Right Ventricular Function After Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention (from the Glycometabolic Intervention as Adjunct to Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction III Trial)

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Right ventricular (RV) dysfunction is a powerful risk marker after acute myocardial infarction (MI). Primary percutaneous coronary intervention (PCI) has markedly reduced myocardial damage of the left ventricle, but reliable data on RV damage using cardiac magnetic resonance imaging (MRI) are scarce. In a recent trial of patients with acute MI treated with primary PCI, in which the primary end point was left ventricular (LV) ejection fraction after 4 months measured with MRI, we conducted a prospectively defined substudy in which we examined RV function. RV ejection fraction (RVEF) and RV scar size were measured with MRI at 4 months. Tricuspid annular plane systolic excursion (TAPSE) and RV free wall longitudinal strain (FWLS) were assessed using echocardiography before discharge and at 4 months. We studied 258 patients without diabetes mellitus; their mean age was 58 ± 11 years, 79% men and mean LV ejection fraction was 54 ± 8%. Before discharge, 5.2% of patients had TAPSE < 17 mm, 32% had FWLS > L 20% and 11% had FWLS > L 15%. During 4 months, TAPSE increased from 22.8 ± 3.6 to 25.1 ± 3.9 mm (p < 0.001) and FWLS increased from −22.6 ± 5.8 to −25.9 ± 4.7% (p < 0.001). After 4 months, mean RVEF on MRI was 64.1 ± 5.2% and RV scar was detected in 5 patients (2%). There was no correlation between LV scar size and RVEF (p [0.9), TAPSE (p [0.1), or RV FWLS (p [0.9). In conclusion, RV dysfunction is reversible in most patients and permanent RV ischemic injury is very uncommon 4 months after acute MI treated with primary PCI. © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). (Am J Cardiol 2016;118:338e344)

Right ventricular (RV) dysfunction is a powerful predictor of outcome after acute myocardial infarction (MI). Most studies on RV injury after acute MI was performed in the thrombolysis era. Despite the current large-scale use of primary percutaneous coronary intervention (PCI), RV dysfunction after acute MI remains common and associated with worse prognosis. In most studies, results are based on conventional echocardiography early after MI, whereas the RV frequently recovers from ischemic injury in the post-MI period. In the current era of primary PCI, the degree of left ventricular (LV) damage is increasingly limited. In a recent study on the potential value of metformin in acute MI, it was demonstrated that mean left ventricular ejection fraction (LVEF) 4 months after PCI was 54%. Any effects on RV functional parameters of this early intervention, in such cohort of patients with large myocardial areas at risk, were not reported. Since the RV is relatively protected against ischemic injury, we hypothesize that RV systolic function remains preserved after early PCI. In the present study, we therefore aimed to evaluate RV function after acute MI treated with PCI using both MRI and echocardiography.

Methods

The design and results of the Glycometabolic Intervention as Adjunct to Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction (GIPS) III trial have been published previously. In brief, the GIPS-III was a prospective, double-blind, randomized placebo-controlled trial, in patients who underwent primary PCI for ST-segment elevation MI (STEMI). The trial was...
Coronary Artery Disease/RV Function After Acute Myocardial Infarction

Patients randomized after successful infarct-artery PCI

380

105 Did not undergo cardiac MRI
36 Experienced claustrophobia
35 Refused
14 Had contraindication for MRI
10 Underwent CABG surgery
4 Received ICD or pacemaker
4 Too large for scanner
1 Could not tolerate scanner sound
1 Withdraw consent

275 Underwent cardiac MRI

17 MRI studies excluded
14 Due to insufficient image quality for functional assessment
3 Basal part of RV not included in short-axis stacks

258 Included in the current study
258 RVEF assessment
254 RV LGE assessment
233 TAPSE assessment
142 RV FWLS assessment

Figure 1. Flow of patients included in the present study. In case of multiple reasons for exclusion, only the primary reason of each case is shown. CABG = coronary artery bypass grafting; ICD = implantable cardioverter–defibrillator. (TAPSE) was obtained with M-mode parallel to the RV free wall and across the tricuspid annular plane and TAPSE <17 mm was defined abnormal. The longitudinal systolic movement of the lateral RV annulus was measured. RV free wall longitudinal strain (FWLS) was analyzed on the standard apical 4-chamber view using 2-dimensional (2-D) speckle tracking software by 2 investigators (TMG and YMH) using GE EchoPAC version BT12. Echocardiographic images with poor quality or poor tracking of 2 or more RV wall segments were excluded from the analysis. The endocardial border of the RV wall was manually traced according to current recommendations. On the most basal part, sampling of the right atrium, tricuspid annulus, and pericardium was avoided. RV FWLS was calculated as the mean of basal, mid, and apical segments of the RV free wall (Supplementary Data). RV FWLS >−20% is suggested moderately reduced and >−15% severely reduced. Intraobserver and interobserver reliability for RV FWLS measurements was assessed using 30 randomly selected studies.

