The impact of high-intensity interval training on ventricular remodeling in patients with a recent acute myocardial infarction—A randomized training intervention pilot study

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Abstract
Background: Aerobic exercise training is associated with beneficial ventricular remodeling and an improvement in cardiac biomarkers in chronic stable heart failure. High-intensity interval training (HIIT) is a time-efficient method to improve VO2peak in stable coronary heart disease patients. This pilot study aimed to compare the effect of HIIT on ventricular remodeling in patients with a recent acute myocardial infarction (AMI).

Methods: Nineteen post-AMI patients were randomized to either HIIT (n = 9) or usual care (n = 10). A cardiopulmonary exercise test (CPET), transthoracic echocardiography, and cardiac biomarker assessment (ie, N-terminal pro B-type natriuretic peptide levels and G protein-coupled receptor kinase 2 expression) were performed before and after a 12-week training intervention. CPET parameters including oxygen uptake efficiency slope (OUES) and VO2 at the first ventilatory threshold (VO2 VT1) were calculated. Left ventricular (LV) structural and functional echocardiographic parameters including myocardial strain imaging were assessed.

Results: VO2peak and OUES improved solely in the HIIT group (P < .05 for group/time, respectively). There was a significant training effect for the improvement of peak work load in both groups (P < .05). O2 pulse and VO2 at VT1 both improved only in the HIIT group (P < .05 for time, no interaction). HIIT improved radial strain and pulsed-wave tissue Doppler imaging derived e’ (P < .05 for time, no interaction). Cardiac biomarkers did not change in either group.

Conclusions: In post-AMI patients, HIIT lead to significant improvements in prognostic CPET parameters compared to usual care. HIIT was associated with favorable ventricular remodeling regarding certain echocardiographic parameters of LV function.
1 | INTRODUCTION

Acute myocardial infarction (AMI) can induce changes in left ventricular (LV) topography (ie, ventricular remodeling) and is a major contributor in the development of heart failure despite advances in coronary revascularization and optimal medical therapy.1 Myocardial strain imaging using speckle-tracking echocardiography allows quantification of regional and global LV function and has been increasingly implemented in clinical practice.2 It is more sensitive for the detection of subclinical LV changes as compared to standard LV ejection fraction (LVEF) measurement.2 The best evaluated parameter, global longitudinal strain (GLS) is superior to LVEF in the prediction of prognosis and cardiac remodeling after AMI.4-6 Among others, cardiac β-adrenergic receptor (β-AR) signal dysregulation represents a hallmark abnormality potentially leading to LV remodeling post-AMI and progression to heart failure. β-AR kinase (GRK2) is the most abundant G protein-coupled receptor kinase expressed in the heart.7 Importantly, abnormalities of β-AR signaling in the failing heart, including GRK2 over-expression, are mirrored in circulating white blood cells (ie, lymphocytes) and correlate with severity of LV dysfunction.8 Therefore, GRK2 provides potential as a biomarker of cardiac dysfunction.9

Exercise-based secondary prevention programs have confirmed improvements in mortality and morbidity in patients with stable coronary heart disease (CHD) and after AMI, respectively.10,11 The importance of starting aerobic exercise training early post-AMI and the beneficial effects on LV remodeling have been emphasized in a recent meta-analysis.12 Furthermore, aerobic exercise training has been shown to be associated with a lowering of GRK2 expression and to predict outcomes in patients with chronic ischemic heart failure in a prospective study.13 High-intensity interval training (HIIT) is more effective at improving VO2peak and can be performed safely compared to the more established moderate-intensity continuous exercise training (MICET) in stable CHD patients.14-16

However, most prior studies included predominantly stable patients. To the best of our knowledge, the effect of HIIT on cardiac remodeling including advanced echocardiography (ie, myocardial strain imaging) and GRK2 expression has not yet been studied in patients with a recent AMI. This pilot investigation aimed to evaluate the effect of HIIT on cardiopulmonary exercise test (CPET) variables, left ventricular remodeling, and GRK2 expression in CHD patients who recently suffered an AMI. We hypothesized that HIIT would result in a higher VO2peak improvement and a more favorable cardiac remodeling with a substantial reduction in GRK2 expression compared to a usual care group.

2 | MATERIALS AND METHODS

2.1 | Participants

Subjects with an AMI within the preceding 6 weeks referred for cardiac rehabilitation at the Cardiovascular Prevention and Rehabilitation (ÉPIC) Center of the Montreal Heart Institute were enrolled in a longitudinal, randomized prospective clinical training intervention study. They had access to multidisciplinary educational services usually offered in a secondary prevention program (ie, smoking cessation, nutritional counseling, etc.). Details on the inclusion and exclusion criteria have been previously described elsewhere.17,18 Importantly, AMI (ST elevation myocardial infarction or non-ST elevation myocardial infarction) was based on the universal definition.19 For more detailed information on the exclusion criteria see section S1 of the Supporting Information. Patients had to be stable with regard to symptoms and doses of medication during the 4 weeks prior to enrolment.

