Prognostic Implications of Ventricular Ectopy One Week, One Month, and Sixteen Months after an Acute Myocardial Infarction

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Summary

Background: Ventricular ectopy early after an acute myocardial infarction (AMI) has previously been demonstrated to predict mortality. Less information is available about the prognostic implications of ventricular ectopy occurring late after an AMI, and no information is available about the prognostic implication of the development of ventricular ectopy during the first year after an AMI.

Hypothesis: The purpose of the present prospectively conducted trial, a part of the Danish Verapamil Infarction Trial II (DAVIT II), was to evaluate the prognostic implication of (1) ventricular premature complexes (VPCs) recorded by 24-h Holter monitoring 1 week, 1 month, and 16 months after an AMI; and (2) development of > 10 VPCs/h or of any complex ventricular ectopy, that is, pairs, more than two types of VPCs, ventricular tachycardia, or > 10 VPCs/h during follow-up after an AMI.

Methods: Patients were monitored 1 week ($n = 250$), 1 month ($n = 210$), and 16 months ($n = 201$) after AMI.

Results: Multivariate analyses based on history, clinical findings, and ventricular ectopy showed the following results: After 1 week, > 10 VPCs/h ($p = 0.0006$) and heart failure ($p < 0.007$); after 1 month, > 10 VPCs/h ($p = 0.003$) and resting heart rate ($p < 0.02$); and after 16 months, ventricular tachycardia ($p = 0.002$) independently predicted long-term mortality. Mortality was significantly predicted by the development

of > 10 VPCs/h from 1 week to 1 month ($p = 0.003$) and 16 months ($p = 0.03$), and from 1 to 16 months ($p = 0.007$) after AMI, as well as by the development of any complex ventricular ectopy from 1 week to 1 month ($p = 0.02$) and 16 months ($p = 0.01$), and from 1 to 16 months ($p = 0.04$) after AMI.

Conclusion: The present study demonstrated that 1 week and 1 month after an AMI the quantity of VPCs, that is, > 10 VPCs/h, predicted mortality, whereas 16 months after an AMI the quality of VPCs, that is, ventricular tachycardia, predicted mortality.

Key words: ventricular arrhythmias, ventricular ectopy, mortality, acute myocardial infarction

Introduction

Ventricular ectopy early after an acute myocardial infarction (AMI) has previously been demonstrated to predict mortality.^{1–11} Less information is available about the prognostic implications of ventricular ectopy occurring late after an AMI, and no information is available about the prognostic implication of the development of ventricular ectopy during the first year after an AMI. Thus, the purpose of the present prospectively conducted study was to evaluate the prognostic implications of (1) ventricular ectopy recorded by 24-h Holter monitoring 1 week, 1 month, and 12–18 months (mean 16 months) after an AMI; and (2) development of ventricular ectopy during follow-up after an AMI.

Methods

Study Population

The present prospectively conducted study was planned in conjunction with the Danish Verapamil Infarction Trial II (DAVIT II).¹² Randomization to treatment started in the second postinfarction week. Patients with AMI < 76 years of age were eligible. Exclusion criteria of DAVIT II were treatment with calcium antagonists or beta blockers for angina pectoris, hypertension, or arrhythmias; heart failure not controlled on

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furosemide 160 mg/day; sinoatrial, second- or third-degree atrioventricular block; hypotension or other severe diseases; unwillingness of the patient to participate; or residence outside the catchment area. Of the eligible patients, 45% were included in the study. Additional exclusion criteria were permanent atrial fibrillation and treatment with antiarrhythmic drugs or digoxin. Patients from five of the departments participating in DAVIT II were consecutively included and were followed in the outpatient clinic 1, 3, and then every third month after AMI.

Holter Monitoring

Electrocardiograms (ECGs) were recorded on Hittman Comp Act IV (Hittman Medical Systems, Inc., Columbia, Md., USA), Oxford Medilog 4-24 (Oxford Medical Ltd., Abington, UK), ICR 7200 (Instruments for Cardiac Research, Liverpool, N.Y., USA), and SpaceLabs 90201 (SpaceLabs, Inc., Redmond, Wash., USA) tape recorders. The recorders were applied by a trained laboratory technician or nurse who was blinded to the patients' histories. Analyses of Holter tapes were done "blindly," and the results were not known to the doctors responsible for the patients. The recording time was at least 12 h (median 23, ranges 12–26 h). The tapes were analyzed semiautomatically using a Hittman Compu Scan computer and were visually controlled. Printouts (25 mm/s) were made of examples of different types of VPCs; of pairs, that is, two consecutive VPCs; and of all episodes of ventricular tachycardia, that is, $\geq$ three consecutive VPCs. Complex ventricular ectopy is defined as pairs of VPCs, more than two types of VPCs, ventricular tachycardia, and/or > 10 VPCs/h. The CM5 chest lead was recorded on one channel and a modified orthogonal Y-lead on the other channel.¹³

