Influence of left ventricular hypertrophy on microvascular dysfunction and left ventricular remodelling after acute myocardial infarction

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Aims
To ascertain whether the presence of left ventricular (LV) hypertrophy in patients with ST-segment elevation myocardial infarction (STEMI) influences microvascular dysfunction and LV remodelling at 6 months of follow-up.

Methods and results
Fifty-six consecutive STEMI patients successfully treated with primary or rescue percutaneous coronary intervention underwent conventional two-dimensional and myocardial contrast echocardiography within 24 h and at 6 months. Left ventricular mass, end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction, and wall motion score index (WMSI) were measured. Left ventricular hypertrophy was defined as LV mass index >116 g/m² in men and >104 g/m² in women. In order to evaluate the potential influence of microvascular dysfunction on LV remodelling, myocardial perfusion was semiquantitatively scored by contrast score index (CSI). Patients with LV hypertrophy had higher EDV and ESV both at 24 h and at 6 months, compared with patients without LV hypertrophy (P<0.05). No significant changes over time were observed in both groups. Both WMSI and CSI were similar between groups at 24 h and at follow-up, but improved in both groups over time (P<0.05).

Conclusion
Left ventricular hypertrophy does not appear to influence the development of post-acute myocardial infarction LV remodelling. Hypertrophic and non-hypertrophic left ventricles showed the same extent and temporal improvement in regional contractile function and microvascular perfusion.

Keywords
Left ventricular hypertrophy • Myocardial infarction • Microvascular dysfunction • Left ventricular remodelling

Introduction
Unfavourable left ventricular (LV) remodelling, characterized by progressive chamber dilation, wall thinning, and systolic/diastolic dysfunction, can occur after acute myocardial infarction (AMI). This process involves several cellular and molecular mechanisms that begin days after AMI and persist for weeks or months after the initial insult, both at the site of infarction and in the surviving unaffected areas.1–4 In patients with ST-segment elevation AMI, persistent microvascular damage following successful reperfusion represents a powerful predictor of LV dilation, whereas reversible microvascular damage is associated with the prevention of LV remodelling.5

Myocardial hypertrophy represents an important adaptive response to abnormal global or regional increase in cardiac work, although, at long-term follow-up, a transition to maladaptive remodelling may occur, due to an imbalance of the implicated signalling pathways. Previous studies in several clinical conditions have shown that myocardial hypertrophy is associated with the reduction of coronary flow reserve and vascular remodelling. It is currently unknown whether LV hypertrophy may also influence post-AMI microvascular damage and LV remodelling. Thus, in the present study, we investigated the relation between LV hypertrophy and post-AMI LV remodelling, taking into account its possible effect on the extent and temporal changes of microvascular damage.
Contrast images were acquired in apical four-chamber, two-chamber, and long-axis views. As soon as myocardial videointensity had reached a plateau, a flash of ultrasound with very high mechanical index was given to destroy microbubbles in the area of interest. Then, as the peak of myocardial replenishment of bubbles was observed, images were digitally acquired and stored for off-line analysis.

**Data analysis**

Visual interpretation of echocardiograms was done by two experienced observers (L.G., F.A.G.), both blinded to patient’s clinical data. Disagreement was resolved by consensus.

Left ventricular mass was calculated from M-mode records taken on parasternal long-axis images according to the formula: LV mass = 0.8 × 1.04[(interventricular septum thickness at diastole + posterior wall thickness at diastole + LV diastolic diameter)³ – (LV diastolic diameter)³] × 0.6 g (corrected American Society of Echocardiography cube method).⁹,¹⁰ Left ventricular hypertrophy was diagnosed when LV mass index (LV mass corrected for body surface) was >116 g/m² in men and >104 g/m² in women.¹¹

Regional wall motion was evaluated according to the recommendations of the American Society of Echocardiography,¹² and a regional wall motion score index (WMSI) was calculated by the sum of the score of dysfunctional segments divided by the number of these segments. Left ventricular end-diastolic (EDV) and end-systolic (ESV) volumes were calculated from four-chamber and two-chamber views using the modified Simpson biplane method. Left ventricular ejection fraction (EF) was then calculated with the formula [(LV EDV – LV ESV)/LV EDV] × 100. Left ventricular remodelling was defined as an increase in LV EDV ≥20% at follow-up, as previously demonstrated.¹³

Myocardial opacification at MCE of each myocardial segment was visually assessed and semiquantitatively scored as previously published.¹⁴ A single perfusion score was assigned based on both the change in myocardial signal intensity throughout the replenishment curve and the degree of opacification at the peak contrast effect.¹⁵ Scores were graded as 1—normal (homogeneous opacification approximating that of the normal region at peak and normal rate of increase in signal); 2—reduced (partial or reduced opacification compared with the normal region at peak and/or reduced rate of increase in signal intensity); 3—absent (no opacification throughout replenishment time). A regional contrast score index (CSI) was calculated by the sum of MCE scores in each of the dysfunctional segments divided by the number of segments.