Data were reported as mean ± SD for normally distributed data, median (interquartile range) for skewed distributed data or n (%) for categorical variables. Differences in continuous variables between subgroups were assessed using independent samples t tests, Mann–Whitney U tests or one-way analysis of variance, according to distribution and the level of subgroups. Differences in categorical variables between groups were performed using chi-square tests. Change in RV FWLS during the 4 months was compared using paired samples t tests. Correlations between continuous variables were performed using Pearson’s correlation. Intraobserver and interobserver variability of RV FWLS
designed to study the effect of metformin. All patients had an electrocardiographic recording with ST-segment elevation of more than 0.1 mV in 2 or more leads and were treated with at least 1 stent sized ≥3.0 mm. Major exclusion criteria were: previous MI, diabetes, and need for coronary artery bypass grafting. In the GIPS-III clinical trial, 380 patients were randomized 1:1 to receive metformin or placebo. The primary efficacy measure was LVEF measured by MRI 4 months after PCI. The GIPS-III trial demonstrated no significant difference in LVEF. All patients underwent additional echocardiographic assessment before discharge and 4 months. The study complies with the Declaration of Helsinki and was approved by the local ethics committee (Groningen, the Netherlands). All patients included in the GIPS-III trial provided written informed consent.

MRI studies were performed on 3.0-T scanner (Achieva, Philips, Best, The Netherlands). Electrocardiogram-gated cine steady state, free precession images were acquired with breath holding in contiguous short-axis slices covering the entire RV and LV (TR 3.9 ms; TE 1.94 ms; flip angle 45°; matrix 180 × 220; voxel size 1.25 × 1.25 × 10 mm; slice thickness 10 mm; and slice gap 0 mm). Using identical slice locations, late gadolinium enhancement (LGE) images were acquired 10 minutes after intravenous administration of a gadolinium-based contrast agent (Dotarem, Gorkinchem, the Netherlands; 0.2 mmol/kg) with an inversion recovery, gradient echo pulse sequence to identify the location and extent of MI. The inversion time was individually set to null the signal of viable myocardium (TR 5.2 ms; TE 2.5 ms; flip angle 5°; matrix 192 × 157; voxel size 1.25 × 1.25 × 10 mm; slice thickness 10 mm; and slice gap 0 mm).

RV volumetric measurements were performed by a single experienced observer (TMG), blinded for medical history and treatment allocation. The endocardial and epicardial contours of the RV were traced manually on all end-systolic and end-diastolic slices, using QMass 7.6 (Medis, Leiden, the Netherlands). On the most basal slice, the right atrium and the pulmonary artery were excluded. Papillary muscle and trabeculae were included in the RV blood volume. RV end-systolic and end-diastolic volumes, stroke volume, ejection fraction (RVEF), and mass were calculated. The presence of RV LGE was visually determined by 2 independent observers, blinded for medical history and treatment allocation. The endocardial border of the RV wall was manually traced according to current recommendations. On the most basal part, sampling of the right atrium, tricuspid annulus, and pericardium was avoided. RV FWLS was calculated as the mean of basal, mid, and apical segments of the RV free wall (Supplementary Data). RV FWLS >−20% is suggested moderately reduced and >−15% severely reduced. Intraobserver and interobserver reliability for RV FWLS measurements was assessed using 30 randomly selected studies.

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was assessed using 2-way mixed intraclass correlation coefficient. Statistical significance was considered achieved with a p value < 0.05. Statistical analyses were performed using SPSS statistical software for Windows (version 20, 2011).

Results

In total, 380 patients were randomized in the GIPS-III trial, and a total of 258 patients were included in the present study (Figure 1). In a large subset of patients, sufficient echocardiographic imaging was available both before discharge and at 4 months. Baseline characteristics of the study population are outlined in Table 1.

