Left ventricular dilatation and neurohumoral activation as arrhythmogenic factors in myocardial infarction
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Association between reduced heart rate variability and left ventricular dilatation in patients with a first anterior myocardial infarction

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5see Appendix

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Abstract

Background. Reduced heart rate variability has been identified as an important prognostic factor after myocardial infarction. This parameter is thought to reflect an imbalance between sympathetic and parasympathetic activity, which may lead to unfavorable loading conditions, thus promoting left ventricular dilatation.

Methods. Before discharge, 24-hour Holter monitoring was performed to evaluate heart rate variability as a possible risk factor for left ventricular dilatation after myocardial infarction. Patients were divided in a group with reduced (index of ≤ 25) and a group with normal heart rate variability (index of > 25). Left ventricular volumes were assessed by echocardiography before discharge and three and 12 months after myocardial infarction. Extent of myocardial injury, severity of coronary artery disease, functional class, hemodynamics and medication were also considered as possible determinants of left ventricular dilatation. All patients participated in a multi-center clinical trial, in which 298 patients were randomized to captopril or placebo after a first anterior myocardial infarction. All patients were treated with streptokinase before randomization. In the present substudy, full data including heart rate variability and echocardiographic measurements were available in 80 patients.

Results. Before discharge, end-systolic and end-diastolic volume was not different in patients with or without a reduced heart rate variability. However, after 12 months, end-systolic volume (mean ± SD) had increased in patients with a reduced heart rate variability with 6 ± 14 ml/m² (p=0.043), and end-diastolic volume had increased with 8 ± 17 ml/m² (p=0.024). Left ventricular volumes were unchanged in patients with a normal heart rate variability. In addition, patients with left ventricular dilatation were characterized by a larger enzymatic infarct size, higher heart rates and rate-pressure products. A reduced heart rate variability index before discharge proved an independent risk factor for the occurrence of left ventricular dilatation during follow up. Measurement of heart rate variability after three months had no predictive value for this event.

Conclusion. Assessment of the heart rate variability index before discharge, but not at three months, yields important additional information for identifying patients at risk for left ventricular dilatation.

Introduction

Reduced heart rate variability after acute myocardial infarction is an important risk factor for mortality and the occurrence of life-threatening ventricular arrhythmias after hospital discharge. Changes in heart rate variability are
thought to reflect an imbalance between sympathetic and parasympathetic activity. After myocardial infarction, a relative increase in sympathetic activity may result in a higher wall stress by elevating loading conditions. An increase in wall stress may enhance dilatation of the left ventricle, and by this mechanism increased sympathetic activity may form an important causative factor in the process of left ventricular remodeling. Since persisting sympathetic activity after myocardial infarction is usually paralleled by activation of the renin-angiotensin system, wall stress may increase even more, and thus activation of both systems may contribute to progressive dilatation of the ventricle.

In this study, we investigated the association between heart rate variability assessed before hospital discharge and at three months and left ventricular dilatation during one year of follow up after a first anterior myocardial infarction. Since heart rate variability can be assessed reliably and reproducibly, this may provide important additional information for identifying patients at risk after myocardial infarction.

Methods

Patients. This study was part 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 infarction. Main endpoints included left ventricular remodeling, neurohumoral activation and ventricular arrhythmias. In the CATS study, 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 electrocardiographic 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). Twenty-four-hour Holter monitoring before discharge and at month 3 was part of the CATS study protocol.

Heart rate variability assessment. Heart rate variability was assessed at discharge and after three months using an automated procedure described by
HEART RATE VARIABILITY AND DILATATION

Malik et al. The width of the frequency distribution curve of all selected RR intervals was used as an index for heart rate variability. This method is operator independent and has been validated previously. In addition, patients were dichotomized into a group with a heart rate variability index less than or equal to 25 and a group with a heart rate variability index more than 25. It has been demonstrated that patients with a heart rate variability index below 25 have an increased risk for serious arrhythmic events, suggesting a clinically relevant change in autonomic balance. The two groups thus dichotomized were used to evaluate the association between heart rate variability and left ventricular dilatation during follow up. Tracker Holter recording equipment and a Reynolds Pathfinder 3 analysis system was used for heart rate variability assessment. This type of analysis system has been validated for heart rate variability measurements. The Reynolds analysis system identifies the different shapes of aberrant beats. The triggering level for this identification can be adjusted by the operator. Aberrant-normal and normal-aberrant RR intervals were excluded from analysis; only normal-normal RR intervals were used.