Holter quality control: The accuracy of the Hittman Compu Scan computer for quantifying VPCs was assessed by comparing results of the semiautomatic computer analysis with 30 "handcounted" tapes. Spearman rank correlation coefficient between the measurements of prevalence of VPCs was 0.90; the Kappa statistic of complex VPCs was 0.91, of sinoatrial or atrioventricular block 1.0, and of supraventricular tachycardia 0.89. Reproducibility was tested by blinded reanalysis of 52 tapes, the Spearman rank correlation coefficient between the measurements of prevalence of VPCs was 0.97 and the Kappa statistic of complex forms of VPCs was 0.94. The interobserver variability was evaluated from 30 tapes reanalyzed by two experienced observers; Spearman rank correlation coefficient between the measurement of VPCs was 0.92 and the Kappa statistic of complex forms of VPCs was 0.91. The intraobserver variability was evaluated from 10 tapes reanalyzed by the same observer; the correlation coefficient between the measurement of VPCs was 0.93 and the Kappa statistic of complex forms of VPCs was 0.92.¹⁴

As the effect of verapamil on ventricular ectopy is limited,¹⁴ the present study is based on all randomized patients with Holter monitoring from the five participating centers. The first Holter monitoring was performed in 250 patients 7 ± 2 days (mean $\pm$ standard deviation), the second in 210 patients $42 \pm$

19 days, and the third in 201 patients 489 ± 100 days after the index infarct. In patients with < 10 VPCs/h in one recording, registration of > 10 VPCs/h was assessed in a later recording. This evaluation took place in 169 patients from the first to the second recording, in 151 patients from the first to the third recording, and in 126 patients from the second to the third recording. Correspondingly, in patients without any complex ventricular ectopy, development was assessed in 137 patients from the first to the second recording, in 127 patients from the first to the third recording, and in 98 patients from the second to the third recording.

Statistical Methods

Fisher's exact test and chi-square test were used when appropriate. Mortality rates were calculated according to Kaplan-Meier and curves were compared with the Tarone-Ware test (BMDP statistical program package 1990). Cox multivariate analysis was applied to disclose independent predictors of mortality. The Spearman rank correlation test for ordinal variables and the Kappa statistic for categorical variables was used for quality control of the Holter system.

Multivariate Analysis

History and clinical findings: In the DAVIT II study, a multivariate analysis was performed including all baseline variables which, at univariate analyses, were correlated with death at $p < 0.05$. The result of this multivariate analysis was that the following variables independently predicted mortality: Age [as a continuous variable, $p = 0.004$, hazard ratio (HR) 1.03], previous AMI ($p = 0.001$, HR 1.79); history of angina pectoris ($p = 0.001$, HR 1.62); diabetes mellitus ($p = 0.002$, HR 1.59); intermittent claudication ($p = 0.001$, HR 2.08); index AMI involving anterior and inferior or posterior wall ($p = 0.009$, HR 1.58); resting heart rate (as a continuous variable, $p = 0.001$, HR 1.02); left bundle-branch or intraventricular block on electrocardiogram (ECG) ($p = 0.001$, HR 2.41); and heart failure, that is, clinical heart failure prior to randomization and treatment with diuretics, and/or congestion on chest x-ray at randomization ($p = 0.04$, HR 1.39). These variables were included in the multivariate analysis of the present study. In the multivariate analyses based on the findings of the second and third recordings, the presence of angina pectoris; resting heart rate as a continuous variable; and heart failure, that is, treatment with diuretics and dyspnea, dependent edema, and/or pulmonary rales at the outpatient clinic visits closest to the Holter monitoring were included as well.

Arrhythmias: Ventricular ectopy with a predictive value of mortality of $p < 0.05$ at univariate analysis was also included in the multivariate analyses.

End Points and Follow-Up Period of Study Populations

Mortality: Information about all-cause mortality was obtained from the Danish National Person Register, recording all deaths in the country.

Arrhythmias and mortality: Follow-up time was a maximum of 1,702 days and minimum of 615 days. The mean follow-up period in surviving patients was 1,326 days from the first, 1,309 days from the second, and 838 days from the third recording.

Results

In the present study populations of $n = 250$, $n = 210$, and $n = 201$, respectively, the findings at baseline including gender, age, history, and complications in the coronary care units do not differ significantly from those of the total DAVIT II study population ($n = 1,775$) (Table I).

Mortality, and Ventricular Ectopy 1 Week, 1 Month, and 16 Months after Acute Myocardial Infarction

Prevalence of ventricular ectopy 1 week, 1 month, and 16 months after AMI and mortality at the end of the observation period are presented in Table II.

