

# The effect of exercise training on biventricular myocardial strain in heart failure with preserved ejection fraction

Siddhartha S. Angadi<sup>1,2\*</sup> , Catherine L. Jarrett<sup>1</sup>, Moustafa Sherif<sup>2</sup>, Glenn A. Gaesser<sup>1</sup> and Farouk Mookadam<sup>2</sup>

<sup>1</sup>School of Nutrition and Health Promotion, Arizona State University, Phoenix, AZ, USA; <sup>2</sup>Department of Cardiovascular Diseases, Mayo Clinic Arizona, Scottsdale, AZ, USA

## Abstract

**Aims** High-intensity interval training (HIIT) improves peak oxygen uptake and left ventricular diastology in patients with heart failure with preserved ejection fraction (HFpEF). However, its effects on myocardial strain in HFpEF remain unknown. We explored the effects of HIIT and moderate-intensity aerobic continuous training (MI-ACT) on left and right ventricular strain parameters in patients with HFpEF. Furthermore, we explored their relationship with peak oxygen uptake ( $VO_{2peak}$ ).

**Methods and results** Fifteen patients with HFpEF (age =  $70 \pm 8.3$  years) were randomized to either: (i) HIIT ( $4 \times 4$  min, 85–90% peak heart rate, interspersed with 3 min of active recovery;  $n = 9$ ) or (ii) MI-ACT (30 min at 70% peak heart rate;  $n = 6$ ). Patients were trained 3 days/week for 4 weeks and underwent  $VO_{2peak}$  testing and 2D echocardiography at baseline and after completion of the 12 sessions of supervised exercise training. Left ventricular (LV) and right ventricular (RV) average global peak systolic longitudinal strain (GLS) and peak systolic longitudinal strain rate (GSR) were quantified. Paired *t*-tests were used to examine within-group differences and unpaired *t*-tests used for between-group differences ( $\alpha = 0.05$ ). Right ventricular average global peak systolic longitudinal strain improved significantly in the HIIT group after training (pre =  $-18.4 \pm 3.2\%$ , post =  $-21.4 \pm 1.7\%$ ;  $P = 0.02$ ) while RV-GSR, LV-GLS, and LV-GSR did not ( $P > 0.2$ ). No significant improvements were observed following MI-ACT. No significant between-group differences were observed for any strain measure.  $\Delta LV\text{-GLS}$  and  $\Delta RV\text{-GLS}$  were modestly correlated with  $\Delta VO_{2peak}$  ( $r = -0.48$  and  $r = -0.45$ ;  $P = 0.1$ , respectively).

**Conclusions** In patients with HFpEF, 4 weeks of HIIT significantly improved RV-GLS.

**Keywords** Exercise training; Ventricular strain; High-intensity interval exercise; Heart failure with preserved ejection fraction

Received: 29 July 2016; Revised: 8 December 2016; Accepted: 17 February 2017

\*Correspondence to: Siddhartha S. Angadi, Arizona State University, 425 N. 5th St. #145, Phoenix, AZ 85004, USA. Tel: + 602 827 2254; Fax: + 602 496 1873. Email: sangadi@asu.edu

## Background

Heart failure is a leading cause of hospitalization among the elderly, and nearly half of the patients with a heart failure diagnosis have heart failure with preserved ejection fraction (HFpEF).<sup>1</sup> Heart failure with preserved ejection fraction is also associated with significant impairments in left ventricular (LV) global longitudinal strain (GLS), which in turn is associated with multiple adverse patient outcomes.<sup>2</sup>

We have previously demonstrated improvements in LV diastolic function following high-intensity interval training (HIIT).<sup>3</sup> However, recently published data with regard to acute and chronic effects of high-intensity interval exercise are mixed with some data suggesting worsening of strain characteristics in otherwise healthy individuals<sup>4,5</sup> and no adverse changes in individuals with heart failure and reduced ejection fraction.<sup>6,7</sup> Given that the effects of HIIT on ventricular strain characteristics in patients with HFpEF remain unknown, we carried out secondary analyses to

explore the effects of HIIT on biventricular strain characteristics.

## Aims

The primary aim of these secondary analyses was to explore the changes in right and LV-GLS and global longitudinal systolic strain rate (GSR) following 1 month of HIIT in comparison to a more traditional moderate-intensity aerobic continuous training program (MI-ACT). Secondly, we examined the relationships between change in LV and right ventricular (RV) strain parameters and change in cardiorespiratory fitness ( $VO_{2peak}$ ).

