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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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Abstract

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

***Patients and methods*—298 patients in a multicentre clinical trial were randomised to captopril or placebo after a first anterior myocardial infarction. All patients were treated with streptokinase before randomisation. In the present substudy full data including heart rate variability and echocardiographic measurements were available from 80 patients. Patients were divided into two groups: those with a reduced ($\leq$25) heart rate variability index and those with normal heart rate variability index (>25). Heart rate variability was evaluated by 24 h Holter monitoring before discharge. 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, haemodynamic variables, and medication were also considered as possible determinants of left ventricular dilatation.**

***Results*—Before discharge end systolic and end diastolic volumes were not different in the two groups. After 12 months in patients with a reduced heart rate variability, end systolic volume (mean (SD)) had increased by 6 (14) ml/m^2 (P = 0·043) and end diastolic volume had increased by 8 (17) ml/m^2 (P = 0·024). Left ventricular volumes were unchanged in patients with a normal heart rate variability. Also, patients with left ventricular dilatation had a larger enzymatic infarct size and higher heart rates and rate-pressure products. A reduced heart rate variability index before discharge was an independent risk factor for 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, gave important additional information for identifying patients at risk of left ventricular dilatation.**

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Reduced heart rate variability after acute myocardial infarction is an important risk factor for mortality[1–3] and life threatening ventricular arrhythmias[4–6] after discharge from hospital. Changes in heart rate variability are thought to reflect an imbalance between sympathetic and parasympathetic activity.[7–9] After myocardial infarction, a relative increase in sympathetic activity may result in a higher wall stress by raising loading conditions. An increase in wall stress may enhance dilation of the left ventricle,[10 11] and by this mechanism increased sympathetic activity may form an important causative factor in the process of left ventricular remodelling.[12] As 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 dilation of the ventricle.

In this study, we investigated the association between heart rate variability assessed before discharge from hospital and at three months and left ventricular dilatation at one year of follow up after a first anterior myocardial infarction. As heart rate variability can be assessed reliably and reproducibly,[13 14] this may provide important additional information for identifying patients at risk after myocardial infarction.

Patients and 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.[15] Witnessed oral consent was obtained and later confirmed by written informed consent after the acute phase of myocardial infarction. Main end points included left ventricular remodelling, neurohumoral activation, and ventricular arrhythmias. In the CATS study, 298 patients were included from 12 hospitals in The Netherlands. The study was approved by the review board of all participating hospitals (see appendix). Selection criteria included a typical history of chest pain consistent with myocardial infarction with onset of symptoms no longer than six hours before admission, and electrocardiographic criteria for acute anterior myocardial infarction that included at least 1 mm ST segment elevation in leads I and aVL or 2 mm ST segment elevation in two or more precordial leads of the 12 lead electrocardiogram, consistent with anterolateral, anteroseptal, or anterior wall infarction. Patients had to be eligible for thrombolytic

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treatment. Exclusion criteria included presence of a previous myocardial infarction, left bundle branch block, and severe heart failure (Killip class III or IV). Twenty four hour Holter monitoring before discharge and at three months was part of the CATS study protocol.

ASSESSMENT OF HEART RATE VARIABILITY

Heart rate variability was assessed at discharge and after three months with an automated procedure described by Malik *et al.*[16] The width of the frequency distribution curve of all selected RR intervals was used as an index for heart rate variability. This method is independent of the operator and has been validated previously.[16] Also, patients were dichotomised into two groups with heart rate variability indices $\leqslant 25$ or >25. It has been shown that patients with a heart rate variability index $\leqslant 25$ have an increased risk for serious arrhythmic events, which suggests a clinically relevant change in autonomic balance.[4] These two groups 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 III analysis system were used for assessment of heart rate variability. This type of analysis system has been validated for measurements of heart rate variability.[17] The Reynolds analysis system identifies the different shapes of aberrant beats. The triggering level for this identification can be adjusted by the operator. Aberrant to normal and normal to aberrant RR intervals were excluded from the analysis; only normal to normal RR intervals were used.

ECHOCARDIOGRAPHY

Echocardiograms were made before discharge from hospital 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 with the modified biplane Simpson's rule.[18] From these volume measurements the ejection fraction was calculated. Measurements were made off line from end diastolic and end systolic still frames with a 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 discharge from hospital and one year after myocardial infarction.

Regional wall motion abnormalities were evaluated with the wall motion score recommended by the American Society of Echocardiography.[18] In this scoring system the left ventricle was divided into 16 segments, and each segment scored 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 evaluated segments were considered to be a minimum to reliably assess the wall motion score.