Although by definition the study was unblinded, individuals involved in data assessment and analysis were blinded to the allocation group (assessor-blinded study). The study protocol was approved by the Research Ethics and New Technology Development Committee (CERDNT) of the Montreal Heart Institute (ClinicalTrials.gov identifier number: NCT02048696).

2.2 | Study design and measurement

Baseline clinical assessment (ie, medical history, physical examination, and anthropometric measurements), blood analysis, transthoracic echocardiography, and CPET were performed at baseline and after completion of the program (for more detailed information on study design and measurement see section S2 of the Supporting Information).

2.3 | Maximal CPET

Maximal CPET was performed on a cycle ergometer (Ergoline 800S, Bitz, Germany) according to the recommendations of the American Heart Association, and as previously published (for more detailed information see section S3 of the Supporting Information).20-22

2.4 | Transthoracic echocardiography

Standard transthoracic 2D echocardiography was performed on a Vivid 9 cardiac ultrasound system with a 7.5-MHz transducer (GE Medical system, New Jersey). All echocardiographic images were obtained by two cardiology fellows using standard tomographic views. All data were stored on an external hard-drive and analyzed offline on
2.5 | 2D speckle-tracking strain analysis

Peak systolic LV longitudinal strain and strain rates were assessed using standard 2D apical four-chamber, two-chamber, and three-chamber view using speckle-tracking analysis. All images were recorded using high frame rate loops (50-80 Hz) for reliable analysis by the software. Manual tracing of the endocardial borders on an end-systolic frame (aortic valve closure) was performed and the myocardial region of interest was adjusted to include all the endocardium and epicardium, excluding the pericardium. Automatically tracing was then applied on subsequent frames. Adequate tracing for each segment was verified and manually corrected, if necessary. If tracing was still judged incorrect, the specific segment was excluded from the global strain measurement. If more than two segments were discarded, GLS and strain rates were not reported for that patient. The GLS and strain rates were determined by averaging all values of the 18 segments of the three views. Strain analysis with optimal tracking was feasible in 93% of all segments.

2.6 | Blood samples and biomarkers

Blood samples were obtained by venipuncture in the antecubital vein for the evaluation of N-terminal pro B-type natriuretic peptide (NT-pro BNP) and GRK2. The blood was then centrifuged to separate the cellular and plasmatic fraction and was stored at −80°C until the day of the assay. N-terminal pro B-type natriuretic peptide was assessed by electrochemiluminescence immunoassay on an Elecsys 2010 analyzer using Roche assay kits (Roche Diagnostic, Mannheim, Germany) according to the manufacturer’s instructions.

2.7 | G protein-coupled receptor kinase 2

The expression of G protein-coupled receptor kinase 2 (GRK2) was measured by Western blotting (for more detailed information on GRK2 evaluation see section S4 of the Supporting Information).

2.8 | Exercise training intervention

Patients were randomized to either a 12-week structured exercise training program including two weekly supervised HIIT sessions or a usual care group. An additional resistance training (RT) was performed following each HIIT session. All trainings were center-based under supervision of an experienced kinesiologist. The HIIT training protocol was recently described by Guiraud et al. Following a 5-minute warm-up at 30% of peak work load obtained at the CPET, patients performed two to three sets of 6 to 8 minutes with repeated bouts of 15 to 30 seconds at 100% of peak work load alternated by 15 to 30 seconds of passive recovery. The targeted Borg rating of perceived exertion (RPE) was set at 15 during the HIIT bouts. The sets were separated by a 5-minute active recovery phase at 30% of peak work load. The training session was terminated by a 5-minute cool-down phase at 30% of peak work load. RT consisted of 20 minutes of circuit weight training performed with elastic bands and free weight adapted to each patient’s capacity. For each muscle group, patients performed one set of 15 to 20 repetitions, followed by a 30-second rest period at a target RPE of 15.

2.9 | Usual care group

The control group received recommendations regarding physical activity for a period of 12 weeks by their discharging cardiologist. If there were no recommendations at discharge, physical activity recommendations consistent with recent guidelines were given. Patients were encouraged for 30 to 60 minutes of moderate-intensity (target RPE of 12-14) at least 5 days and preferably 7 days per week. Following completion of the study, subjects randomized into the usual care group had the opportunity to participate in structured supervised exercise training program offered by the ÉPIC Center of the Montreal Heart Institute.