Multivariate analysis involving the predictive arrhythmias displayed that only >10 VPCs/h recorded 1 week [$p = 0.0002$, HR 3.09, 95% confidence interval (CI) 1.72, 5.55] or 1 month ($p < 0.003$, HR 3.05, CI 1.47, 6.34) after the infarct independently predicted long-term mortality (Figs. 1, 2). Sixteen months after the index infarct, ventricular tachycardia ($p = 0.002$, HR 4.42, CI 1.72, 11.33, Fig. 3) and more than two

TABLE I Baseline characteristics of the study populations and the total DAVIT II population

Characteristics	1 Week		1 Month		16 Months		DAVIT II	
	N	(%)	N	(%)	N	(%)	N	(%)
Mean age $\pm$ SD	60 $\pm$ 9		59 $\pm$ 9		60 $\pm$ 9		60 $\pm$ 9	
Age (years) < 64	162	(65)	150	(71)	141	(70)	1166	(66)
≥ 65	88	(35)	60	(29)	60	(30)	609	(34)
Gender								
Male	187	(75)	156	(74)	157	(78)	1416	(80)
Female	63	(25)	54	(26)	44	(22)	359	(20)
History								
Previous AMI								
No	216	(86)	184	(88)	176	(88)	1503	(85)
Yes	34	(14)	26	(12)	25	(12)	272	(15)
Previous hypertension								
No	212	(85)	181	(86)	174	(87)	1525	(86)
Yes	38	(15)	29	(14)	27	(13)	250	(14)
Previous angina pectoris								
No	186	(74)	164	(78)	153	(76)	1304	(73)
Yes	64	(26)	46	(22)	48	(24)	471	(27)
Previous diabetes								
No	240	(96)	202	(96)	195	(97)	1677	(94)
Yes	10	(4)	8	(4)	6	(3)	98	(6)
Index AMI								
Q wave								
No	73	(29)	59	(28)	56	(28)	469	(26)
Yes	177	(71)	151	(72)	145	(72)	1306	(74)
Anterior								
No	123	(49)	100	(48)	100	(50)	907	(51)
Yes	127	(51)	110	(52)	101	(50)	868	(49)
Complications in CCU								
Shock								
No	243	(97)	204	(97)	194	(97)	1708	(96)
Yes	7	(3)	6	(3)	7	(3)	67	(4)
Instinctio cordis								
No	240	(96)	201	(96)	193	(96)	1698	(96)
Yes	10	(4)	9	(4)	8	(4)	77	(4)
Heart failure								
No	175	(70)	155	(74)	148	(74)	1161	(65)
Yes	75	(30)	55	(26)	53	(26)	614	(35)

Abbreviations: DAVIT II = Danish Verapamil Infarction Trial II, SD = standard deviation, AMI = acute myocardial infarction, CCU = cardiac care unit.

TABLE II Prevalence and univariate analysis of ventricular ectopy after acute myocardial infarction

Type of Arrhythmias	1 Week Mortality				1 Month Mortality				16 Months Mortality			
	Patients N	N	Rate %	p Value	Patients N	N	Rate %	p Value	Patients N	N	Rate %	p Value
Pairs												
—	207	35	17.3	0.006	153	16	10.6	0.008	147	12	8.2	0.04
+	43	15	34.9		53	13	25.1		52	10	21.4	
>2 Types of VPC												
—	230	44	19.4	0.17	176	22	12.8	0.19	155	12	8.4	0.002
+	20	6	30.0		34	7	20.6		44	10	22.8	
VT												
—	223	42	19.2	0.09	188	26	14.1	0.61	183	15	8.8	0.000
+	26	8	30.8		17	3	17.7		17	7	41.2	
>10 VPCs/h												
—	208	33	16.2	0.0001	163	16	10.1	0.001	147	11	7.7	0.008
+	42	17	40.5		47	13	27.8		53	11	22.1	
Complex VPCs												
—	175	29	17.0	0.03	128	11	8.7	0.004	113	6	5.3	0.003
+	74	21	28.4		77	18	23.8		86	16	19.7	

Abbreviations: VPC = ventricular premature complexes, VT = ventricular tachycardia, i.e., ≥ 3 consecutive VPCs, complex VPC = presence of pairs and/or > 2 types of VPCs, and/or VT, and/or > 10 VPC/h, + = present, — = not present, h = hour.

FIG. 1 Cumulative survival of patients with (B) and without (A) >10 VPCs/h 1 week after acute myocardial infarction.

FIG. 2 Cumulative survival of patients with (B) and without (A) >10 VPCs/h 1 month after acute myocardial infarction.