INFARCT SIZE

Enzymatic infarct size was estimated by cumulative values of α hydroxybutyrate dehydrogenase over the first 72 hours after myocardial infarction as described by van der Laarse *et al.*[19] This method is not influenced by the presence or absence of reperfusion.

STATISTICAL ANALYSIS

Results are presented as means (SD). Differences between groups were examined by Student's t test. Logistic regression analysis was applied to identify independent relations between baseline characteristics and left ventricular dilatation.[20] Calculations were made with SPSS/PC + software.

Results

HEART RATE VARIABILITY

Holter tapes of 199 CATS patients (199/298, 66%) were available for assessment of heart rate variability at discharge. Analysis was not possible in 24 cases due to speed errors (three 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. Table 1 shows the baseline characteristics of all CATS patients and patients that were part of the heart rate variability study. There were no significant differences in age, sex, infarct size, and measures of left ventricular dysfunction between the groups. The mean recording time was 22·8 (3·2) hours (range 4·4 to 26 (90% of recordings >21 hours)), and 92 849 (22 538) RR intervals were analysed (range 14 426 to 145 033). Before discharge, 74 patients (42%) had a reduced heart rate variability index ($\leqslant 25$, mean (SD) 19·09 (4·06)) and 101 (58%) had a normal heart rate variability index (>25, mean (SD) 35·43 (8·40)).

A second heart rate variability assessment was available in 120/175 patients (69%) after three months. Serial measurements in this subgroup showed that after three months, heart rate variability had increased both in patients with and without a reduced heart rate variability at discharge. The increase in heart rate variability was more pronounced in patients with an index $\leqslant 25$ (increase 11·16 (7·37) *v* 5·97 (12·14), P = 0·004). After three months, 31/120 (25%) patients who had an

Table 1 Mean (SD) patient characteristics on admission to hospital

	Total CATS population	*Cohort assessed for HRV*
No	298	175
Men (%)	75	79
Age (yr)	59 (10)	59 (10)
α-HBDH (U/l)	1277 (1007)	1323 (843)
LVEDVI (ml/m^2)	56 (13)	54 (12)
LVESVI (ml/m^2)	25 (10)	24 (9)
LVEF (%)	55 (10)	57 (9)
WMSI	1·91 (0·36)	1·88 (0·37)

HRV, heart rate variability; α HBDH, 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 areas; WMSI, wall motion score index.

index ≤25 at discharge showed an improvement to an index >25 and in 5/120 (4%) patients with an index >25 at discharge their index had deteriorated to ≤25. All other patients did not change category; (70/120 (58%) had an index >25 and 14/120 (11%) had an index ≤25).

ECHOCARDIOGRAPHY

Before discharge, an echocardiogram was available in all 175 patients. Assessment of left ventricular volumes was possible in 125/175 cases (71%). Serial measurements before discharge and after 12 months were available in 80/175 patients (45%). Table 2 shows the echocardiographic follow up of the two groups with and without a reduced heart rate variability at discharge. Before discharge, there was a slight but not significant difference in end systolic volume between the 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 ≤25. After three months, both end systolic and end diastolic volumes had increased in patients with a reduced heart rate variability, whereas left ventricular dimensions decreased in patients with an index >25. Between three and 12 months, a small increase in left ventricular volumes was found 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. Figure 1 shows changes in end systolic volume in both groups after one year of follow up.

Ejection fraction had remained relatively stable in both groups, but the wall motion score index showed a slight improvement in patients with an index >25, whereas in patients with a reduced heart rate variability a deterioration of this index was found. Figure 2 shows 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 >15 ml/m² increase in end systolic volume after one year than in patients with no dilatation.

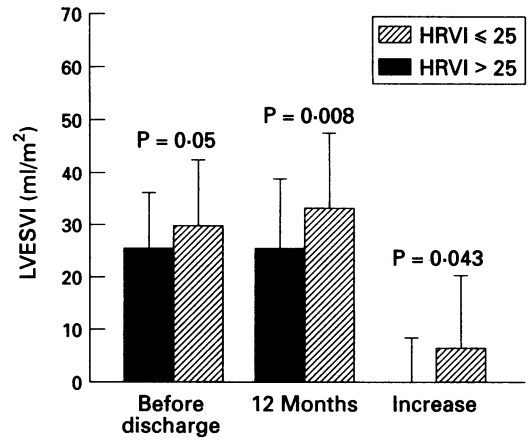

Figure 1 A small (NS) in left ventricular end systolic volume indexed for body surface area (LVESVI) was present before discharge in patients with (HRVI ≤25) and without (HRVI >25) reduced heart rate variability index (HRVI). After one year LVESVI had increased in those with HRVI ≤25, but not in patients with HRVI >25.