2.10 | Statistical analyses

Data are presented as mean ± SD for continuous variables, while frequencies and percentages are presented for categorical variables. Baseline characteristics were compared between the two groups using Student t test in case of continuous variables and categorical variables were compared using chi-square test. Repeated measures ANOVA models were used to study the CPET and echocardiographic parameters across time and between groups. Models with time, group, and group × time interaction as independent variables were used. The group × time interaction was the main focus of the analysis as it tested the difference in the change (post-pre) between the two groups. As a measure of effect size to evaluate the strength of the intervention effect (HIIT) vs usual care, the Hedge’s g calculated by the formula below was presented.

\[
Hedge's
g = \frac{M_1 - M_2}{\sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 1}}}
\]

where \(M_1\) = mean of the change (post-pre) in HIIT group, \(M_2\) = mean of the change (post-pre) in usual care group, \(SD_1\) = SD of the change (post-pre) in HIIT group, \(SD_2\) = SD of the change (post-pre) in usual care group, \(n_1\) = number of subjects in HIIT group, \(n_2\) = number of subjects in usual care group.

An absolute value between 0.5 and 0.8 for g was considered as a medium effect and an absolute value >0.8 for g was considered as a high effect. In addition, under the repeated measures ANOVA model, the change (post-pre) within each group was formally tested against zero. All analyses were done with SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and conducted at the 0.05 significance level.
3 | RESULTS

3.1 | Clinical characteristics

A total of 19 were included in the final analysis (HIIT: n = 9, usual care group: n = 10). Baseline clinical characteristics of CHD patients with a recent AMI, either randomized to the HIIT or usual care group are summarized in Table 1. There were no significant differences between the groups with regards to demographic data, event details and baseline medication except for a lower number of patients on inhibitors of the renin angiotensin aldosterone system (ACE inhibitor or angiotensin receptor blocker) in the HIIT group (P < .05).

TABLE 1 Baseline characteristics of CHD patients randomized to the HIIT or usual care group

| Variable                      | HIIT, n = 9 (mean ± SD) | Usual care, n = 10 (mean ± SD) | P-value |
|-------------------------------|-------------------------|-------------------------------|---------|
| Age (y)                       | 60 ± 10                 | 57 ± 13                       | .494    |
| Male sex                      | 6 (67)                  | 7 (70)                        | .876    |
| Height (m)                    | 1.70 ± 0.13             | 1.71 ± 0.11                   | .798    |
| Weight (kg)                   | 81.9 ± 9.1              | 86.5 ± 18.2                   | .508    |
| Body mass index (kg/m²)       | 28.7 ± 4.2              | 29.4 ± 4.8                    | .719    |
| Lean body mass                | 58.3 ± 10.8             | 58.6 ± 13.8                   | .956    |
| Fat mass (%)                  | 29.0 ± 9.6              | 32.3 ± 8.3                    | .433    |
| Systolic BP (mm Hg)           | 116 ± 11                | 121 ± 10                      | .300    |
| Diastolic BP (mm Hg)          | 68 ± 9                  | 74 ± 10                       | .184    |

Event characteristics

| AMI                           | 9 (100)                 | 10 (100)                      | NA      |
| STEMI                         | 4 (44)                  | 8 (80)                        | .109    |
| Primary PCI                   | 9 (100)                 | 10 (100)                      | NA      |

Cardiovascular risk profile

| Active smoking                | 1 (11)                  | 2 (20)                        | .596    |
| Hypertension                  | 5 (56)                  | 5 (50)                        | .809    |
| Type 2 diabetes mellitus      | 0 (0)                   | 1 (10)                        | .330    |
| Dyslipidemia                  | 7 (78)                  | 10 (100)                      | .115    |

Baseline medication

| Aspirin                       | 8 (89)                  | 10 (100)                      | .279    |
| DAPT                          | 9 (100)                 | 10 (100)                      | NA      |
| Lipid-lowering therapy        | 9 (100)                 | 10 (100)                      | NA      |
| RAAS inhibitors               | 2 (22)                  | 7 (70)                        | .037    |
| Beta-blockers                 | 7 (78)                  | 9 (90)                        | .466    |
| CCB                           | 1 (11)                  | 1 (10)                        | .937    |

Note: Data are expressed as mean ± SD, dichotomous variables are expressed as numbers and percentages.

Abbreviations: AMI, acute myocardial infarction; BP, blood pressure; CCB, calcium channel blocker; CHD, coronary heart disease; DAPT, dual antiplatelet therapy; HIIT, high-intensity interval training; NA, not applicable; PCI, percutaneous coronary intervention; RAAS inhibitors; inhibitors of the renin angiotensin aldosterone system; STEMI, ST elevation myocardial infarction.