Echocardiography. Echocardiograms were made before discharge and at 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. From these volume measurements the ejection fraction was calculated. Measurements were made off-line from end-diastolic and end-systolic stillframes using a Dataview Microsonics cardiac analysis system (Nova Microsonics). Left ventricular volumes were indexed for body surface area. Left ventricular dilatation was defined as the increase in end-systolic volume indexed for body surface area between hospital discharge and one year after myocardial infarction. Furthermore, regional wall motion abnormalities were evaluated using the wall motion score recommended by the American Society of Echocardiography. 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 values over the first 72 hours (α-HBDH Q72) after myocardial infarction as described by van der Laarse et al. This method is not influenced by the presence or absence of reperfusion.

Statistical analysis. Results are presented as means ± standard deviation. Differences between groups were examined using the Student’s t-test. Logistic regression analysis was applied to identify independent relations between baseline
CHAPTER 6

Table 6.1. Patient characteristics upon hospital admission

<table>
<thead>
<tr>
<th></th>
<th>Total CATS population</th>
<th>Cohort with heart rate variability assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>298</td>
<td>175</td>
</tr>
<tr>
<td>Male (%)</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 10</td>
<td>59 ± 10</td>
</tr>
<tr>
<td>α-HBDH Q72 (U/l)</td>
<td>1277 ± 1007</td>
<td>1323 ± 843</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>56 ± 13</td>
<td>54 ± 12</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>25 ± 10</td>
<td>24 ± 9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55 ± 10</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>WMSI</td>
<td>1.91 ± 0.36</td>
<td>1.88 ± 0.37</td>
</tr>
</tbody>
</table>

α-HBDH Q72 indicates cumulative α-hydroxybutyrate dehydrogenase over the first 72 hours after myocardial infarction (enzymatic infarct size); LVEDVI, left ventricular end-diastolic volume indexed for body surface area; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume indexed for body surface area; WMSI, wall motion score index.

characteristics and left ventricular dilatation.\textsuperscript{20} Calculations were made using SPSS/PC+ software.

Results

Heart rate variability

Holter tapes of 199 CATS patients (199/298, 66%) were available for heart rate variability assessment at discharge. Analysis was not possible in 24 cases due to speed errors (3 tapes) or incompatibility of Holter tapes and the analysis system used (21 tapes). Therefore, data on heart rate variability were available in 175 out of 298 (58%) cases. Baseline characteristics of all CATS patients and patients that were part of the heart rate variability study are listed in Table 6.1.

There were no significant differences in age, gender, infarct size and parameters of left ventricular dysfunction between both groups. The mean recording time was 22.8 ± 3.2 hours (range 4.4 to 26, 90% of recordings longer than 21 hours), and 92,849 ± 22,538 RR intervals were analyzed (range 14,426 to 145,033 intervals). Before discharge, 74 patients (42%) had a reduced heart rate variability (index of less or equal to 25) and 101 (58%) had a normal heart rate variability (index of more than 25). The heart rate variability index was 19.09 ±
4.06 and 35.43 ± 8.40 in both groups, respectively. A second heart rate variability assessment was available in 120/175 patients (69%) after three months. Serial measurements in this subgroup revealed that after three months, heart rate variability had increased both in patients with (index of less or equal to 25) and patients without (index of more than 25) a reduced heart rate variability at discharge. However, the increase in heart rate variability was more pronounced in patients with an index of less or equal to 25 (increase 11.16 ± 7.37 versus 5.97 ± 12.14, p=0.004). After three months, 31/120 (25%) patients who had an index of less or equal to 25 at discharge showed an improvement to an index of more than 25 and 5/120 (4%) patients with an index of more than 25 at discharge had a worsening of their index to of less or equal to 25. All other patients remained in the same category as they were at discharge (70/120 (58%) with an index of more than 25 and 14/120 (11%) with an index of less or equal to 25).

