Low adiponectin blood concentration predicts left ventricular remodeling after ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention

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Abstract

Background: Left ventricular remodeling (LVR), an increase in left ventricular end-diastolic volume index ≥ 20%, is an adverse consequence of myocardial infarction. The aim of this study was to assess the association between LVR and adiponectin, which has been shown to protect against myocardial ischemia-reperfusion injury.

Methods: In 75 patients echocardiographic examination was performed one year after ST-segment elevation myocardial infarction, successfully treated with primary percutaneous coronary intervention (pPCI). Two groups of patients were analyzed: those with LVR (n = 15) and those without LVR (n = 60).

Results: The predictors of LVR were: anterior myocardial infarction, glucose at admission, baseline C-reactive protein, adiponectin, and echocardiographic parameters: left ventricular end-diastolic and end-systolic volume indices, ejection fraction < 40% and left ventricular wall motion score index (WMSI) at discharge. On multivariable regression analysis, lower adiponectin level (OR = 0.67, 95% CI 0.49–0.91, p < 0.05) and higher WMSI (OR = 20.14, 95% CI 2.62–154.82, p < 0.01) were the only independent negative predictors of LVR. The optimal cut-off for adiponectin for predicting LVR was ≤ 4.7 μg/mL (sensitivity: 73%, specificity: 85%) and this level increased the risk of LVR 15-fold (95% CI 4.05–59.87, p = 0.0001).

Conclusions: Baseline low blood adiponectin concentration, along with WMSI, can be considered as a predictor of the LVR in male patients one year after myocardial infarction and pPCI. (Cardiol J 2010; 17, 1: 49–56)

Key words: adiponectin, myocardial infarction, left ventricular remodeling
**Introduction**

Left ventricular remodeling (LVR) after myocardial infarction (MI) is a dynamic process resulting in global enlargement, changes in geometry and mass of the left ventricle. Remodeling is an important determinant of subsequent heart failure: a major source of morbidity and mortality in the post-infarction population. This adverse consequence occurs in response to the loss of myocardium and sudden increase in ventricular loading conditions, subsequent infarct extension and late hypertrophy in the remote ventricular myocardium [1, 2]. Opening of the infarct-related artery is crucial in the prevention of the LVR [3–5], but several other important factors have been recognized. These are infarct size, anterior location, microvascular dysfunction, mitral regurgitation after MI, contractile reserve and inducible ischaemia [6–11]. The association between inflammation [12] and stress hyperglycaemia [13, 14] on the remodeling process have attracted attention recently.

Adiponectin, an adipose tissue-derived hormone that is down-regulated in obese individuals, affects several signaling pathways in skeletal muscles, liver, cardiac myocytes and vascular cells [15]. Adiponectin has a favorable effect on endothelial function and angiogenesis [16, 17] and suppresses the atherogenic process [18, 19]. Several studies suggest that adiponectin has anti-inflammatory properties [20, 21], reduces endothelial cell apoptosis [22] and promotes nitric oxide production [23]. The protective action of adiponectin against myocardial ischemia-reperfusion injury has been shown recently [24, 25]. The value of adiponectin as a prognostic factor of left ventricular function [26] and future adverse cardiac events [27] after MI has been recently suggested. To our knowledge, the association between blood adiponectin concentration and LVR following MI has not been analyzed.

The aim of the study was to assess the impact of adiponectin on the LVR one year after acute MI successfully treated with primary percutaneous coronary intervention (pPCI).

**Methods**

**Study population**

From the group of patients with the first ST-segment elevation MI, successfully treated with pPCI, 80 men aged ≤ 65 years were initially selected for the study. Successful PCI was defined as the restoration of TIMI 3 grade flow and residual stenosis < 30% at the end of the procedure. In 99% of patients, bare metal stents were implanted. Significant valvular heart disease, atrial fibrillation, atrioventricular block, temporary or permanent stimulation, acute and chronic inflammation or infection, autoimmune diseases, liver kidney and thyroid diseases were considered as grounds for exclusion.

In 68% of patients, glycoprotein IIb/IIIa inhibitor was administered in the course of MI. In patients with multivessel disease, staged PCI of another significant lesion was performed according to agreement reached by the cardiologist and the interventional cardiologist on an individual basis. The pharmacological treatment according to the current standards was recommended at discharge (aspirin, clopidogrel for at least 30 days and statins in 100% of patients, beta-blockers in 94% of patients, and angiotensin converting enzyme-inhibitors in 66% of patients).