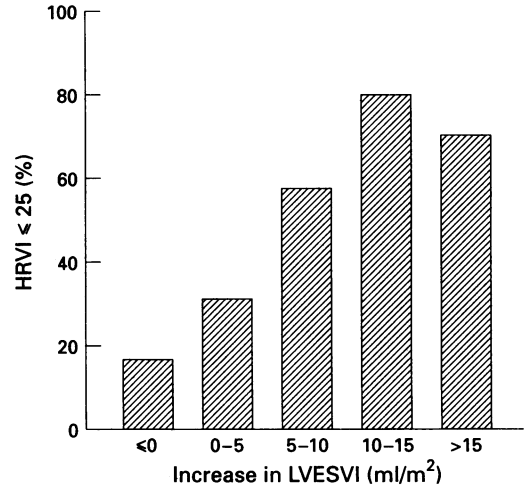

Figure 2 Percentage of patients with a reduced heart rate variability index (HRVI ≤25) for five categories of left ventricular dilatation. More dilatation, measured as increase in end systolic volume after 12 months (LVESVI) is accompanied by a higher frequency of patients with a reduced HRVI.

Table 2 Summary of all echocardiographic data (mean (SD))

	HRVI ≤25 (n)	HRVI >25 (n)	P value
Diastolic volume (ml/m²):			
Before discharge	59 (16) 51	59 (13) 74	0·916
3 Months	64 (19) 44	58 (13) 63	0·065
12 Months	65 (19) 36	58 (18) 68	0·079
Systolic volume (ml/m²):			
Before discharge	29 (13) 51	25 (11) 74	0·050
3 Months	32 (14) 44	24 (10) 63	0·003
12 Months	33 (14) 36	25 (13) 68	0·008
Ejection fraction (%):			
Before discharge	52 (11) 51	58 (9) 74	<0·001
3 Months	51 (10) 44	59 (9) 63	<0·001
12 Months	51 (10) 36	59 (10) 68	<0·001
Wall motion score index:			
Before discharge	1·97 (0·38) 51	1·69 (0·43) 74	<0·001
3 Months	1·91 (0·45) 44	1·61 (0·39) 63	<0·001
12 Months	1·97 (0·46) 36	1·58 (0·39) 68	<0·001
Change in first year:			
Diastolic volume	8 (17) 28	−1 (12) 52	0·024
Systolic volume	6 (14) 28	0 (8) 52	0·043
Ejection fraction	−4 (10) 28	0 (9) 52	0·162
Wall motion score	0·07 (0·31)28	−0·08 (0·24) 52	0·018

HRVI, heart rate variability index.

Table 3 shows univariate analysis of possible predictive factors for the development of left ventricular dilatation. As well as a reduced heart rate variability, only an enzymatic infarct size >1000 U/l significantly increased 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 on 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 4). A stepwise regression model (entry criterion: P = 0·15) showed that a heart rate variability index ≤25 was a stronger predictor for the occurrence of left ventricular dilatation >5 ml/m² than was an enzymatic infarct size >1000 U/l.

Table 3 Mean (SD) characteristics before discharge from hospital of patients with and without left ventricular dilatation >5 ml/m² after 12 months

	Dilation (n)	*No dilation (n)*	*P value*
Demographics:			
Age	56·5 (8·4) 40	57·8 (10·4) 79	0·495
Men (%)	75 40	84 79	0·385
Myocardial injury:			
α-HBDH (U/l)	1552 (974) 35	1072 (766) 71	0·007
Ejection fraction (%)	55 (10) 40	56 (10) 79	0·564
WMSI	1·92 (0·42) 40	1·78 (0·45) 79	0·090
Extent of CAD (%):			
⩾2 Vessel disease	36 25	29 49	0·282
LAD occluded	28 25	16 49	0·381
Functional class:			
Heart failure (KILLIP)	1·4 (0·6) 39	1·3 (0·5) 79	0·710
Angina pectoris (NYHA)	1·2 (0·5) 39	1·4 (0·6) 79	0·210
Left ventricular modelling:			
LVESVI (ml/m²)	28 (12) 40	26 (12) 79	0·361
LVEDVI (ml/m²)	58 (15) 40	61 (16) 79	0·300
Haemodynamics:			
Heart rate (beats/min)	76 (8) 24	69 (8) 56	0·002
Blood pressure (mm Hg):			
Systolic	117 (17) 39	120 (17) 75	0·365
Diastolic	72 (11) 39	75 (10) 75	0·121
Rate-pressure product	9278 (1756) 24	8321 (1630) 52	0·023
Neurohumoral activation:			
Heart rate variability	24 (7) 24	32 (10) 56	0·001
Medication (%):			
β-Blockers	28 40	33 79	0·694
ACE inhibitors	55 40	48 79	0·605
Diuretics	20 40	17 79	0·822
Digoxin	8 40	3 79	0·428

CAD, coronary artery disease; LAD, left anterior descending artery. Coronary angiograms were made 31 (68) days after myocardial infarction. Other abbreviations as for table 1.