Table 2 summarizes RV and LV function on MRI at 4 months. No patient had reduced RVEF. RVEF was not different according to culprit lesion (i.e., left anterior descending coronary artery [LAD], right coronary artery [RCA], and left circumflex coronary artery [LCX]; p = 0.11). There was no difference in RVEF between patients with LV LGE septal involvement (n = 171) and without septal involvement (n = 72); p = 0.43. RVEF was higher in women compared with men (67% vs 63%, p < 0.001). Age was weakly correlated with RVEF (r = 0.15, p = 0.02). RVEF
Table 2
Right and left ventricular volumes and function

<table>
<thead>
<tr>
<th>MRI after 4 months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RV end-diastolic volume (ml)</td>
<td>159 ± 36</td>
<td></td>
</tr>
<tr>
<td>RV end-systolic volume (ml)</td>
<td>58 ± 18</td>
<td></td>
</tr>
<tr>
<td>RV ejection fraction (%)</td>
<td>64 ± 5</td>
<td></td>
</tr>
<tr>
<td>RV infarct size (% , n=5)</td>
<td>7.4 ± 4.9</td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>193 ± 44</td>
<td></td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>90 ± 33</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>54 ± 8</td>
<td></td>
</tr>
<tr>
<td>LV infarct size (% , n=243)</td>
<td>8.9 ± 7.6</td>
<td></td>
</tr>
</tbody>
</table>

Echocardiography before discharge

| Tricuspid annular plane systolic excursion (mm) | 22.8 ± 3.6 |
| Tricuspid annular plane systolic excursion (% | -22.6 ± 5.8 |

Echocardiography after 4 months

| Tricuspid annular plane systolic excursion (mm) | 25.1 ± 3.9* |
| Tricuspid annular plane systolic excursion (%) | -25.9 ±4.7* |

Variables are expressed as mean ± standard deviation.
* p <0.001 compared with value before discharge.

Table 3
Right ventricular late enhancement after 4 months

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex/age (yrs)</th>
<th>Right coronary artery</th>
<th>RV scar size</th>
<th>LV scar size</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/45</td>
<td>Mid</td>
<td>1.3%</td>
<td>7.0%</td>
<td>Inferoseptal</td>
</tr>
<tr>
<td>2</td>
<td>M/53</td>
<td>Mid</td>
<td>13.2%</td>
<td>6.5%</td>
<td>Inferolateral</td>
</tr>
<tr>
<td>3</td>
<td>M/81</td>
<td>Proximal</td>
<td>7.0%</td>
<td>8.9%</td>
<td>Inferoseptal</td>
</tr>
<tr>
<td>4</td>
<td>M/63</td>
<td>Mid</td>
<td>11.4%</td>
<td>20.6%</td>
<td>Inferoseptal</td>
</tr>
<tr>
<td>5</td>
<td>F/68</td>
<td>Proximal</td>
<td>4.1%</td>
<td>13.2%</td>
<td>Inferoseptal</td>
</tr>
</tbody>
</table>

was not different according to myocardial blush grade (p = 0.24). LVEF was fairly correlated with RVEF (r = 0.25, p <0.001); LV end-diastolic volume index did not correlate with RVEF (r = −0.04, p = 0.55) and also LV scar size was not associated with RVEF (r = −0.01, p = 0.91). There was a slight difference in RVEF between the metformin and placebo group (63% vs 65%, p = 0.03). After adjustment for age, gender and LVEF, this difference did not remain significant (p = 0.11). Indexed RVEDVs above normal reference values were seen in 2 patients (0.8%). RVEDVi was higher in men compared with women (80 vs 70 ml/m², p <0.001) and was fairly correlated with age (r = −0.27, p <0.001). RV LGE was detected in 5 patients (2%; Table 3). All RV infarctions were not isolated but extended throughout the inferior wall. Figure 2 is an example of such patient.

Table 2 depicts echocardiographic measurements of RV function. Before discharge, 1.6 (interquartile range 1.4 to 2.5) days after STEMI, 12 patients (5.2%) had reduced TAPSE. TAPSE values were the same among culprit vessel (i.e., RCA vs LAD, p = 0.40 and RCA vs LCX, p = 0.17). Before discharge, 46 patients (32%) had RV FWLS > −20% and 15 patients (11%) had RV FWLS > −15%. RV FWLS was lower with RCA (−20.6%) than with culprit LAD (−23.6%, p = 0.007) or LCX (−24.9%, p = 0.002).

TAPSE and RV FWLS increased significantly during 4 months (Figure 3). Increase in TAPSE was the same for all culprit vessels (Figure 3). Increase in RV FWLS was more pronounced with culprit RCA (from −20.6% to −24.9%, p <0.001) and LAD (from −23.6% to −26.9%, p <0.001) than in patients with culprit LCX (from −24.9% to 26.0%, p = 0.33; Figure 3).

