Left ventricular dilatation and neurohumoral activation as arrhythmogenic factors in myocardial infarction
Dambrink, Jan Hendrik Everwijn

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CHAPTER 2

Left ventricular dilatation and high-grade ventricular arrhythmias in the first year after myocardial infarction

Jan-Henk E. Dambrink,¹ MD; Willem P. Beukema,¹ MD; Wick H. van Gilst,² PhD; Kathinka H. Peels,³ MD; K.I. Lie,⁴ MD; and J. Herre Kingma,¹,² MD for the CATS investigators⁵

¹Department of Cardiology, St Antonius Hospital, Nieuwegein
²Department of Clinical Pharmacology, University of Groningen, Groningen
³Department of Cardiology, Catharina Hospital, Eindhoven
⁴Department of Cardiology, Groningen University Hospital, Groningen
⁵see Appendix

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Abstract

Background. Progressive left ventricular dilatation is an important determinant of prognosis after myocardial infarction. The association of this process with the occurrence of ventricular arrhythmias is less well established.

Methods and Results. Of 153 patients with a first anterior myocardial infarction treated with thrombolytic therapy 34 (22%) had high-grade ventricular arrhythmias (Lown classes 4A and B) during Holter monitoring after one year. Patients with high-grade ventricular arrhythmias had a larger end-systolic volume (38 ± 12 vs 25 ± 11 ml/m², p < 0.001) at hospital discharge and more left ventricular dilatation (10 ± 18 vs 1 ± 9 ml/m², p=0.011) during follow up. Both an increased end-systolic volume at discharge and subsequent dilatation proved independent predictors of high-grade ventricular arrhythmias. Six patients died suddenly during the first 12 months after myocardial infarction. Four of these patients had an enlarged end-systolic volume (LVESVI > 22 ml/m²) at discharge, and the three patients who died suddenly after three months showed a significant increase in end-systolic volume from discharge to three months compared to survivors (16 ± 6 vs 2 ± 9, p=0.008).

Conclusion. Left ventricular remodeling after myocardial infarction is an independent predictor for the occurrence of ventricular arrhythmias late after myocardial infarction.

Introduction

Left ventricular remodeling after myocardial infarction is characterized by dilatation of the infarcted and noninfarcted regions of the ventricle.¹ These morphological changes are frequently associated with the occurrence of heart failure² and sudden death.³ Although the anatomical changes after myocardial infarction are well described,⁴⁻⁸ little is known about accompanying electrophysiological changes in the left ventricle. Recently, it has been demonstrated that increased loading and subsequent dilatation of the heart can lead to an increase in ventricular arrhythmias.⁹,¹⁰ This may be explained by increased dispersion in refractoriness¹¹⁻¹⁴ and early afterdepolarizations,¹²,¹⁴ caused by an increase in ventricular wall stress (contraction-excitation feedback).¹⁵

Although clinical evidence is available that increased left ventricular dimensions lead to a higher incidence of life-threatening ventricular arrhythmias after myocardial infarction,³ the relation between left ventricular dilatation and the occurrence of ventricular arrhythmias is less well established.
In the present study, we investigated the relation between left ventricular dilatation and ventricular arrhythmias during the first year after anterior myocardial infarction.

**Methods**

Patients. This study was an ancillary investigation of the Captopril And Thrombolysis Study (CATS), in which the effect of captopril treatment, started during thrombolysis, was evaluated in patients with a first anterior myocardial infarction. Informed consent was obtained by witnessed oral consent, later confirmed by written informed consent following the acute phase of myocardial
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Figure 2.1. Left ventricular end-systolic volume (LVESVI) of patients with (open circles) and without (filled circles) high-grade ventricular arrhythmias during Holter monitoring at 12 months. LVESVI is already higher upon admission in patients with high-grade arrhythmias. In these patients, there is a clear increase in end-systolic volume in the first year of follow up, whereas in patients without high-grade arrhythmias there is no significant increase in LVESVI. *p < 0.05, **p < 0.005.

Infarction. Main endpoints included left ventricular volumes, neurohumoral activation and ventricular arrhythmias. In CATS, 298 patients were included in 12 hospitals in The Netherlands. The study was approved by the Institutional Review Board of all participating hospitals. Selection criteria included a typical history of chest pain consistent with myocardial infarction with onset of symptoms no longer than 6 hours before admission, and ECG criteria for acute anterior myocardial infarction including at least 1 mm ST segment elevation in leads I and aVL and/or 2 mm ST segment elevation in two or more precordial leads of the 12-lead electrocardiogram, consistent with anterolateral, anteroseptal and/or anterior wall infarction.