## Methods

The study was approved by the Mayo Clinic and the Arizona State University institutional review boards, and all study procedures were carried out in accordance to the Declaration of

Helsinki (Clinical trials registration: NCT02147613). The design and primary outcomes of this clinical trial have been described in detail by the authors previously.<sup>3</sup> Briefly, 19 patients with HFpEF (age =  $70 \pm 8.3$  years; median diastolic dysfunction grade = II and median NYHA Class II) were randomized to either 4 weeks of HIIT (eight men, one woman;  $4 \times 4$  min at 85–90% peak heart rate, with 3 min active recovery between bouts) or MI-ACT (four men, two women; 30 min at 70% peak heart rate). Subjects underwent supervised exercise training 3 days/week for 4 weeks and were on stable pharmacotherapy for >3 months (Table 1).

Transthoracic echocardiography was carried out 72–96 h after the last bout of exercise and utilized standard American Society of Echocardiography guidelines for views and measurements for systolic and diastolic assessment. Left ventricular and RV strain analyses using velocity vector imaging were measured at baseline and again at completion of the exercise training program for all patients.<sup>8–10</sup> Semi-automated signal processing software (Syngo US workstation, Siemens Medical Solutions, Mountain View, CA, USA) was used offline to track myocardial borders in order to measure the average GLS and GSR for both left ventricle and right ventricle (using the apical four-chamber view). We excluded the segments which were not adequately tracked. The indices obtained from the velocity vector imaging were averaged from three consecutive cardiac cycles.

Paired *t*-tests were used to compare pre- and post-training differences within groups, and unpaired *t*-tests were used to compare between-group differences. Data are reported as means  $\pm$  standard deviation (Tables 1 and 2). Alpha was set at 0.05 for significance and  $\alpha = 0.1$  for trends. Effect sizes (Cohen's *d*) for within-group and between-group ( $d_b$ ) differences were calculated and reported as moderate ( $0.5 < d < 0.8$ ) or large ( $d \geq 0.8$ ).<sup>11</sup> Finally, data were pooled across both exercise intervention groups, and Pearson correlation coefficients were computed to examine relationships between changes in biventricular strain and change in  $VO_{2peak}$  (change in  $VO_{2peak}$  reported in a previous publication).<sup>3</sup>

**Table 1** Baseline characteristics

	HIIT (n = 9)	MI-ACT (n = 6)
Age (years)	69 $\pm$ 6.1	71.5 $\pm$ 11.7
HR (bpm)	62.4 $\pm$ 7.2	61.7 $\pm$ 7.8
BP (mmHg)	134 $\pm$ 14/85 $\pm$ 8	134 $\pm$ 24/78 $\pm$ 7
BNP (pg/mL)	62.4 $\pm$ 42.6	118.3 $\pm$ 90.4
ACE-I	5/9	1/6
ARB	0/9	2/6
$\alpha$ - $\beta$ -Blockers	6/9	4/6
Aspirin	5/9	4/6
Diuretics	4/9	4/6
Coumadin	3/9	2/6
Statins	6/9	4/6
CCBs	2/9	4/6

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCBs, calcium channel blockers; HIIT, high-intensity aerobic interval training; HR, heart rate; MI-ACT, moderate-intensity aerobic continuous training.