**Results**

The study population comprised 56 patients (48 males, 8 females, age 59 ± 10 years) with AMI successfully treated with primary/rescue percutaneous coronary intervention. Eleven patients were diabetics, 29 hypertensive, 41 smokers, 26 hypercholesterolaemic, and 23 had coronary artery disease in their family history. AMI was anterior in 38 patients, inferior in 14 patients, and lateral in 4 patients. The culprit vessel was the left anterior descending
coronary artery in 38 patients, the right coronary artery in 14 patients, and the circumflex coronary artery in 4 patients. Peak creatine kinase was 3200.1 ± 1696.2 UI/L. End-diastolic volume measured within 24 h from percutaneous coronary intervention in the whole population was 111.3 ± 29.2 mL, ESV was 60.0 ± 21.7 mL, and EF 46.7 ± 9.0%.

Echocardiographic findings

The study population was divided in patients with LV hypertrophy (group A; n = 18) and patients without LV hypertrophy (group B; n = 38). Clinical characteristics of the two groups are reported in Table 1.

Both LV EDV and LV ESV measured within 24 h from percutaneous coronary intervention were higher in group A than in group B (123.7 ± 28.3 vs. 105.4 ± 28.1 mL; P < 0.05; 65.5 ± 17.4 vs 57.4 ± 23.3 mL; P < 0.05, respectively) (Figures 1 and 2), whereas LV EF did not differ between the two groups (47.2 ± 6.5 vs 46.5 ± 10.1%; P = NS) (Figure 3).

At 6-month follow-up, both LV EDV and LV ESV remained higher in group A than in group B (132.2 ± 33.1 vs 114.4 ± 34.9 mL; P < 0.05, and 68.6 ± 25.2 vs 57.9 ± 27.6 mL, P < 0.05, respectively) (Figures 1 and 2), whereas LV EF did not differ between groups (48.4 ± 9.2 mL vs 51.6 ± 9.9%; P = NS) (Figure 3). Temporal changes in LV EDV, LV ESV, and LV EF in both groups did not reach statistical significance by two-way ANOVA.

Left ventricular remodelling occurred in 5/18 (22%) of group A patients and in 8/38 (21%) of group B patients (P = NS).

Figures 4 and 5 represent examples of MCE in group A and group B, respectively. At 24 h, both WMSI and CSI did not differ between group A and group B (WMSI: 2.4 ± 0.7 vs. 2.1 ± 0.8, P = NS, respectively; CSI: 1.8 ± 0.5 vs 1.6 ± 0.5; P = NS, respectively) (Figures 6 and 7). At 6-month follow-up, both WMSI and CSI significantly improved in the two groups (for group A: WMSI 2.1 ± 0.5, P < 0.01 vs. 24 h; CSI: 1.6 ± 0.4, P < 0.05 vs. 24 h; for

<table>
<thead>
<tr>
<th>Patients</th>
<th>Group A (18)</th>
<th>Group B (38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>15</td>
<td>33</td>
<td>0.73</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 11</td>
<td>59 ± 10</td>
<td>0.63</td>
</tr>
<tr>
<td>Smokers</td>
<td>15</td>
<td>26</td>
<td>0.24</td>
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<tr>
<td>Hypertension</td>
<td>12</td>
<td>17</td>
<td>0.13</td>
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<tr>
<td>Hypercholesterolaemia</td>
<td>6</td>
<td>20</td>
<td>0.18</td>
</tr>
<tr>
<td>Family history</td>
<td>9</td>
<td>14</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
<td>8</td>
<td>0.70</td>
</tr>
<tr>
<td>Known ischaemic heart disease</td>
<td>2</td>
<td>6</td>
<td>0.64</td>
</tr>
<tr>
<td>Angina pre-AMI</td>
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<td>4</td>
<td>0.52</td>
</tr>
<tr>
<td>Culprit LAD artery</td>
<td>14</td>
<td>24</td>
<td>0.28</td>
</tr>
<tr>
<td>Culprit RCA artery</td>
<td>3</td>
<td>11</td>
<td>0.33</td>
</tr>
<tr>
<td>Culprit LCX artery</td>
<td>1</td>
<td>3</td>
<td>0.76</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>11</td>
<td>26</td>
<td>0.59</td>
</tr>
<tr>
<td>Rescue PCI</td>
<td>7</td>
<td>12</td>
<td>0.59</td>
</tr>
<tr>
<td>Pre-coronary time (min)</td>
<td>284.0 ± 420.8</td>
<td>196.4 ± 224.0</td>
<td>0.33</td>
</tr>
<tr>
<td>Troponin T peak (ng/mL)</td>
<td>10.9 ± 6.3</td>
<td>11.1 ± 8.4</td>
<td>0.92</td>
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<tr>
<td>CK peak (UI/L)</td>
<td>3289.6 ± 1583.8</td>
<td>3144.1 ± 1811.5</td>
<td>0.84</td>
</tr>
<tr>
<td>LDH peak (UI/L)</td>
<td>1988.3 ± 885.6</td>
<td>1993.7 ± 961.7</td>
<td>0.99</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; CK-MB, creatine kinase MB isoenzyme; CK, creatine kinase; LAD, left anterior descending; LCX, left circumflex; LDH, lactic dehydrogenase; PCI, percutaneous coronary intervention; RCA, right coronary artery.
Discussion