Patients had to be eligible for thrombolytic therapy. Exclusion criteria included presence of a prior myocardial infarction, left bundle branch block and
severe heart failure (Killip class III or IV). Patients were followed for 12 months after myocardial infarction. Sudden death was defined as death within one hour of symptoms, but also included unwitnessed death in patients who were otherwise stable.

Holter recording. The occurrence of ventricular arrhythmias was assessed by two-channel 12-hour Holter monitoring upon admission, before discharge and three and 12 months after myocardial infarction. Analysis was performed with help of a Reynolds Medical Pathfinder 3 analysis system. Tapes were analyzed for the presence of uniform and multiform premature ventricular beats,
pairs of premature ventricular beats and ventricular tachycardia. Pairs were defined as a repetition of two ventricular beats with a maximum interval of 0.6 s. Ventricular tachycardia was defined as a repetition of 3 or more ventricular beats with a rate exceeding 100 beats per minute. Paired ventricular premature beats and ventricular tachycardia (Lown classes 4A and 4B) were defined as high-grade ventricular arrhythmias; all other ventricular arrhythmias were classified as low-grade. The presence of high-grade ventricular arrhythmias during Holter monitoring after one year was chosen as the primary end point for the logistic regression analysis.

Echocardiography. Echocardiograms were made within 24 hours after admission, at day 3, before discharge and three and 12 months after myocardial infarction. Left ventricular end-systolic and end-diastolic volumes were calculated from a two- and four-chamber view using the modified biplane Simpson’s rule.\textsuperscript{17} From these volume measurements the ejection fraction was calculated. Measurements were made off-line from end-diastolic and end-systolic still-frames using a Dataview Microsonics cardiac analysis system (Nova Microsonics). Left ventricular volumes were indexed for body surface area. Furthermore, regional wall motion abnormalities were evaluated using the wall motion score recommended by the American Society of Echocardiography.\textsuperscript{17} In this scoring system the left ventricle is divided into 16 segments, scoring each segment as 1 for normokinesia, 2 for hypokinesia, 3 for akinesia, 4 for dyskinesia and 5 for an aneurysmal segment. A wall motion score index was computed as the sum of scores of all segments divided by the number of segments evaluated. Twelve evaluable segments were considered a minimum to reliably assess the wall motion score.

Infarct size. Enzymatic infarct size was estimated by cumulative alpha-hydroxybutyrate dehydrogenase (\(\alpha\)-HBDH) values over the first 72 hours after myocardial infarction. This method is not influenced by the presence or absence of reperfusion.\textsuperscript{18}

Statistical analysis. Results are presented as mean ± standard deviation. Differences in end-systolic volume between groups were examined using analysis of variance and the modified t-test according to the Bonferroni method. The Chi-squared test was used for discrete data. Logistic regression analysis was used to identify independent relations between baseline characteristics and the occurrence of high-grade ventricular arrhythmias.\textsuperscript{19} Calculations were made using SPSS/PC+ v 4.0 software. A two-sided p-value of less than 0.05 was considered statistically significant.
Results

Of all 298 patients included in CATS, 65 (21%) did not complete a follow-up period of 12 months due to withdrawal of consent, death, or other clinical events. In 34 patients (11%) Holter monitoring was not performed due to unspecified reasons. Of 199 patients with Holter monitoring available, 46 tapes were of inadequate quality (15%). Holter monitoring after one year was available in 153 patients (51%).

Table 2.2. Characteristics of patients with and without high-grade ventricular arrhythmias after 12 months