**Table 2** Changes in right and left ventricular parameters

	Pre	Post	<i>P</i>	<i>d</i>	Pre	Post	<i>P</i>	<i>d</i>	$d_b$
RV-GLS (%)	-18.4 $\pm$ 3.2	-21.4 $\pm$ 1.7	0.02	0.95	-18.4 $\pm$ 4.1	-19.5 $\pm$ 4.9	0.41	0.37	0.60
RV-GSR ( $s^{-1}$ )	-1.2 $\pm$ 0.3	-1.3 $\pm$ 0.4	0.71	0.13	-1.2 $\pm$ 0.4	-1.4 $\pm$ 0.5	0.22	0.58	0.51
LV-GLS (%)	-15.8 $\pm$ 2.9	-17.9 $\pm$ 3.9	0.20	0.50	-16.0 $\pm$ 3.2	-15.8 $\pm$ 4.2	0.89	0.06	0.53
LV-GSR ( $s^{-1}$ )	-0.9 $\pm$ 0.2	0.9 $\pm$ 0.3	0.48	0.26	-0.9 $\pm$ 0.2	-0.9 $\pm$ 0.3	0.96	0.02	0.21
LV mass (g)	210.1 $\pm$ 61.2	180.6 $\pm$ 59.3	0.06	0.50	219.2 $\pm$ 18.3	220.0 $\pm$ 45.3	0.97	0.02	0.75
LVMl ( $g/m^2$ )	101.1 $\pm$ 22.5	87.6 $\pm$ 23.5	0.14	0.93	109.6 $\pm$ 15.7	112.0 $\pm$ 19.5	0.8	0.13	1.16
LVEF (%)	63.7 $\pm$ 6.4	62.4 $\pm$ 5.5	0.44	0.27	66.0 $\pm$ 4.7	61.6 $\pm$ 5.3	0.08	0.71	0.15
SV (cc)	93.8 $\pm$ 24.8	88.2 $\pm$ 19.2	0.47	0.25	89.2 $\pm$ 16.3	97.2 $\pm$ 26.7	0.29	0.33	0.39
SVI ( $cc/m^2$ )	45.3 $\pm$ 8.4	36.9 $\pm$ 8.2	0.56	0.25	54.4 $\pm$ 8.6	50.0 $\pm$ 15.8	0.29	0.35	1.04

*d*, within-group effect size;  $d_b$ , between-group effect size; LV-GLS, left ventricular global longitudinal strain; LV-GSR, left ventricular global longitudinal systolic strain rate; LV mass, left ventricular mass; LVMl, left ventricular mass index; LVEF, left ventricular ejection fraction; RV-GLS, right ventricular global longitudinal strain; RV-GSR, right ventricular global longitudinal systolic strain rate; SV, left ventricular stroke volume; SVI, left ventricular stroke volume index.

## Results

No baseline differences between both groups were noted with regard to age, ejection fraction, diastolic function and strain measurements as well as demographic characteristics as previously reported (Table 1).<sup>3</sup> High-intensity interval training resulted in significant improvements in RV-GLS (pre =  $-18.4 \pm 3.2\%$  vs. post =  $-21.4 \pm 1.7\%$ ;  $P = 0.02$ ;  $d = 0.95$ ; Table 2). No significant between-group differences were noted for RV-GLS ( $P > 0.2$ ) although moderate between-group effect sizes were noted ( $d_b = 0.60$ ; Table 2). Moderate effect sizes were noted for between-group differences for improvements in RV-GSR ( $d_b = 0.51$ ) and LV-GLS ( $d_b = 0.53$ ). Trends for associations were noted between  $\Delta VO_{2peak}$  and  $\Delta LV\text{-GLS}$  ( $r = -0.48$ ;  $P = 0.1$ ) and  $\Delta RV\text{-GLS}$  ( $r = -0.45$ ,  $P = 0.1$ ). Finally,  $\Delta LV\text{-GLS}$  and  $\Delta RV\text{-GLS}$  were strongly related ( $r = 0.68$ ,  $P = 0.01$ ). No significant improvements were observed in parameters regarding LV hypertrophy following either intervention although a trend for improvement of LV mass and LV mass index was noted (Table 2).

## Conclusions

To our knowledge, this is the first study to examine the effects of HIIT on biventricular strain in HFpEF patients with impaired LV<sup>12</sup> and RV strain.<sup>10</sup> The principal novel finding of these secondary analyses was that RV-GLS improved after 4 weeks of HIIT. Importantly, none of the LV strain parameters worsened following one month of HIIT as has been previously described in healthy populations.<sup>4,5</sup> Alternatively, because we tested individuals 72–96 h following the last bout of exercise, it is possible that acute, adverse alterations were missed. However, it is important to note the persistence of the salutary strain phenotype beyond the acute post-exercise period. The time-course of biventricular strain-related changes during the initial 72 h after a single bout of high-intensity exercise remains unknown. The lack of improvement in LV strain parameters is consistent with what has been reported following 12 weeks of HIIT in patients with heart failure and reduced ejection fraction.<sup>6</sup>