Table 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 to 14·92)
Infarct size >1000 U/l	1·7524	0·5775	0·1856	2·15 (0·69 to 6·66)

HRVI, heart rate variability index; B, regression coefficient; CI, confiendence intervals; OR, odds ratio.

Table 5 Data from the six patients that had ventricular arrhythmias or died suddenly in the first year after myocadial infarction

Case	*Event*	*Days after AMI*	*HRVI*	*LVESVI at discharge (ml/m²)*	*LVESVI at 3 months (ml/m²)*
1	VT*	12	26	19	33
2	VF*	14	17	37	NA
3	VT	19	12	43	NA
4	SCD	171	17	23	NA
5	SCD	171	53	19	37
6	SCD	277	34	14	23
Mean (SD)	—	110 (112)	26 (15)	26 (12)	31 (7)
All patients	—	—	29 (11)	27 (12)	29 (15)

*After HRVI assessment but in hospital. AMI, acute myocardial infarction; VF, ventricular fibrillation; VT, ventricular talchycardia; SCD, sudden cardiac death; NA, not available; other abbreviations as for tables 1 and 2.

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 >5 ml/m² after one year (24·24 (7·34) *v* 32·33 (9·91), P < 0·001, fig 3). After three months, heart rate variability had improved in patients with and without dilatation. This improvement was more pronounced, however, in patients with dilatation, and after three months heart rate variability was no longer different between these groups (36·30 (12·33) *v* 38·91 (10·09), P = 0·371).

VENTRICULAR ARRHYTHMIAS DURING FOLLOW UP

Table 5 shows the six patients that had ventricular arrhythmias or died suddenly in the first year after myocardial infarction. Before discharge, heart rate variability was reduced in 3/6 (50%) of these patients compared with 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 (cases 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; follow up echocardiography was not available in this case.

These data show that early or late left ventricular dilation occurred in 5/6 (83%) of the patients with arrhythmic events.

SELECTION OF THE OPTIMAL VALUE OF THE HEART RATE VARIABILITY INDEX TO DISCRIMINATE BETWEEN DILATATION AND NO DILATATION

Figure 4 shows the receiver operator characteristics curve 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 medical

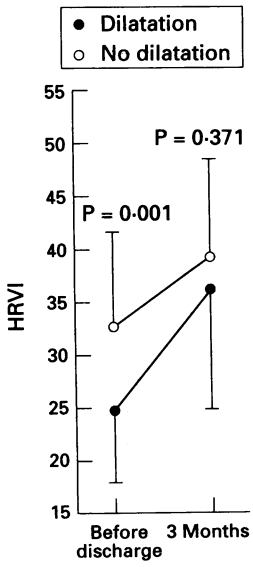

Figure 3 Before discharge, there was a significant difference in heart rate variability index (HRVI) between patients who had and had not > 5 ml/m² increase in indexed end systolic volume after 12 months. After three months, the difference between these groups had disappeared, indicating that the relation between left ventricular dilatation and heart rate variability is limited to the period before discharge.

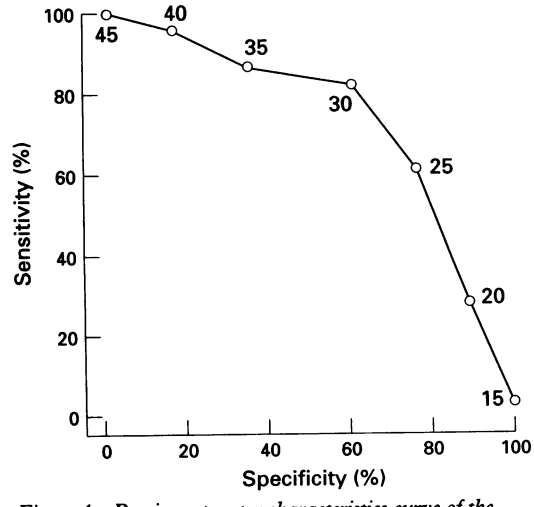

Figure 4 Receiver operator characteristics curve of the heart rate variability index as a predictor of left ventricular dilatation.

literature.[4] 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 $\leqslant 25$ for the occurrence of left ventricular dilatation was 54% (15/28), and the negative predictive value was 83% (43/52).