Echocardiography

Figure 6.1. A small but not significant difference in left ventricular end-systolic volume indexed for body surface area (LVESVI) was present before discharge in patients with (HRVI ≤ 25) and without reduced heart rate variability (HRVI > 25). After one year, LVESVI had increased in those with HRVI ≥ 25, but in patients with HRVI > 25, LVESVI had remained unchanged. HRVI indicates heart rate variability index; LVESVI, left ventricular end-systolic volume.
Before discharge, an echocardiogram was available for all patients (175/175). Assessment of left ventricular volumes was possible in 125/175 cases (71%). Serial measurements before discharge and after 12 months were available for 80/175 patients (45%). Echocardiographic follow-up of the two groups with and without a reduced heart rate variability at discharge is summarized in Table 6.2.

Before discharge, there was a slight but not significant difference in end-systolic volume between both groups. End-diastolic volume was also comparable between groups, but wall motion abnormalities were more pronounced in patients with reduced heart rate variability. Ejection fraction was lower before discharge in the group with an index of less or equal to 25. After three months, both end-systolic and end-diastolic volume had increased in patients with a reduced heart rate variability, whereas left ventricular dimensions decreased in

<table>
<thead>
<tr>
<th>Table 6.2. Summary of all echo data</th>
<th>HRVI ≤ 25</th>
<th>N</th>
<th>HRVI &gt; 25</th>
<th>N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic volume (ml/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predischarge</td>
<td>59 ± 16</td>
<td>51</td>
<td>59 ± 13</td>
<td>74</td>
<td>0.916</td>
</tr>
<tr>
<td>3 months</td>
<td>64 ± 19</td>
<td>44</td>
<td>58 ± 13</td>
<td>63</td>
<td>0.065</td>
</tr>
<tr>
<td>12 months</td>
<td>65 ± 19</td>
<td>36</td>
<td>58 ± 18</td>
<td>68</td>
<td>0.079</td>
</tr>
<tr>
<td>Systolic volume (ml/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predischarge</td>
<td>29 ± 13</td>
<td>51</td>
<td>25 ± 11</td>
<td>74</td>
<td>0.050</td>
</tr>
<tr>
<td>3 months</td>
<td>32 ± 14</td>
<td>44</td>
<td>24 ± 10</td>
<td>63</td>
<td>0.003</td>
</tr>
<tr>
<td>12 months</td>
<td>33 ± 14</td>
<td>36</td>
<td>25 ± 13</td>
<td>68</td>
<td>0.008</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predischarge</td>
<td>52 ± 11</td>
<td>51</td>
<td>58 ± 9</td>
<td>74</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3 months</td>
<td>51 ± 10</td>
<td>44</td>
<td>59 ± 9</td>
<td>63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>12 months</td>
<td>51 ± 10</td>
<td>36</td>
<td>59 ± 10</td>
<td>68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Wall motion score index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predischarge</td>
<td>1.97 ± 0.38</td>
<td>51</td>
<td>1.69 ± 0.43</td>
<td>74</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3 months</td>
<td>1.91 ± 0.45</td>
<td>44</td>
<td>1.61 ± 0.39</td>
<td>63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>12 months</td>
<td>1.97 ± 0.46</td>
<td>36</td>
<td>1.58 ± 0.39</td>
<td>68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Change in first year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diastolic volume</td>
<td>8 ±17</td>
<td>28</td>
<td>-1 ± 12</td>
<td>52</td>
<td>0.024</td>
</tr>
<tr>
<td>systolic volume</td>
<td>6 ±14</td>
<td>28</td>
<td>0 ± 8</td>
<td>52</td>
<td>0.043</td>
</tr>
<tr>
<td>ejection fraction</td>
<td>-4 ±10</td>
<td>28</td>
<td>0 ± 9</td>
<td>52</td>
<td>0.162</td>
</tr>
<tr>
<td>wall motion score</td>
<td>0.07 ± 0.31</td>
<td>28</td>
<td>-0.08 ± 0.24</td>
<td>52</td>
<td>0.018</td>
</tr>
</tbody>
</table>

HRVI indicates heart rate variability index.
patients with an index of more than 25. Between three and 12 months, a small increase in left ventricular volumes was observed in both groups. The total increase in systolic and diastolic volume after one year was more pronounced in patients with a reduced heart rate variability.