At one year follow-up (12 ± 1.2 months) we had lost contact with one patient, two patients had died and two patients had experienced subsequent MI. In the other 75 patients who formed the study group echocardiographic examination was performed. An increase in left ventricular end-diastolic volume index (LVEDVI) ≥ 20% was accepted as a surrogate for remodeling. The data was finally analyzed in groups of patients divided into those with LVR (n = 15; 20%) and those without LVR (n = 60; 80%).

**Echocardiographic examination**

Echocardiographic study was performed on the second or third day after admission with Sonos 5500, S3 probe. The harmonic option was used to enhance the visualization of the endocardium. LVEDV, left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) was assessed at four-chamber and two-chamber apical views with the biplane Simpson’s formula. Left ventricular volumes indexed by body surface area (LVEDVI, LVESVI) were calculated. Impaired systolic function was diagnosed in cases of LVEF below 40%. For each segment of LV, wall motion was scored from one (normal) to four (dyskinetic) and global wall motion score index (WMSI) was calculated as the average over 16 segments. From the pulse-wave Doppler mitral inflow tracings recorded from the four-chamber apical view the following parameters were measured: early (E), and late (A) transmitral peak flow velocities, E/A ratio and E wave deceleration time (DT).

**Laboratory measurements**

Fasting blood samples for measurements of adiponectin were taken on the next day after ad-
mission for ST elevation myocardial infarction. Plasma for measurements was frozen at –70° until analysis with the quantitative sandwich enzyme immunoassay technique (ELISA) obtained from R&D Systems Inc. Plasma triglycerides (TG) and total cholesterol (TCH) were measured by enzymatic analytical chemistry. HDL-cholesterol (HDL-CH) was precipitated using dextran-sulphate and measured enzymatically. The LDL-cholesterol (LDL-CH) was calculated using the Friedewald equation: 

\[ \text{LDL-CH} = \text{TCH} - \left( \frac{\text{TG}}{5} \right) - \text{HDL-CH} \]

Hyperlipidemia was diagnosed in case of hypercholesterolemia (TCH > 200 mg/dL) with LDL-CH (LDL > 100 mg/dL) and/or hypertriglyceridemia (TG > 150 mg/dL) and low HDL-CH (HDL-CH < 40 mg/dL).

### Statistical analysis

Continuous variables were presented as mean ± standard deviation. Variables were log-transformed before statistical analysis if necessary. Comparisons between analyzed groups (with LVR and without LVR) were performed using the two-tailed, non-paired Student t test or Mann-Whitney test, as appropriate. Differences in echocardiographic variables at baseline and at one-year follow-up were assessed with the paired Student’s t test. Categorical data were summarized as frequencies and percentages, and comparisons between the groups were performed with \( \chi^2 \) test or Fisher’s exact test. The independent predictors of LVR were assessed using the multivariate logistic regression analysis, including variables that were significantly associated with LVR in univariate analysis. The variables included in the univariate logistic regression analysis were: age, smoking, obesity, diabetes mellitus, hypertension, dyslipidemia, time since the onset of symptoms to admission, anterior myocardial infarction, multivessel disease, glucose at admission, baseline blood levels of adiponectin and C-reactive protein (CRP), baseline LVEDVI, LVESVI, LVEF < 40%, WMSI, E/A and DT. Results were expressed as odds ratio (OR) and confidence interval (CI). A receiver-operating characteristics (ROC) curve analysis was used to determine the cut-off values for adiponectin for predicting LVR. P value < 0.05 was considered statistically significant. Statistical analysis was performed using Statistica software (version 6.0; Tulsa, OK, USA) and MedCalc statistical software (version 7.2.1.0 for Windows; Mariakerke, Belgium).

The study was approved by the Internal Ethics Committee of the Medical University of Łódź, and each patient gave informed consent.

### Results

Baseline clinical, biochemical, angiographic and echocardiographic characteristics are presented in Table 1. In the group with remodeling, the number of patients with anterior localization of MI, glucose at admission and baseline levels of CRP were significantly higher and adiponectin concentration lower than in the group without remodeling.