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Arrhythmias (N)</th>
<th>No arrhythmias (N)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.8 ± 8.8 (34)</td>
<td>57.5 ± 9.6 (119)</td>
<td>0.070</td>
</tr>
<tr>
<td>Male</td>
<td>26/34 (76%)</td>
<td>97/119 (82%)</td>
<td>0.683</td>
</tr>
<tr>
<td>Myocardial injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-HBDH Q72 (U/l)</td>
<td>1499 ± 928 (27)</td>
<td>1066 ± 832 (113)</td>
<td>0.019</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>48 ± 9 (17)</td>
<td>57 ± 9 (84)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Wall Motion Score</td>
<td>2.07 ± 0.31(27)</td>
<td>1.74 ± 0.44 (113)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Extent of CAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2-vessel disease</td>
<td>11/23 (48%)</td>
<td>23/67 (34%)</td>
<td>0.367</td>
</tr>
<tr>
<td>LAD occluded</td>
<td>7/23 (30%)</td>
<td>9/67 (13%)</td>
<td>0.110</td>
</tr>
<tr>
<td>LV remodeling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVESVI discharge(ml/m²)</td>
<td>38 ± 12 (17)</td>
<td>25 ± 11 (84)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVESVI one year (ml/m²)</td>
<td>43 ± 17 (19)</td>
<td>26 ± 14 (77)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dilatation (ml/m²)</td>
<td>10 ± 18 (14)</td>
<td>1 ± 9 (60)</td>
<td>0.011</td>
</tr>
<tr>
<td>LV aneurysm (%)</td>
<td>4/30 (13%)</td>
<td>11/108 (10%)</td>
<td>0.624</td>
</tr>
<tr>
<td>Neurohumoral activation</td>
<td>27.1 ± 5.6 (20)</td>
<td>30.0 ± 11.0 (77)</td>
<td>0.108</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>10/24 (42%)</td>
<td>6/97 (6%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ectopic activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPBs &gt; 10/hour</td>
<td>9/34 (27%)</td>
<td>44/119 (37%)</td>
<td>0.352</td>
</tr>
<tr>
<td>Medication</td>
<td>12/34 (35%)</td>
<td>55/119 (46%)</td>
<td>0.349</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>6/34 (18%)</td>
<td>6/119 (5%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACE indicates angiotensin converting enzyme; CAD, coronary artery disease; VPBs, ventricular premature beats. Other abbreviations as in Table 2.1.
Table 2.1 shows baseline characteristics after hospital admission of all CATS patients, those with Holter monitoring after 12 months, and patients who died suddenly during the first year of follow up. There were no differences in characteristics between all CATS patients and patients with Holter monitoring after 1 year. However, patients who died suddenly showed a tendency to larger end-systolic volumes, resulting in a significantly lower ejection fraction compared to the other patient groups.

Echocardiographic data of patients with and without high-grade ventricular arrhythmias during Holter monitoring (Lown classes 4A and B) after 12 months were investigated. In Figure 2.1, the mean end-systolic volume during follow up in patients with and without high-grade ventricular arrhythmias during Holter recording after one year is shown. In patients with high-grade ventricular arrhythmias, a higher end-systolic volume was present from admission. In addition, left ventricular dilatation was prominent in this group, whereas end-systolic volume remained relatively unchanged in patients without high-grade arrhythmias. In Figure 2.2, the percentage of patients with high-grade ventricular arrhythmias divided in 4 quartiles of left ventricular dilatation are shown. At hospital admission, there is little or no difference in the percentage of patients with high-grade arrhythmias between these groups. However, at hospital discharge, the prevalence of arrhythmias has decreased more in those without dilatation (groups I and II) compared to those with dilatation (groups III and IV). During follow up, this difference in prevalence of arrhythmias persists, and at 12 months the percentage of patients with high-grade arrhythmias in patient group IV is still about 50%, whereas in patients with less or no dilatation, this is about 10 percent.

In Table 2.2, differences in characteristics in patients with and without high-grade ventricular arrhythmias are listed. In addition to a higher end-systolic volume and progressive dilatation, patients with high-grade ventricular arrhythmias

<table>
<thead>
<tr>
<th>B</th>
<th>SE</th>
<th>p</th>
<th>OR (95%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilatation &gt; 8 ml/m^2</td>
<td>1.6361</td>
<td>0.8252</td>
<td>0.0474</td>
</tr>
<tr>
<td>LVESVI &gt; 35 ml/m^2</td>
<td>1.8387</td>
<td>0.8234</td>
<td>0.0256</td>
</tr>
<tr>
<td>VPBs &gt; 10 /hour</td>
<td>1.9890</td>
<td>0.9027</td>
<td>0.0276</td>
</tr>
<tr>
<td>Constant</td>
<td>-3.3344</td>
<td>0.7662</td>
<td></td>
</tr>
</tbody>
</table>

B indicates regression coefficient; CI, confidence intervals; OR, odds ratio; SE, standard error. Other abbreviations as in Table 2.1 and 2.2.
are characterized by a larger enzymatic infarct size, a lower ejection fraction, relatively more frequent ventricular premature beats and more use of digoxin.