3.2 | Maximal CPET parameters

Table 2 shows maximal CPET parameters pre- and post-training in CHD patients randomized to the HIIT or usual care group (for a more detailed description of the results of CPET parameters we refer to section S5 of the Supporting Information).

3.3 | Echocardiographic parameters

Echocardiographic parameters of LV geometry, systolic and diastolic function in both groups are summarized in Table 3 for a more detailed description of the results of echocardiographic parameters we refer to section S6 of the supplemental text.

3.4 | Cardiac biomarkers

N-terminal pro B-type natriuretic peptide levels were 290 ± 420 pg/mL in the HIIT and 200 ± 154 pg/mL in the usual care group at baseline. No significant group × time interaction was found (P = .647; g = −0.23) nor time effect but patients in the HIIT group exhibited a more pronounced decrease in NT-pro BNP levels after completion of the training intervention. No significant group × time interaction was found for GRK2 expression (P = .128; g = −0.72) nor time effect. However, in the HIIT group, GRK2 expression decreased with training, while there was an increase in the usual care group (Δ post-pre: −34.3 ± 54.3% in the HIIT and +23.0 ± 95.7% in the usual care group; P > .05 for Δ post-pre in both groups). GRK2 protein expressions for the two groups pre- and post-training are presented in Figure 1.

4 | DISCUSSION

The main findings in our pilot investigation evaluating the effects of HIIT on ventricular remodeling in a highly vulnerable patient group (ie, patients who suffered a recent AMI) are: (a) VO2peak, oxygen uptake efficiency slope (OUES), and O2 pulse improved solely in the HIIT group. (b) HIIT overall exhibited a more favorable cardiac remodeling with regard to echocardiographic parameters of LV function as compared to the usual care group. (c) These changes were not associated with a significant change in cardiac biomarkers (ie, NT-pro BNP levels and GRK2 expression).