Mean values of several echocardiographic parameters measured at baseline and at one year follow-up differed between the analyzed groups: LVEDVI, LVESVI, LVEF and WMSI were significantly higher in patients with LVR. Systolic dysfunction (LVEF < 40%) was detected in more patients in this group (Table 2).

| Table 1. Baseline characteristics of the study groups. |
|---------------------------------|-----------------|---------|
|                                | With remodeling (n = 15) | Without remodeling (n = 60) | p          |
| Age (years)                    | 55 ± 5           | 54 ± 6  | NS        |
| Hypertension                   | 9 (60%)          | 30 (50%)| NS        |
| Diabetes mellitus              | 5 (33%)          | 12 (20%)| NS        |
| Dyslipidemia                   | 14 (93%)         | 46 (77%) | NS       |
| Obesity                        | 7 (46%)          | 27 (45%) | Ns       |
| Smoking                        | 11 (73%)         | 37 (62%)| NS        |
| Time since the onset of symptoms to admission [h] | 5.0 ± 2.4 | 4.3 ± 2.8 | NS |
| Anterior infarct localization  | 10 (67%)         | 22 (37%)| < 0.05    |
| Multivessel disease            | 6 (40%)          | 23 (38%)| NS        |
| Glucose at admission [mg/dL]   | 166.5 ± 49.7     | 128.0 ± 34.1 | < 0.0001 |
| C-reactive protein [mg/dL]     | 9.7 ± 6.8        | 5.1 ± 4.7 | < 0.01    |
| Adiponectin [μg/mL]            | 4.6 ± 2.2        | 10.1 ± 6.6 | < 0.0001 |
In univariate logistic regression analysis, predictors of LVR were: anterior myocardial infarction, glucose at admission, baseline blood levels of adiponectin and CRP, baseline LVEDVI, LVESVI, LVEF < 40% and WMSI. The final model of multivariable regression analysis demonstrated that lower adiponectin levels and higher WMSI were the independent negative predictors of LVR (Table 3).

Figure 1 shows the area under the ROC curves for adiponectin concentration for predicting LVR (AUC = 0.842; 95% CI = 0.740–0.916). The optimal value of adiponectin for predicting LVR was defined as the concentration with the largest sum of sensitivity plus specificity for each of the curve. The optimal cut-off for adiponectin was £4.7 mg/mL; the sensitivity and specificity were 73% and 85%, respectively.

LVEDVI, LVESVI, LVEF and WMSI significantly differed between the group of patients with blood adiponectin level £4.7 μg/mL (20 patients) and > 4.7 μg/mL (55 patients) both at baseline (58 ± 11 vs 48 ± 11; 27 ± 10 vs 21 ± 7; 50 ± 10 vs 57 ± 9; 1.69 ± 0.43 vs 1.33 ± 0.31, respectively) and at follow up (65 ± 11 vs 49 ± 12; 30 ± 11 vs 22 ± 8; 51 ± 11 vs 58 ± 9; 1.65 ± 0.45 vs 1.26 ± 0.27, respectively). LVEDVI significantly increased from baseline until the follow-up only in the group of patients with blood adiponectin level £4.7 μg/mL and WMSI significantly decreased at follow-up in both groups (Fig. 2A–F). Blood adiponectin level below 4.7 μg/mL 15.5-fold increased the risk of LVR (95% CI 4.05–59.87, p = 0.0001).

### Discussion

At present, despite the introduction of pPCI into the treatment of MI and recommended widespread use of ‘anti-remodeling’ medications, LVR remains an important late complication. It is related to microvascular dysfunction and the no-reflow phenomenon within the risk area [11, 28] and with the reduced coronary flow reserve [29].

The most interesting finding of our study is that low baseline blood adiponectin concentration is an independent predictor of the LVR after MI. The efficacy of adiponectin as a prognostic factor of left ventricular function following successful reperfusion has been shown by Shibata et al. [30]. These authors, using the scintigraphic imaging, have revealed that adiponectin levels were negatively associated with changes in LVEF at six months observation. This finding, together with the detected association of adiponectin with myocardial salvage parameters, inclined the authors to suggest that adiponectin could be indicative of long-term myocardial remodeling after MI. Our study confirms this suggestion in a one year follow-up. There are several potential explanations of the protective function of adiponectin. The possible molecular mechanisms mediating metabolic and vascular activity of

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**Table 2.** Echocardiographic parameters at baseline and at one year follow-up in the study groups.