After 4 months, 1 patient (0.4%) had reduced TAPSE, 14 patients (10%) had RV FWLS > −20%, and 2 patients (1.4%) had RV FWLS > −15%. RV FWLS was significantly lower with RCA than with LAD lesions (−24.8% vs −26.9%, respectively; p = 0.02). There was no significant difference in RV FWLS between culprit RCA and LCX (−24.8 vs −26.0, respectively; p = 0.21). There was no difference in TAPSE and RV FWLS at 4 months between patients with LGE septal involvement and without septal involvement; p = 0.89 and 0.98, respectively. TAPSE was weakly correlated with LVEF (r = 0.15, p = 0.02) but not with LV infarct size (p = 0.18). RV FWLS was not correlated with LVEF (r = −0.07, p = 0.44) nor LV infarct size (r = 0.03, p = 0.71). There was no significant difference in
In contrast to the LV, the vulnerability of the RV to ischemic and reperfusion stimuli is different. In normal physiologic conditions, myocardial oxygen demand of the RV is lower than for the LV, due to lower vascular resistance in the pulmonary compared with the systemic circulation. In addition, because of the thinner free wall and less intracavitary pressure, the RV receives transmural and direct endocardial perfusion in both systole and diastole. Therefore, RV myocardium in the absence of coronary flow still receives a marginal amount of oxygen and nutrients, resulting in “stunning” rather than cell death.

More recently, Masci et al.²¹ yield new insights in this myocardial stunning pattern. RV ischemic injury was reversible in 20% of cases and permanent RV myocardial damage at 4 months after STEMI was demonstrated in 10%. Our study showed an even lower incidence of irreversible damage late after STEMI. As can be expected with this low percentage of RV damage, no RV dysfunction in terms of RVEF and TAPSE was seen. Although MRI is the gold standard RV function, RVEF is a rather gross, volumetric measure. Although MRI derived myocardial strain is useful in assessing regional myocardial function of the LV,²² RV myocardium is often too thin for reliable measurements. In addition, TAPSE is an angle-dependent measurement and only represents longitudinal displacement of the tricuspid annulus. In contrast, 2-D strain echocardiography has demonstrated its value to detect subtle RV myocardial dysfunction in various cardiac diseases.²³,²⁴ Recently, RV global longitudinal strain (GLS) was suggested to be a strong indicator of RV systolic function and prognosis after PCI for acute MI.⁷ However, these echocardiographic assessments were performed within 3 days after PCI, after which the stunning RV may well recover. Furthermore, for RV GLS, the investigators averaged RV free wall and interventricular septal longitudinal strain measurements. Since GLS is intentionally designed for the LV, and RV geometry and contraction pattern are distinctively different, in our opinion, this method cannot be easily adopted to the RV. In the present study, RV function recovered during 4 months after the PCI. This stunning pattern was most pronounced in patients with culprit RCA and LAD, compared with LCX, in whom no post-MI RV dysfunction was observed. This observation is not unexpected because the RV is frequently involved in left-sided anterior and inferior infarctions,²⁵,²⁶ and LAD occlusion often results in apical inferior injury, which may affect the RV.²⁷

How do we explain the absence of permanent RV injury in the current cohort with large myocardial areas at risk, compared with previous studies? The principle of “time is muscle” has led to the critical threshold of <90 minutes door-to-balloon time for primary PCI.²⁸,²⁹ However, symptom-to-balloon time may vary considerably, for instance due to differences in patient awareness or delay in emergency response. Total ischemic times varied between 211 and 297 minutes in previous studies investigating RV injury in STEMI,⁷,²¹,³⁰ which is considerably lower than our 156 minutes. This is similar with previously published data of patients with STEMI in the Netherlands,³⁰ and may be the result of several factors, including favorable geographic conditions and well organized multidisciplinary STEMI health care.³¹ Early successful, primary PCI for STEMI, in a

**Discussion**

This study demonstrated that early after primary PCI for STEMI, RV function was reduced in several patients. Yet, the RV recovered in most patients, and permanent ischemic damage of RV myocardium at 4 months was very uncommon. LV ischemic injury had almost no impact on RV global and regional function.

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**Figure 3. Change in right ventricular function after acute MI.** (A): TAPSE measured before discharge (T0) increased during 4 months (T1) after acute myocardial infarction in all patients. This increase was demonstrated in all subgroups with culprit RCA (p <0.001), LAD (p <0.001), and LCX (p = 0.032). (B): RV FWLS measured before discharge (T0) increased during 4 months (T1) after acute MI in all patients. This increase was more pronounced in patients with culprit RCA (p <0.001) and LAD (p <0.001), than with culprit LCX (p = 0.33). Patients with culprit RCA had the lowest RV FWLS early and late after the infarction.
discussed.

Some limitations merit emphasis. First, serial MRI data were lacking in this study; hence, we were not able to assess right ventricular infarction as a surrogate measure of RV involvement at baseline. Second, the authors have no conflicts of interest to disclose.

**Supplementary Data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.05.006.


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