Changes in end-systolic volume in both groups after one year of follow up is shown in Figure 6.1. Ejection fraction had remained relatively stable in both groups, but the wall motion score index showed a slight improvement in patients with an index of more than 25, while in patients with a reduced heart rate variability a worsening of this index was observed. Figure 6.2 features the percentage of patients with reduced heart rate variability at discharge in five subgroups of left ventricular dilatation. The percentage of patients with a reduced heart rate variability was higher in the subgroups with 5-10, 10-15 and more than 15 ml/m\(^2\) increase in end-systolic volume after one year in comparison to patients with no dilatation.

![Figure 6.2](image-url)

*Figure 6.2.* The percentage of patients with a reduced heart rate variability (index ≤ 25) is given for five categories of left ventricular dilatation. More dilatation, quantified as increase in end-systolic volume after 12 months, is accompanied by a higher frequency of patients with a reduced heart rate variability.
In Table 6.3, univariate analysis of possible predictive factors for the development of left ventricular dilatation is shown. Besides a reduced heart rate variability, only an enzymatic infarct size of more than 1000 U/l significantly in-
creased the risk for dilatation during the first year of follow up. Age of the patient, left ventricular volumes, ejection fraction and wall motion score index at discharge had no significant predictive value for the occurrence of left ventricular dilatation. Logistic regression analysis was applied to investigate whether heart rate variability provided independent prognostic information for the development of dilatation (Table 6.4). A stepwise regression model (entry criterion: $p < 0.15$) revealed that a heart rate variability index of less or equal to 25 was a stronger predictor for the occurrence of left ventricular dilatation of more than 5 ml/m$^2$ than an enzymatic infarct size of more than 1000 U/l.

Heart rate variability in patients with and without dilatation after three months

Before discharge, there was a significant difference in heart rate variability index between patients with and without left ventricular dilatation more than 5 ml/m$^2$ after one year (24.24 ± 7.34 versus 32.33 ± 9.91), $p < 0.001$. After three months, heart rate variability had improved in patients with and without dilatation. However, this improvement was more pronounced in patients with dilatation, and after three months heart rate variability was no longer different between these groups (36.30 ± 12.33 versus 38.91 ± 10.09, $p=0.371$).

Ventricular arrhythmias during follow up

In Table 6.5, the six patients that showed ventricular arrhythmias or died suddenly in the first year after myocardial infarction are listed. Before discharge, heart rate variability was reduced in 3/6 (50%) of these patients (HRVI ≤ 25) compared to 74/175 (42%) in all patients. It is interesting to note that two patients (cases 2 and 3) already had a large end-systolic volume at discharge (above the 75th percentile), and another three patients (case 1, 5 and 6) showed an increase in end-systolic volume after three months above the 75th percentile of the study population. One patient (case 4) had a normal end-systolic volume;

| Table 6.4 . Independent predictors of left ventricular dilatation |
|-----------------|------|------|--------|---------|
|                 | B    | SE   | p-value| OR (95%-CI) |
| Constant        | -1.9710 | 0.5248 | 0.0002 |         |
| HRVI ≤ 25       | 1.5934 | 0.5660 | 0.0049 | 4.92 (1.62 - 14.92) |
| Infarct size > 1000 U/l | 1.7524 | 0.5775 | 0.1856 | 2.15 (0.69 - 6.66) |

B indicates regression coefficient; CI, confidence intervals; HRVI, heart rate variability index; OR, odds ratio; SE, standard error.
follow-up echocardiography was not available in this case. These data show that early or late left ventricular dilatation occurred in 5/6 (83%) of the patients with arrhythmic events.