The present study investigates, for the first time, the influence of LV hypertrophy on microvascular damage and LV remodelling after AMI treated with primary or rescue percutaneous coronary intervention. We demonstrate that patients with myocardial hypertrophy do not show different incidence of LV remodelling compared with patients without LV hypertrophy and that both groups of patients have similar extent and temporal changes of microvascular and myocardial dysfunction.

Left ventricular remodelling and myocardial hypertrophy

Left ventricular remodelling is characterized by structural parietal changes and progressive LV chamber dilatation. This process may occur in response to chronic increase in loading conditions in the setting of arterial hypertension or as a possible unfavourable evolution of AMI. Left ventricular remodelling is associated with unfavourable haemodynamic performance and adverse outcome at long-term follow-up, including symptomatic heart failure, death due to pump failure, and sudden cardiac death.1,2

In the setting of chronic pressure overload, myocardial hypertrophy is a major predictor of LV remodelling and adverse prognosis. In fact, LV hypertrophy is associated with alterations of myocardial perfusion, with a reduction of coronary flow reserve and vascular remodelling. In the setting of AMI, the role of LV hypertrophy in the transition towards LV remodelling has never been explored. In our study, we found that pre-existing myocardial hypertrophy is not associated with a higher occurrence of LV remodelling in patients with AMI, nor in a different pattern.
Microvascular dysfunction and myocardial hypertrophy

In order to explore the mechanisms underlying the possible interaction between myocardial hypertrophy and LV remodelling after AMI, we assessed coronary microcirculation in vivo using MCE. Indeed, microvascular damage post-AMI is an important independent predictor of LV dilation.\textsuperscript{16} We have previously demonstrated that microvascular damage is associated with LV dilation only when it is ‘sustained’ over time, whereas ‘reversible’ damage is associated with preserved LV volumes.\textsuperscript{3} We have also reported that the recovery of microvascular perfusion is associated with the prevention of LV remodelling independent of the recovery of LV function.\textsuperscript{17}

In this study, the extent of microvascular damage was similar in patients with and without myocardial hypertrophy. Moreover, microvascular function recovered over time of the same amount in both groups. Thus, our data suggest that LV hypertrophy present at the time of AMI is not associated with additional impairment of microvascular perfusion and does not limit progressive improvement in post-ischaemic microvascular damage. Similarly, post-AMI myocardial dysfunction showed the same extent and temporal improvement in patients with and without LV hypertrophy.

Thus, the lack of correlation between LV hypertrophy and post-AMI microvascular and myocardial damage further supports the conclusion that pre-existing LV hypertrophy cannot be considered an additional adverse factor in the development of post-AMI LV remodelling.

Limitations

In this study, we have enrolled a relatively small study population and this might have affected the absence of clinical characteristics between the two groups. It is possible that a larger population may have also allowed to distinguish specific patterns of hypertrophy (concentric hypertrophy, eccentric hypertrophy, concentric remodelling) analysing the relative wall thickness and left ventricular mass index together, thus identifying a possible different response to AMI. Furthermore, the follow-up was limited to the first 6 months after AMI when it is known that most of LV remodelling occurs. Thus, this study does not allow to provide data on morbidity and mortality, which are known to be influenced by left ventricular mass.\textsuperscript{18} Lastly, we did not perform systematic quantification of replenishment curve of our MCE data. Despite possible introduction of errors, this analysis could have given additional information regarding the amount of myocardial perfusion.\textsuperscript{19}

However, MCE quantification of flow has been shown to provide additional information only in the non-invasive assessment of coronary artery disease, such as during pharmacological stress MCE test.\textsuperscript{20,21} On the other hand, in the setting of AMI, semi-quantitative MCE analysis is adequate to assess the extent of microvascular damage.

Conclusions

This study provides novel pathophysiological information on the role of LV hypertrophy on post-AMI LV remodelling, completed with the evaluation of post-AMI extent and temporal changes of coronary microcirculation. For the first time, we demonstrate that, in patients with AMI successfully treated by percutaneous coronary intervention, pre-existing myocardial hypertrophy is not associated with a higher occurrence of LV remodelling. In addition, in these patients, LV hypertrophy does not imply larger post-ischaemic microvascular and myocardial damage and it does not limit their temporal improvement.

Funding

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Conflict of interest: none declared.

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