Discussion

This study shows 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 gives 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 that can be harmful in the early phase of remodelling, when formation of scar tissue is not yet fully complete.[21] This is the first study linking persistent sympathetic activation after myocardial infarction to the occurrence of left ventricular dilatation during follow up.

HEART RATE VARIABILITY AS AN INDICATOR FOR NEUROHUMORAL ACTIVATION

A reduced heart rate variability is thought to reflect an imbalance between sympathetic and parasympathetic activity.[7-9] Direct stimulation of the vagus nerve[22] and the infusion of atropine[8 23] or isoproterenol[23] cause reproducible shifts in the power spectrum of heart rate variability in normal subjects. In patients with heart failure, it has been shown that a reduced heart rate variability is directly related to plasma noradrenaline concentrations and sympathetic nervous activity of the muscles.[7] These studies indicate that changes in heart rate variability reflect changes in autonomic balance.

No studies are available that have shown a relation between a reduced heart rate variability and activation of the renin-angiotensin system. Especially in patients with considerable left ventricular dysfunction, persistent sympathetic activity after myocardial infarction is paralleled by activation of the renin-angiotensin system.[24] 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 studies on rats it has been shown that if myocardial infarction is limited to $<40\%$ of the free wall, the loss of contractile tissue is compensated by physiological hypertrophy of the non-infarcted area, and the resulting dilatation is limited.[25] When infarct size exceeds 40% of the free wall, however, compensatory mechanisms fail, hypertrophy becomes pathological, and progressive dilatation occurs. This association between infarct size and left ventricular dilatation has been confirmed in humans[26] and has also been reproduced in our 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.[21] During this period, the infarcted area is highly vulnerable to an increase in wall stress.[27]

NEUROHUMORAL ACTIVATION AND LEFT VENTRICULAR DILATATION

Increased loading conditions lead to higher levels of wall stress and have been shown to promote left ventricular dilatation in humans.[10] Increased sympathetic activity, possibly paralleled by activation of the renin-angiotensin system, increase preload and afterload due to vasoconstriction and fluid retention, which leads to higher wall stress. Therefore, neurohumoral activation early after myocardial infarction is liable to promote left ventricular dilatation by increasing wall stress in a vulnerable phase of left ventricular remodelling. This is supported by the finding that heart rate variability was reduced in patients with left ventricular dilatation at discharge. After 3 months, however, no difference in heart rate variability could be detected between patients with and without left ventricular dilatation (fig 3). This suggests 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

Several other possible determinants of left ventricular dilatation were considered in this study (table 3). Occlusion of the infarct related artery is known to promote left ventricular dilatation.[28] In our study, the left anterior descending artery was occluded in 28% of patients with dilatation *v* 16% of patients without dilatation. This difference was not statistically significant. It should be noted that coronary angiography was not part of the study protocol, and was performed at a wide range of time intervals, usually because of recurrent angina pectoris. Coronary angioplasty and other procedures may have interfered with the relation between patency of the infarct related artery and left ventricular dilatation.

The rate-pressure product before discharge was high in patients with left ventricular dilatation, and was primarily determined by a high mean heart rate. This finding confirms the assumption that a high workload promotes left ventricular dilatation. This variable did not independently predict the occurrence of dilatation (table 4).

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

shown the beneficial effect of angiotensin converting enzyme inhibition on left ventricular remodelling.[29-31] This lack of effect may be due to the limited number of patients studied.

IMPLICATIONS OF THE STUDY

To identify patients at risk of left ventricular dilatation after myocardial infarction is a difficult but important task. Our study confirms the importance of infarct size as a determinant of dilatation. 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 of left ventricular dilatation.[28 32 33] When present this should be taken into account in assessment of the risk of ventricular dilatation after myocardial infarction. A reduced heart rate variability before discharge as an indicator of persistent neurohumoral activation is also a strong predictor of left ventricular dilatation. Selection of a heart rate variability index of 30 as the cut off point between reduced and normal heart rate variability would improve the sensitivity of this method.

The predictive value of heart rate variability for the occurrence of dilatation is limited to the late period in hospital. This possibly reflects the importance of persistent sympathetic activity in the early (vulnerable) phase of remodelling. Assessment of heart rate variability before discharge can be helpful to identify patients at risk of dilatation after myocardial infarction at little cost in time and manpower.

LIMITATIONS

In this study, a selected population of patients 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 groups of patients with caution. Patients with both small and large infarcts were part of the study, however, and therefore the complete range of left ventricular remodelling was investigated.

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

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