4.1 | The impact of HIIT on CPET parameters

Key CPET parameters like VO2peak, OUES, and O2 pulse (including O2 pulse trajectory) are highly relevant predictors of mortality and morbidity in CHD patients.28-30 Structured exercise training regardless of training modality has proven to improve these parameters.29,31 However, in our study only patients in the HIIT group showed a substantial VO2peak improvement and reached a normal age-predicted VO2peak after completion of the program with the identical level of exhaustion (ie, RER) as compared to the usual care group. This improvement is consistent with existing data in the identical population and with the
|                          | HIIT, n = 9 (mean ± SD) | Usual care, n = 10 (mean ± SD) | Group × time interaction P-value (Hedge’s g) |
|--------------------------|-------------------------|---------------------------------|---------------------------------------------|
| **VO₂ peak/LBM (mL/min/kg)** |                         |                                 |                                             |
| Pre                      | 27.6 ± 6.9              | 29.2 ± 4.3                      | 0.012 (1.29)                                |
| Post                     | 30.6 ± 6.6              | 29.3 ± 4.6                      |                                             |
| Δ (post-pre)             | 3.1 ± 2.4               | 0.1 ± 2.3                       |                                             |
| P-value Δ (post-pre)*    | 0.0009                  | 0.879                           |                                             |
| **VO₂ peak % predicted** |                         |                                 |                                             |
| Pre                      | 93.4 ± 27.0             | 90.9 ± 26.4                     | 0.026 (1.12)                                |
| Post                     | 101.4 ± 29.8            | 90.0 ± 24.7                     |                                             |
| Δ (post-pre)             | 8.0 ± 7.8               | −0.9 ± 8.1                      |                                             |
| P-value Δ (post-pre)*    | 0.008                   | 0.725                           |                                             |
| **Peak work load (W)**  |                         |                                 |                                             |
| Pre                      | 120.0 ± 46.3            | 127.1 ± 39.9                    | 0.533 (0.29)                                |
| Post                     | 132.2 ± 49.6            | 135.7 ± 43.5                    |                                             |
| Δ (post-pre)             | 12.2 ± 12.8             | 8.6 ± 12.0                      |                                             |
| P-value Δ (post-pre)*    | 0.009                   | 0.042                           |                                             |
| **Peak RER**             |                         |                                 |                                             |
| Pre                      | 1.19 ± 0.05             | 1.16 ± 0.08                     | 0.182 (−0.78)                               |
| Post                     | 1.14 ± 0.09             | 1.14 ± 0.05                     |                                             |
| Δ (post-pre)             | −0.05 ± 0.06            | −0.00 ± 0.06                    |                                             |
| P-value Δ (post-pre)*    | 0.034                   | 0.723                           |                                             |
| **RPP**                  |                         |                                 |                                             |
| Pre                      | 22 205 ± 4581           | 24 361 ± 5802                   | 0.215 (0.59)                                |
| Post                     | 22 430 ± 4509           | 22 689 ± 4635                   |                                             |
| Δ (post-pre)             | 224 ± 3964              | −1 672 ± 2 328                  |                                             |
| P-value Δ (post-pre)*    | 0.836                   | 0.117                           |                                             |
| **Peak sBP (mm Hg)**     |                         |                                 |                                             |
| Pre                      | 178.0 ± 26.2            | 185.1 ± 25.6                    | 0.068 (0.90)                                |
| Post                     | 179.9 ± 23.6            | 175.2 ± 21.7                    |                                             |
| Δ (post-pre)             | 1.9 ± 14.0              | −9.9 ± 12.3                     |                                             |
| P-value Δ (post-pre)*    | 0.672                   | 0.029                           |                                             |
| **Peak dBP (mm Hg)**     |                         |                                 |                                             |
| Pre                      | 78.3 ± 11.7             | 79.0 ± 10.2                     | 0.882 (0.07)                                |
| Post                     | 74.7 ± 10.1             | 76.0 ± 10.2                     |                                             |
| Δ (post-pre)             | −3.7 ± 7.1              | −3.0 ± 11.3                     |                                             |
| P-value Δ (post-pre)*    | 0.268                   | 0.337                           |                                             |
| **Peak HR (bpm)**        |                         |                                 |                                             |
| Pre                      | 124.3 ± 13.8            | 130.6 ± 21.2                    | 0.799 (0.12)                                |
| Post                     | 124.8 ± 22.3            | 129.5 ± 22.5                    |                                             |
| Δ (post-pre)             | 0.4 ± 16.6              | −1.1 ± 8.6                      |                                             |
| P-value Δ (post-pre)*    | 0.920                   | 0.793                           |                                             |
| **HR Res (bpm)**         |                         |                                 |                                             |
| Pre                      | 59.6 ± 10.8             | 59.5 ± 20.3                     | 0.958 (−0.03)                               |
| Post                     | 61.1 ± 14.5             | 61.2 ± 19.3                     |                                             |
| Δ (post-pre)             | 1.5 ± 13.3              | 1.8 ± 7.3                       |                                             |
| P-value Δ (post-pre)*    | 0.745                   | 0.466                           |                                             |
| **OUES**                 |                         |                                 |                                             |
| Pre                      | 1619 ± 409              | 1832 ± 399                      | 0.032 (1.08)                                |
| Post                     | 1830 ± 481              | 1838 ± 507                      |                                             |
| Δ (post-pre)             | 211 ± 168               | 6 ± 209                         |                                             |
| P-value Δ (post-pre)*    | 0.004                   | 0.918                           |                                             |
| **VE/VCO₂ slope**        |                         |                                 |                                             |
| Pre                      | 32.4 ± 3.4              | 30.8 ± 4.7                      | 0.358 (−0.43)                               |
| Post                     | 31.2 ± 3.1              | 30.6 ± 3.3                      |                                             |
| Δ (post-pre)             | −1.2 ± 1.7              | −0.2 ± 3.0                      |                                             |
| P-value Δ (post-pre)*    | 0.157                   | 0.852                           |                                             |

(Continues)
TABLE 2 (Continued)

|                  | HIIT, n = 9 (mean ± SD) | Usual care, n = 10 (mean ± SD) | Group × time interaction P-value (Hedge’s g) |
|------------------|-------------------------|--------------------------------|---------------------------------------------|
| ΔVO₂/ΔWork load slope | Pre 9.1 ± 1.7           | 10.5 ± 1.2                     | 0.178 (0.68)                              |
|                   | Post 9.4 ± 1.1          | 10.0 ± 1.2                     |                                             |
| Δ (post-pre)      | 0.3 ± 0.8               | −0.5 ± 1.6                     |                                             |
| P-value Δ (post-pre)* | 0.234                  | 0.363                          |                                             |
| O₂ pulse (mL/beat) | Pre 13.5 ± 4.0          | 13.2 ± 2.6                     | 0.110 (0.77)                              |
|                   | Post 15.1 ± 4.3         | 13.5 ± 3.3                     |                                             |
| Δ (post-pre)      | 1.5 ± 1.4               | 0.3 ± 1.7                      |                                             |
| P-value Δ (post-pre)* | 0.011                  | 0.588                          |                                             |
| VO₂ at VT1 (%)    | Pre 67 ± 24             | 64 ± 23                        | 0.256 (0.15)                              |
|                   | Post 76 ± 23            | 67 ± 23                        |                                             |
| Δ (post-pre)      | 8 ± 7                   | 3 ± 12                         |                                             |
| P-value Δ (post-pre)* | 0.023                  | 0.373                          |                                             |