Logistic regression analysis was used to assess the relative importance of end-systolic volume and dilatation after discharge for the occurrence of arrhythmias after 12 months. First, five baseline variables strongly associated with the occurrence of high-grade ventricular arrhythmias after one year were selected (enzymatic infarct size, ejection fraction, wall motion score, end-systolic volume, VPBs during Holter monitoring; see also Table 2.2). These variables were then converted into binary variables with the 75th percentile as the cut-off point. These variables were then entered in a forward stepwise logistic regression model to identify the variables that provided independent information. This analysis showed that end-systolic volume > 35 ml/m$^2$ and > 10 VPBs/hour were the only independent variables. After this, a second analysis was performed. We entered end-systolic volume and VPBs > 10/hour as independent predictors of ventricular arrhythmias, and then entered left ventricular dilatation (increase in end-systolic volume). The results of this analysis are given in Table 2.3. Left ventricular dilatation proved to increase the risk for high grade arrhythmias independently. In addition, this analysis was repeated using end-diastolic volume in stead of end-systolic volume as a determinant of arrhythmias. End-diastolic volume also proved an independent predictor of high-grade ventricular arrhythmias, but further increase in end-diastolic volume did not provide additional independent information.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Time of death after AMI (days)</th>
<th>Cumulative $\alpha$-HBDH (U/l)</th>
<th>Ejection fraction (%)</th>
<th>End-systolic volume at discharge (ml/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>277</td>
<td>2359</td>
<td>37</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>171</td>
<td>2969</td>
<td>53</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>171</td>
<td>543</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>2153</td>
<td>37</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>2129</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>277</td>
<td>631</td>
<td>77</td>
<td>14</td>
</tr>
<tr>
<td>mean</td>
<td>163 ± 106</td>
<td>1797 ± 986</td>
<td>50 ± 15</td>
<td>32 ± 15</td>
</tr>
<tr>
<td>all</td>
<td>-</td>
<td>1277 ± 1007</td>
<td>55 ± 10</td>
<td>27 ± 12</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>0.212</td>
<td>0.237</td>
<td>0.320</td>
</tr>
</tbody>
</table>

AMl indicates acute myocardial infarction; $\alpha$-HBDH, alpha-hydroxybutyrate dehydrogenase.
In Table 2.4, echocardiographic data of the six patients who died suddenly are shown. At discharge, patients 1, 2, 4, and 5 had an enlarged end-systolic volume (> 22 ml/m$^2$). However, all patients who survived the first 3 months but died suddenly afterwards also had an enlarged end-systolic volume (patients 1, 3, and 6). Left ventricular dilatation from discharge to 3 months in these patients was clearly more pronounced than dilatation in the whole study population (16 ± 6 vs 2 ± 9, p=0.008).

Discussion

Previous studies describing the relation between end-systolic volume$^3$ or left ventricular dysfunction$^{20}$ and ventricular arrhythmias are angiographic and radionuclide studies dating from the prethrombolytic era. The present study demonstrates the relation between left ventricular remodeling, quantified by changes in echocardiographically assessed end-systolic volume, and the occurrence of ventricular arrhythmias late after thrombolytic therapy in patients with a first anterior myocardial infarction. Patients with high-grade ventricular arrhythmias during Holter monitoring after 12 months showed a larger end-systolic volume at baseline and progressive left ventricular dilatation during follow up. Patients who died suddenly in CATS were all characterized by progressive left ventricular dilatation after discharge. Although an increased end-systolic volume 4-8 weeks after myocardial infarction has previously been identified as a powerful risk factor for life-threatening arrhythmias,$^3$ the importance of an increased end-
systolic volume at discharge and progressive left ventricular dilatation during follow up has not been appreciated before.

Previous studies

White et al.\textsuperscript{3} first demonstrated the importance of an increased end-systolic volume measured 4-8 weeks after myocardial infarction as a risk factor for the occurrence of life-threatening ventricular arrhythmias i.e. sudden cardiac death. In this study, which evaluated 70 cases of sudden death in a population of 605 postinfarction patients after a follow-up period of more than 10 years, end-systolic volume was superior to ejection fraction in predicting survival. In addition, end-systolic volume proved more important than the extent of coronary artery disease. Patients in this study did not receive thrombolytic therapy. In the present study, all patients received streptokinase for a first anterior myocardial infarction. Although follow up was considerably shorter, and the presence of high-grade ventricular arrhythmias during Holter recording was used as a primary endpoint, end-systolic volume at discharge was also found a better predictor of ventricular arrhythmias than ejection fraction. In addition, it was shown that in patients with these arrhythmias left ventricular dilatation was progressive, and dilatation after discharge also proved an independent predictor of ventricular arrhythmias.