Further, none of the strain parameters improved following 4 weeks of MI-ACT. Right ventricular average global peak systolic longitudinal strain is a sensitive marker of RV dysfunction and is correlated with postoperative mortality in patients with normal ejection fraction<sup>13</sup> as well as with pulmonary vascular resistance.<sup>14</sup> It is plausible that exercise-induced improvements in RV-GLS may have salutary effects on cardiovascular risk. However, long-term clinical outcomes following exercise-based interventions remain unknown. Although no significant between-group

differences were noted, these are likely due to the small sample size as the study was underpowered to detect these differences. However, between-group effect sizes were in the moderate range and may provide guidance to researchers exploring changes in LV and RV strain parameters after short-term exercise training in patients with HFpEF. Changes in RV-GLS and LV-GLS were strongly correlated to each other, and both were modestly correlated with changes in  $VO_{2peak}$ , which is an established predictor of morbidity and mortality in patients with HFpEF.<sup>15</sup> These relationships have been previously reported in larger cross-sectional cohorts, and the magnitude of the association appears to be similar in this training study with a trend towards significance.<sup>15</sup>

In summation, we found significant improvements in RV global longitudinal strain following just 4 weeks of HIIT in individuals with HFpEF. Furthermore, exercise training-induced changes to LV and RV mechanics were positively correlated with improvements in  $VO_{2peak}$ . The long-term implications of these data with regard to hard clinical end-points in individuals with HFpEF remain to be explored.

## Acknowledgements

We thank H. Bright, J. Walsh, A. Royter, P. Thompson, and the rest of the staff at the cardiac rehabilitation facility at the Mayo Clinic, Scottsdale, AZ, for their assistance with exercise training.

This study has Clinical Trials Registration NCT02147613.

## Conflict of interest

None declared.

## Author contributions

S.S.A., F.M., M.S., and G.A.G. made a substantial contribution to research design and the acquisition of data; S.S.A., M.S., and C.L.J. analysed the data; S.S.A., G.A.G., F.M., and C.L.J. drafted the paper; S.S.A., C.L.J., F.M., and G.A.G. revised it critically; and all authors have approved the submitted and final version.

## Funding

This work was supported by Mayo Clinic and Arizona State University Seed Grant [93016001].

## References

- Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355**: 251–259.
- Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, McMurray JJ, Solomon SD, Investigators P. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2014; **63**: 447–456.
- Angadi SS, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ, Gaesser GA. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol (1985)* 2015; **119**: 753–758.
- Cote AT, Bredin SSD, Phillips AA, Koehle MS, Glier MB, Devlin AM, Warburton DER. Left ventricular mechanics and arterial-ventricular coupling following high-intensity interval exercise. *J Appl Physiol* 2013; **115**: 1705–1713.
- Scharf M, Schmid A, Kemmler W, von Stengel S, May MS, Wuest W, Achenbach S, Uder M, Lell MM. Myocardial adaptation to high-intensity (interval) training in previously untrained men with a longitudinal cardiovascular magnetic resonance imaging study (Running Study and Heart Trial). *Circ Cardiovasc Imaging* 2015; **8**: e002566.
- Benda NM, Seeger JP, Stevens GG, Hijmans-Kersten BT, van Dijk AP, Bellersen L, Lamfers EJ, Hopman MT, Thijssen DH. Effects of high-intensity interval training versus continuous training on physical fitness, cardiovascular function and quality of life in heart failure patients. *PLoS One* 2015; **10**: e0141256.
- Tomczak CR, Thompson RB, Paterson I, Schulte F, Cheng-Baron J, Haennel RG, Haykowsky MJ. Effect of acute high-intensity interval exercise on postexercise biventricular function in mild heart failure. *J Appl Physiol (1985)* 2011; **110**: 398–406.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 233–270.
- Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; **29**: 277–314.
- Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685–713.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York, USA: Routledge Academic; 2013.
- Yingchoncharoen T, Agarwal S, Popović ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. *J Am Soc Echocardiogr* 2013; **26**: 185–191.
- Ternacle J, Berry M, Cognet T, Kloeckner M, Damy T, Monin J-L, Couetil J-P, Dubois-Rande J-L, Gueret P, Lim P. Prognostic value of right ventricular two-dimensional global strain in patients referred for cardiac surgery. *J Am Soc Echocardiogr*; **26**: 721–726.
- Park J-H, Negishi K, Kwon DH, Popovic ZB, Grimm RA, Marwick TH. Validation of global longitudinal strain and strain rate as reliable markers of right ventricular dysfunction: comparison with cardiac magnetic resonance and outcome. *J Cardiovasc Ultrasound* 2014; **22**: 113–120.
- Hasselberg NE, Haugaa KH, Sarvari SI, Gullestad L, Andreassen AK, Smiseth OA, Edvardsen T. Left ventricular global longitudinal strain is associated with exercise capacity in failing hearts with preserved and reduced ejection fraction. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 217–224.