroke work; VO = volume overload.

regurgitant volume: ≥ 60 ml; 4 patients with LVEF 50% to 60%; 6 patients with LVEF $> 60\%$). We also examined 10 age- and sex-matched healthy controls (9 males, age 55 ± 9 years). LV pressure curves were estimated from brachial artery cuff pressures as proposed by Russell et al. (3). MR patients had higher LV volumes than controls (MR patients vs. controls: 89.1

± 17.1 ml/m² vs. 56.1 ± 7.1 ml/m²; $p < 0.001$), but there was no difference in LVEF between the 2 groups ($62.3 \pm 4.8\%$ vs. $60.6 \pm 2.7\%$; $p = 0.431$). In the MR patients, GLS was significantly increased ($-22.4 \pm 3.3\%$ vs. $-19.1 \pm 1.6\%$; $p = 0.012$), and GMWI was preserved compared to controls ($2,080 \pm 471$ mm Hg·% vs. $2,032 \pm 281$ mm Hg·%; $p = 0.787$) (Figure 1G). In contrast,

GMWI adjusted to instantaneous LV volume (GMWIV) was markedly reduced (21.6 ± 5.9 mm Hg·%/ml vs. 31.6 ± 7.9 mm Hg·%/ml; $p = 0.005$) (**Figures 1H and 1I**).

By incorporating instantaneous LV size into the pressure-strain relationship, our proposed metric could reflect the adversarial effects of VO on ventricular myocardial function better than GLS and even GMWI. Using 3D echocardiography-derived LV volumes and longitudinal strain in combination with noninvasively estimated LV pressure, this novel analysis can be easily implemented in clinical practice and may overcome some limitations of GLS and GMWI in pathological conditions accompanied by VO. Further work targeting the identification of the turning point where the cumulative effects of increased preload start to diminish cardiac contractility is warranted in different clinical scenarios.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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