Selection of the optimal value of the heart rate variability index discriminating between dilatation and no dilatation

In Figure 6.3, the Receiver Operator Characteristics (ROC) curve is plotted for the heart rate variability index as a predictor of left ventricular dilatation. In this study, the cut-off point between normal and abnormal heart rate variability was selected at a heart rate variability index of 25 on the basis of data in the literature⁴. This value has a sensitivity of 62% and a specificity of 76% in detecting left ventricular dilatation. In this figure it can be seen, that an index of 30 would yield a higher sensitivity of 83%, although this is accompanied by a lower specificity (60%).

The positive predictive value of a heart rate variability index ≤ 25 for the occurrence of left ventricular dilatation was 54% (15/28), and the negative predictive value was 83% (43/52).

<table>
<thead>
<tr>
<th>Case</th>
<th>Event</th>
<th>Days after AMI</th>
<th>HRVI</th>
<th>LVESVI at discharge (ml/m²)</th>
<th>LVESVI at 3 months (ml/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VT</td>
<td>12</td>
<td>26</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>VF</td>
<td>14</td>
<td>17</td>
<td>37</td>
<td>n.a.</td>
</tr>
<tr>
<td>3</td>
<td>VT</td>
<td>19</td>
<td>12</td>
<td>43</td>
<td>n.a.</td>
</tr>
<tr>
<td>4</td>
<td>SCD</td>
<td>171</td>
<td>17</td>
<td>23</td>
<td>n.a.</td>
</tr>
<tr>
<td>5</td>
<td>SCD</td>
<td>171</td>
<td>53</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>SCD</td>
<td>277</td>
<td>34</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>mean</td>
<td>-</td>
<td>110 ± 112</td>
<td>26 ± 15</td>
<td>26 ± 12</td>
<td>31 ± 7</td>
</tr>
<tr>
<td>all pts</td>
<td>-</td>
<td>-</td>
<td>29 ± 11</td>
<td>27 ± 12</td>
<td>29 ± 15</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; HRVI, heart rate variability index; LVESVI, left ventricular end-systolic volume indexed for body surface area; VF, ventricular fibrillation; VT, ventricular tachycardia; SCD, sudden cardiac death; n.a., not available; pts, patients. *After HRVI assessment but in hospital.
Discussion

This study demonstrates the predictive value of a reduced heart rate variability before discharge for the occurrence of left ventricular dilatation during follow up after a first anterior myocardial infarction. Assessment of the heart rate variability index before discharge yields important additional information not obtained by considering infarct size or left ventricular dysfunction alone. A decrease in heart rate variability at discharge may reflect persistent sympathetic activation, which can be harmful in the early phase of remodeling when scar tissue formation is not yet fully completed. This is the first study linking persisting sympathetic activation after myocardial infarction to the occurrence of left ventricular dilatation during follow up.

Heart rate variability as an indicator for neurohumoral activation

Figure 6.3. Receiver Operator Characteristics (ROC) curve of the heart rate variability index as a predictor of left ventricular dilatation. For explanation see text.
A reduced heart rate variability is thought to reflect an imbalance between sympathetic and parasympathetic activity. Direct vagal nerve stimulation and the infusion of atropine or isoproterenol cause reproducible shifts in the power spectrum of heart rate variability in normal subjects. In patients with heart failure, it has been demonstrated that a reduced heart rate variability is directly related to plasma norepinephrine levels and muscle sympathetic nerve activity. These studies indicate that changes in heart rate variability reflect changes in autonomic balance. No studies are available that have demonstrated a relation between a reduced heart rate variability and activation of the renin-angiotensin system. However, especially in patients with considerable left ventricular dysfunction, persisting sympathetic activity after myocardial infarction is paralleled by activation of the renin-angiotensin system. Therefore, heart rate variability after myocardial infarction may well reflect the degree of general neurohumoral activation after myocardial infarction.

Infarct size and left ventricular dilatation

For dilatation to occur, a certain degree of myocardial injury is necessary. In rat studies, it has been demonstrated that if myocardial infarction is limited to less than 40% of the free wall, the loss of contractile tissue is compensated by physiologic hypertrophy of the noninfarcted area, and the resulting dilatation is limited. However, when infarct size exceeds 40% of the free wall, compensatory mechanisms fail, hypertrophy becomes pathological, and progressive dilatation occurs. This association between infarct size and left ventricular dilatation has been confirmed in man and has also been reproduced in the present study. After the acute phase of myocardial infarction, the process of infarct healing becomes an important determinant of left ventricular dilatation. This process can last for weeks after myocardial infarction. During this period, the infarcted area is highly vulnerable to an increase in wall stress.