Note: Variables are expressed as means ± SD.
Abbreviations: BP, blood pressure; CHD, coronary heart disease; CPET, cardiopulmonary exercise test; HIIT, high-intensity interval training; HR, heart rate; HR Res, heart rate reserve; OUES, oxygen uptake efficiency slope; RER, Respiratory exchange ratio; RPP, rate-pressure product at peak exercise; VE/VCO₂ slope, ventilatory efficiency slope; VO₂, oxygen consumption; VT1, first ventilatory threshold.
*P-value Δ (post-pre) within group.

TABLE 3  Echocardiographic parameters pre- and post-training in CHD patients randomized to the HIIT or usual care group

|                  | HIIT, n = 8 (mean ± SD) | Usual care, n = 10 (mean ± SD) | Group × time interaction P-value (Hedge’s g) |
|------------------|-------------------------|--------------------------------|---------------------------------------------|
| LVMi (g/m²)      | Pre 80.8 ± 20.3          | 71.5 ± 16.7                    | 0.147 (–0.72)                              |
|                   | Post 71.4 ± 17.5         | 75.5 ± 15.7                    |                                             |
| Δ (post-pre)      | −9.5 ± 21.8             | 4.0 ± 15.9                     |                                             |
| P-value Δ (post-pre)* | 0.170                  | 0.509                          |                                             |
| LVEDVi (mL/m²)    | Pre 52.5 ± 8.5           | 52.2 ± 15.6                    | 0.574 (–0.44)                              |
|                   | Post 52.0 ± 14.4         | 54.3 ± 19.3                    |                                             |
| Δ (post-pre)      | −0.5 ± 15.1             | 6.0 ± 14.2                     |                                             |
| P-value Δ (post-pre)* | 0.930                  | 0.472                          |                                             |
| LVEF (%)          | Pre 65.9 ± 5.8           | 58.5 ± 8.5                     | 0.114 (–0.90)                              |
|                   | Post 65.0 ± 7.9          | 60.8 ± 6.2                     |                                             |
| Δ (post-pre)      | −0.9 ± 5.6              | 3.6 ± 4.2                      |                                             |
| P-value Δ (post-pre)* | 0.627                  | 0.079                          |                                             |
| GLS (%)           | Pre −20.5 ± 3.2          | −18.1 ± 2.9                    | 0.606 (0.33)                               |
|                   | Post −21.7 ± 3.4         | −19.9 ± 2.2                    |                                             |
| Δ (post-pre)      | −0.8 ± 3.2              | −1.7 ± 2.6                     |                                             |
| P-value Δ (post-pre)* | 0.383                  | 0.076                          |                                             |
| GLSR (s⁻¹)        | Pre −0.95 ± 0.11         | −0.97 ± 0.20                   | 0.616 (0.06)                               |
|                   | Post −1.07 ± 0.26        | −1.14 ± 0.31                   |                                             |
| Δ (post-pre)      | −0.11 ± 0.28            | −0.13 ± 0.21                   |                                             |
| P-value Δ (post-pre)* | 0.298                  | 0.042                          |                                             |
| Circumferential strain (%) | Pre −14.7 ± 2.1          | −14.0 ± 5.7                    | 0.967 (0.02)                               |
|                   | Post −18.5 ± 5.3         | −18.0 ± 5.0                    |                                             |
| Δ (post-pre)      | −4.3 ± 7.5              | −4.5 ± 10.6                    |                                             |
| P-value Δ (post-pre)* | 0.269                  | 0.167                          |                                             |
biggest and latest of numerous meta-analyses comparing HIIT and MICET in a population of CHD patients who reported the most pronounced improvements with HIIT after 7 to 12 weeks of training.16,32

The finding that VO₂ at the VT1 improved only in the HIIT group indicates an improvement in muscular function as a result of structured exercise training and is plausible.33