<table>
<thead>
<tr>
<th></th>
<th>With remodeling (n = 15)</th>
<th>Without remodeling (n = 60)</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
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<tr>
<td>LVEDVI [mL/m²]</td>
<td>57 ± 14</td>
<td>50 ± 11</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LVESVI [mL/m²]</td>
<td>27 ± 11</td>
<td>22 ± 7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>46 ± 8</td>
<td>58 ± 9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LVEF &lt; 40% — number of patients (%)</td>
<td>4 (27%)</td>
<td>1 (2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>WMSI</td>
<td>1.81 ± 0.39</td>
<td>1.33 ± 0.31</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>E/A</td>
<td>1.09 ± 0.31</td>
<td>1.01 ± 0.29</td>
<td>NS</td>
</tr>
<tr>
<td>DT [ms]</td>
<td>195 ± 41</td>
<td>202 ± 38</td>
<td>NS</td>
</tr>
<tr>
<td><strong>One-year follow-up</strong></td>
<td></td>
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<tr>
<td>LVEDVI [mL/m²]</td>
<td>70 ± 15</td>
<td>49 ± 12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LVESVI [mL/m²]</td>
<td>30 ± 12</td>
<td>22 ± 8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>44 ± 9</td>
<td>59 ± 8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>WMSI</td>
<td>1.79 ± 0.40</td>
<td>1.26 ± 0.27</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>E/A</td>
<td>1.00 ± 0.35</td>
<td>1.03 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>DT [ms]</td>
<td>226 ± 48</td>
<td>212 ± 42</td>
<td>NS</td>
</tr>
</tbody>
</table>

LVEDVI — left ventricular end-diastolic volume index; LVESVI — left ventricular end-systolic volume index; LVEF — left ventricular ejection fraction; WMSI — wall motion score index; DT — deceleration time
adiponectin involve stimulation of AMP kinase activity and cyclooxygenase (COX)-2-dependent synthesis of prostaglandin E2 that inhibits TNF-alpha production [20, 24].

Experimental studies by Tao et al. [25] demonstrated that adiponectin protects against ischemia/reperfusion injury by inhibition of nitric oxide, superoxide and their cytotoxic reaction product formation. In animal models, Shibata at al. [26] showed that adiponectin administered into the created myocardial zone suppressed cardiac hypertrophy and interstitial fibrosis, protected against myocyte apoptosis and increased capillary density in the infarct border zone that was associated with decreased left ventricular dilatation and improved left ventricular function.

In our study group, including relatively young men with the first, mostly inferior MI, successful treatment with pPCI remodeling was observed in 20% of patients. Some other studies performed on comparable groups of patients show similar results to ours [6, 31]. Savoye et al. [8] reported the inci-
Figure 2. Changes in echocardiographic parameters from baseline to follow-up in patients with blood adiponectin level below and above the optimal cut-off value for predicting left ventricular remodeling: 4.7 μg/mL; A. Left ventricular end-diastolic volume index (LVEDVI); B. Left ventricular end-systolic volume index (LVESVI); C. Left ventricular ejection fraction (LVEF); D. Left ventricular wall motion score index (WMSI); E. Early (E) to late (A) transmitral peak flow velocities ratio (E/A); F. Early transmitral wave deceleration time (DT).
Limitations of the study

Unfortunately we have not performed serial measurements of adiponectin in the course of MI, whereas plasma adiponectin concentrations decline significantly at 24 hours compared to the concentrations on admission and remains relatively stable only between 24 and 72 hours [41]. Moreover, we have measured CRP levels at admission, not the peak values which have been shown to predict LVR [12]. We have not performed coronary angiography at follow-up, so the condition of the infarct related artery and the late potency of the implanted stents is not known.

The results of our study concern only male patients, so the conclusions cannot be generalized for the whole population as there are sex-related differences in plasma adiponectin concentration [42].

Long-term clinical studies in large number of patients are warranted to fully elucidate the impact of several factors on LVR and consider the action of the cluster of these factors.

Conclusions

Baseline low blood adiponectin concentration, along with WMSI, can be considered as a predictor of LVR in male patients one year after MI and pPCI.

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The authors do not report any conflict of interest regarding this work.

References