Neurohumoral activation and left ventricular dilatation

Increased loading conditions, leading to higher levels of wall stress, have been shown to promote left ventricular dilatation in man. Increased sympathetic activity, possibly paralleled by activation of the renin-angiotensin system, will increase pre- and afterload due to vasoconstriction and fluid retention leading to higher wall stress levels. Therefore, neurohumoral activation early after myocardial infarction is liable to promote left ventricular dilatation by elevating wall stress in a vulnerable phase of left ventricular remodeling. This is supported by the finding that in this study, heart rate variability was reduced in patients
with left ventricular dilatation at discharge. However, after three months no difference in heart rate variability could be detected between patients with and without left ventricular dilatation, suggesting that a reduced heart rate variability is only associated with left ventricular dilatation in the early phase after myocardial infarction.

Other determinants of left ventricular dilatation

A number of other possible determinants of left ventricular dilatation were considered in this study (Table 6.3). Occlusion of the infarct-related artery is known to promote left ventricular dilatation.\cite{28} In the present study, the left anterior descending artery was occluded in 28% of patients with dilatation versus 16% of patients without dilatation. However, this difference was not statistically significant. It should be noted that coronary angiography was not part of the study protocol, and performed at a wide range of time intervals, usually because of recurrent angina pectoris. Coronary angioplasty and other procedures may have troubled the relation between patency of the infarct-related artery and left ventricular dilatation.

The rate-pressure product before discharge was higher in patients with left ventricular dilatation, and was primarily determined by a higher mean heart rate. This finding confirms the assumption that a higher workload promotes left ventricular dilatation. However, this parameter did not independently predict the occurrence of dilatation (Table 6.4). Finally, there was no significant effect of medication, including study medication, on the occurrence of left ventricular dilatation in this subgroup of patients. Other studies have demonstrated the beneficial effect of ACE inhibition on left ventricular remodeling.\cite{29-31} This lack of effect may be due to the limited number of patients studied.

Implications of the study

Identifying patients at risk for left ventricular dilatation after myocardial infarction is a difficult but important task. The importance of infarct size as a determinant of dilatation is confirmed by the present study. Left ventricular end-systolic- and end-diastolic volume, ejection fraction and wall motion score have no additive value for the prediction of dilatation one year after myocardial infarction. An occluded infarct-related vessel is an independent risk factor for the occurrence left ventricular dilatation\cite{28,32,33} and, when available, should be taken into account when assessing the risk for ventricular dilatation after myocardial infarction. A reduced heart rate variability before discharge as an indicator of persisting neurohumoral activation proves to be a strong predictor of left ven-
tricular dilatation. Selection of a heart rate variability index of 30 as the cut-off point between ‘reduced’ and ‘normal’ heart rate variability would even improve the sensitivity of this method. However, the predictive value of heart rate variability for the occurrence of dilatation is limited to the late in-hospital period, possibly reflecting the importance of persisting sympathetic activity in the early (vulnerable) phase of remodeling. Assessment of heart rate variability before discharge can be helpful in identifying patients at risk for dilatation after myocardial infarction at relatively little cost in time and manpower.

Limitations

In this study, a selected patient population was investigated: only patients with a first anterior myocardial infarction treated with streptokinase were included. Therefore, results of this study should be extrapolated to other patient groups with caution. However, both patients with very small and very large infarcts were part of the study, and therefore the complete spectrum of left ventricular remodeling was investigated.

Conclusions

Assessment of the heart rate variability index before discharge, but not three months later, yields important additional information for identifying patients at risk for left ventricular dilatation after myocardial infarction. This information can be obtained at relatively little cost in time and manpower. The therapeutic strategy for patients with a reduced heart rate variability remains to be established.

References

HEART RATE VARIABILITY AND DILATATION