### TABLE 3

(Continued)

|                        | HIIT, n = 8 (mean ± SD) | Usual care, n = 10 (mean ± SD) | Group × time interaction | P-value (Hedge’s g) |
|------------------------|-------------------------|--------------------------------|--------------------------|--------------------|
| Systolic SR (s⁻¹)      |                         |                                |                          |                    |
| Pre                    | −0.77 ± 0.11            | −0.83 ± 0.33                   | 0.634 (0.37)             |                    |
| Post                   | −0.74 ± 0.87            | −1.07 ± 0.35                   |                          |                    |
| Δ (post-pre)           | 0.01 ± 0.99             | −0.25 ± 0.50                   |                          |                    |
| P-value Δ (post-pre)   | 0.981                   | 0.193                          |                          |                    |
| Radial strain (%)      |                         |                                |                          |                    |
| Pre                    | 28.8 ± 9.7              | 24.5 ± 6.1                     | 0.450 (0.40)             |                    |
| Post                   | 41.6 ± 13.3             | 31.5 ± 12.2                    |                          |                    |
| Δ (post-pre)           | 14.7 ± 10.8             | 9.4 ± 14.5                     |                          |                    |
| P-value Δ (post-pre)   | 0.040                   | 0.131                          |                          |                    |
| Systolic SR (s⁻¹)      |                         |                                |                          |                    |
| Pre                    | 1.15 ± 0.41             | 1.35 ± 0.84                    | 0.476 (0.75)             |                    |
| Post                   | 1.75 ± 0.48             | 1.16 ± 0.46                    |                          |                    |
| Δ (post-pre)           | 0.28 ± 0.28             | −0.37 ± 1.04                   |                          |                    |
| P-value Δ (post-pre)   | 0.549                   | 0.621                          |                          |                    |
| Peak E (cm/s)          |                         |                                |                          |                    |
| Pre                    | 68.5 ± 14.8             | 67.6 ± 17.7                    | 0.699 (−0.19)            |                    |
| Post                   | 69.1 ± 11.0             | 71.7 ± 16.1                    |                          |                    |
| Δ (post-pre)           | 0.6 ± 20.6              | 4.1 ± 15.6                     |                          |                    |
| P-value Δ (post-pre)   | 0.933                   | 0.428                          |                          |                    |
| Peak A (cm/s)          |                         |                                |                          |                    |
| Pre                    | 71.9 ± 22.4             | 66.7 ± 16.0                    | 0.214 (0.61)             |                    |
| Post                   | 77.8 ± 15.9             | 64.5 ± 20.8                    |                          |                    |
| Δ (post-pre)           | 5.9 ± 13.6              | −2.2 ± 12.8                    |                          |                    |
| P-value Δ (post-pre)   | 0.224                   | 0.604                          |                          |                    |
| E/A ratio              |                         |                                |                          |                    |
| Pre                    | 1.02 ± 0.38             | 1.06 ± 0.38                    | 0.140 (−0.74)            |                    |
| Post                   | 0.94 ± 0.36             | 1.21 ± 0.43                    |                          |                    |
| Δ (post-pre)           | −0.08 ± 0.33            | 0.15 ± 0.29                    |                          |                    |
| P-value Δ (post-pre)   | 0.479                   | 0.148                          |                          |                    |
| TDI-e' septal (cm/s)   |                         |                                |                          |                    |
| Pre                    | 7.3 ± 1.2               | 8.3 ± 1.6                      | 0.310 (0.50)             |                    |
| Post                   | 8.8 ± 1.4               | 8.9 ± 2.2                      |                          |                    |
| Δ (post-pre)           | 1.5 ± 1.6               | 0.6 ± 2.0                      |                          |                    |
| P-value Δ (post-pre)   | 0.032                   | 0.310                          |                          |                    |
| TDI-e' lateral (cm/s)  |                         |                                |                          |                    |
| Pre                    | 9.1 ± 3.1               | 9.7 ± 3.2                      | 0.650 (0.21)             |                    |
| Post                   | 10.1 ± 2.2              | 10.1 ± 2.5                     |                          |                    |
| Δ (post-pre)           | 1.0 ± 2.4               | 0.4 ± 3.0                      |                          |                    |
| P-value Δ (post-pre)   | 0.317                   | 0.650                          |                          |                    |
| E/e'                   |                         |                                |                          |                    |
| Pre                    | 8.7 ± 1.7               | 7.2 ± 1.7                      | 0.103 (−0.82)            |                    |
| Post                   | 7.8 ± 2.0               | 8.4 ± 1.6                      |                          |                    |
| Δ (post-pre)           | −0.9 ± 2.4              | 1.2 ± 2.7                      |                          |                    |
| P-value Δ (post-pre)   | 0.319                   | 0.167                          |                          |                    |

Note: Variables are expressed as means ± SD.
Abbreviations: CHD, coronary heart disease; GLS, global longitudinal strain; GLSR, global longitudinal strain rate; HIIT, high-intensity interval training; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVMi, left ventricular mass index; SR, strain rate; Peak A, peak late mitral inflow velocity; Peak E, peak early mitral inflow velocity; TDI-e' lateral, tissue Doppler imaging-derived peak early diastolic lateral mitral annulus velocity; TDI-e' septal, tissue Doppler imaging-derived peak early diastolic septal mitral annulus velocity; E/e', peak early mitral inflow velocity to peak early diastolic mitral annulus velocity ratio.