Primary myocardial damage, reflected by end-systolic volume at discharge, and subsequent remodeling, objectivated by an increase in end-systolic volume after discharge, both independently increase the risk for late ventricular arrhythmias.

Finally, our present study confirmed the importance of the number of ventricular premature beats during Holter monitoring as a risk factor for ventricular arrhythmias, which has been demonstrated both with\textsuperscript{21} and without\textsuperscript{22,23} thrombolytic therapy.

Underlying mechanisms

Increased loading conditions of the heart can lead to changes in repolarization characteristics,\textsuperscript{11-13} usually resulting in a shortening of the refractory period. It has been shown, that these changes in repolarization are not uniformly distributed over the ventricle, and therefore dispersion in refractoriness will increase.\textsuperscript{13} Increased dispersion in repolarization may cause a conduction delay sufficient for the development of a sustained ventricular tachyarrhythmia, even without the presence of an anatomical substrate.\textsuperscript{24,25}
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Early afterdepolarizations have also been recorded during increased loading conditions of the heart.\textsuperscript{12,14} Early afterdepolarizations may facilitate the occurrence of ventricular arrhythmias by inducing triggered activity. Finally, derangement of the three-dimensional structure of the heart, characterized by hypertrophy, fibrosis and cell slippage, may lead to anomalous cellular coupling, also resulting in delayed conduction and subsequent arrhythmias.\textsuperscript{26}

Effect of ACE inhibition

Although a slightly larger proportion of patients without high-grade ventricular arrhythmias used ACE inhibitors compared to patients with these arrhythmias (46% vs 35%), there was no clear indication in this study that ACE inhibition reduced the prevalence of ventricular arrhythmias. However, the main results of CATS indicate that nonsustained ventricular tachycardia was significantly reduced by captopril in the acute phase of myocardial infarction. This was paralleled by a significant reduction in norepinephrine levels, but a difference in left ventricular volumes could not be observed.\textsuperscript{27} Other studies investigating the effect of ACE inhibition on the occurrence of ventricular arrhythmias after myocardial infarction do not allow definite conclusions.\textsuperscript{28-30} In patients with congestive heart failure, the evidence is more consistent.\textsuperscript{31-33} It appears that, if ACE inhibitors do reduce the incidence of ventricular arrhythmias after myocardial infarction, this effect seems more pronounced in patients with extensive left ventricular remodeling resulting in heart failure.

Clinical relevance

Although anti-arrhythmic drugs have shown to reduce postinfarction ventricular arrhythmias, this did not result in a reduction of sudden cardiac death.\textsuperscript{34} Since left ventricular dilatation is an important risk factor for the occurrence of sudden death,\textsuperscript{3} modulation of this process may prove a more appropriate approach in reducing sudden death after myocardial infarction. ACE inhibition after myocardial infarction does improve survival.\textsuperscript{35} Part of this effect has been attributed to attenuation of left ventricular dilatation. It is very likely that a reduction in life-threatening ventricular arrhythmias related to this process also plays an important role. Therefore, after myocardial infarction, interventions directed at attenuating left ventricular dilatation may also reduce life-threatening ventricular arrhythmias.

Limitations
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In this study, only patients with a first anterior myocardial infarction treated with streptokinase were investigated. Nonetheless, within this population a broad clinical spectrum of patients was included, from aborted infarctions to large transmural infarctions with or without left ventricular dyskinesia and aneurysm formation. Therefore, the relation between dilatation and ventricular arrhythmias could be studied intensively, but these results should be extrapolated with caution to patients with different infarct sites or multiple infarcts.

Conclusions

After thrombolytic therapy, increased end-systolic volume at discharge is strongly associated with the occurrence of high-grade ventricular arrhythmias. Furthermore, progressive dilatation after discharge also contributes independently to the occurrence of these arrhythmias. Therefore, assessment of end-systolic volume, not only before discharge but also during the follow-up period, may help to detect patients at risk for late arrhythmic events.

References

20. Bigger Jr JT: Relation between left ventricular dysfunction and ventricular arrhythmias after myocardial infarction. Am J Cardiol 1986;57:8B-14B.


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