*P-value Δ (post-pre) within group.
4.2 | The impact of HIIT on echocardiographic parameters of cardiac remodeling

To the best of our knowledge, our pilot study for the first time shows beneficial effects of a HIIT program on cardiac remodeling in patients with a recent AMI. Existing literature has shown that aerobic exercise training starting early after AMI has no detrimental effects and even reverses ventricular remodeling in post-AMI LV dysfunction.12,34,35 Additional data suggest a more favorable cardiac remodeling after HIIT as compared to the more established MICET or a control group in chronic stable post-AMI patients with heart failure.36 However, the effects of HIIT in patients with a recent AMI and potential acute transient LV dysfunction have never been examined.

First of all, patients in our cohort were on optimal and stable medical therapy. The primary explanation for the lower number of patients on inhibitors of the renin angiotensin aldosterone system in the HIIT group is the lower number of STEMI patients in this group and the absence of LV dysfunction requiring this medication in the whole cohort before inclusion into the study. Importantly, after completion of the program all patients in our study except for one had a normal LVEF, left ventricular mass and volumes (indexed by body surface area), and no higher degree diastolic dysfunction (ie, diastolic dysfunction > grade I) based on recent recommendations.23,24 In our pilot study, all these "conventional" parameters remained stable with HIIT, which is in line with other studies that employed lower training intensities.12,35 Furthermore, e' septal as a parameter of diastolic function showed a significant improvement with training only in the HIIT group. However, there were no significant changes with e' lateral and E/e', respectively. Thus far, HIIT has been shown to improve e' in post-AMI heart failure patients only.36 On the other hand, GLS rate showed a slight improvement only in the usual care group in our study. Similarly, the most important parameter in the prediction of ventricular remodeling, GLS, tended to improve over time, but more pronounced in the usual care group.4 A recent explorative non-randomized study found no beneficial effects on left ventricular dimension and function in post-AMI patients (including GLS and LV twist).37 In a comparable but larger cohort of 200 CHD patients without heart failure comparing HIIT and MICET there was no reverse cardiac remodeling over time, regardless of training modality.38 Of note, after completion of the program both patient groups in our study reached normal GLS values compared to those reported in healthy individuals.39 Moreover, radial strain showed a significant training effect with an improvement only in the HIIT group. Being aware of the technical limitations regarding radial strain, this is the first study to show an improvement in radial strain after HIIT in post-AMI patients.40 This contrasts with studies that report a decrease of LV systolic (including strain analysis) and diastolic functional parameters.41,42 However, these findings in healthy subjects and athletes seem to be transient and particularly after prolonged and strenuous exercise and are discussed controversial.

4.3 | The impact of HIIT on cardiac biomarkers

Based on the CPET and echocardiographic findings in our study, the statement that no patient in our study developed heart failure within the first months of a first AMI is of utmost importance. This is confirmed in normal NT-pro BNP levels in our patient cohort. On the one hand this mirrors optimized treating strategies in recent decades, but it also explains that only insignificant changes in cardiac biomarkers (particularly GRK2 expression) were detected in this first exploration of CHD patients who recently suffered an AMI undergoing HIIT.

4.4 | Limitations

Our findings have to be interpreted in the context of numerous limitations. First of all, the sample size in the present pilot study was small with inclusion of predominantly male patients at a single tertiary institution. The initial power calculation to randomize 10 patients to each arm (20 total) calculated to have 80% power to demonstrate a significant reduction of GRK2 expression with HIIT in this population was based on a prospective exercise training study in patients with chronic heart failure.13 Moreover, data of one patient in the HIIT group were
not available for GRK2 expression. Only eight patients in the HIIT group underwent an echocardiographic examination before and after completion of the training intervention. For the most relevant advanced echocardiographic parameters (i.e., GLS) there were no data of at least one more patient in the whole cohort due to insufficient tracing and missing data.

In summary, the finding that no patient developed heart failure in our study may emphasize improved treating strategies over the last decades in this population (i.e., revascularization, medication) on one hand. On the other hand, the fact that no adverse event occurred during the study together with the reported findings may indicate that HIIT is safe in this specific population. Future studies may be applied to a sicker cohort (i.e., patients with confirmed LV dysfunction post-AMI).

5 | CONCLUSIONS

In patients with a recent AMI without LV dysfunction, HIIT leads to significant improvements regarding prognostic CPET parameters ($VO_{2peak}$, OUES) compared to a usual care group. HIIT overall exhibited a more favorable cardiac remodeling with regard to echocardiographic parameters of LV function.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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