FIG. 3 Cumulative survival of patients with (+) and without (-) ventricular tachycardia 16 months after acute myocardial infarction.

types of VPCs ($p = 0.047$, HR 2.44, CI 1.01, 5.90) were independent predictors of long-term mortality.

Results of multivariate analyses based on history, clinical findings, and the arrhythmic variables were as follows: After 1 week, > 10 VPCs/h ($p = 0.0006$, HR 2.81, CI 1.55, 5.08) and heart failure ($p < 0.007$, HR 2.17, CI 1.24, 3.81); after 1 month, > 10 VPCs/h ($p = 0.003$, HR 3.13, CI 1.46, 6.69) and resting HR ($p < 0.02$, HR 1.03, CI 1.01, 1.06); after 16 months, ventricular tachycardia ($p = 0.002$, HR 4.41, CI 1.70, 11.44), and to

some extent more than two types of VPCs ($p < 0.06$, HR 2.35, CI 0.97, 5.74), independently predicted long-term mortality.

Mortality and Development of More Than Ten Ventricular Premature Complexes per Hour or of Any Complex Ventricular Ectopy after an Acute Myocardial Infarction

Mortality of the subgroup of patients with two periods of Holter monitoring and without arrhythmias during the first recording was related to the development of > 10 VPCs/h or any complex ventricular ectopy.

Univariate analysis demonstrated that development of > 10 VPCs/h and any complex ventricular ectopy significantly predicted mortality (Table III).

History and clinical variables at randomization were related to the development of VPCs. Heart failure was the only variable significantly related to the development of > 10 VPCs/h ($p = 0.01$) and complex VPCs ($p = 0.007$) from the first to the second recording.

Discussion

The patients of the DAVIT II study population constituted 45% of the total population with AMI and were characterized by being in a clinically stable state without grave or unstable angina pectoris and without or with only mild to moderate heart failure. The patients of the present substudy were regarded as representative of the total DAVIT II population, since no significant differences regarding gender, age, history, or complications in the coronary care unit could be demonstrated.

Prevalence of Ventricular Ectopy in Postinfarct Patients

In several studies, 24-h Holter monitoring has been performed during hospitalization in order to evaluate the prevalence and prognostic information of ventricular ectopy after an AMI.^{1,5-11} In the present study, which, in contrast to oth-

TABLE III Univariate analysis of development of > 10 VPCs/h and of complex VPCs from 1 week to 1 month, from 1 week to 16 months, and from 1 to 16 months after myocardial infarction

Development from	1 Week to 1 month Mortality				1 Week to 16 months Mortality				1 to 16 Months Mortality			
	Patients N	N	Rate %	p Value	Patients N	N	Rate %	p Value	Patients N	N	Rate %	p Value
Arrhythmias												
> 10 VPCs/h												
-	142	14	14.3	0.003	116	6	6.0	0.03	103	3	3.9	0.007
+	27	8	41.8		35	6	19.8		23	4	21.3	
Complex VPCs												
-	96	9	12.3	0.02	79	2	3.8	0.01	69	1	2.9	0.04
+	41	10	34.9		48	7	16.6		29	3	10.3	

Abbreviations as in Table II.

ers,^{1,5-7} excluded patients under treatment with digoxin or antiarrhythmic drugs, the prevalence of in-hospital ventricular ectopy was in the lower end compared with those reported in other post AMI trials. Thus, 17% of patients in the present study (Table II) displayed pairs compared with 14%,⁵ 22%,¹⁵ 30%,⁶ and 34%¹⁰ in other trials; ventricular tachycardia was seen in 10% of patients in the present trial, compared with 12% of 430 patients in the study of Bigger *et al.*,⁶ and 21% of 378 patients in the study of Andresen *et al.*¹⁰ The prevalence of >10 VPCs/h during hospitalization was 17% in the present trial compared with 13 to 26% in other trials.^{5-8,10-11,17}

Few post AMI studies using 24-h Holter monitoring have examined ventricular ectopy after discharge.^{5,16} Møller⁵ demonstrated pairs in 15 and 16% of 91 patients after 1 and 6 months, respectively; Vorpal and Blümchen¹⁶ demonstrated that 26% of 55 patients 6 to 12 months after AMI had pairs, comparable with the 26% found 1 and 16 months after AMI in the present trial. In the study of Møller,⁵ the prevalence of >10 VPCs/h was 35% 1 month and 31% 6 months after AMI, which was somewhat higher than that in the present study (22% 1 month and 27% 16 months after AMI).

Several studies utilizing 1 h,⁴ 6 h,^{2,3} and 24 h of ECG monitoring^{1,5-11} in the hospital phase of AMI have demonstrated the presence of complex VPCs^{1-4,8} and >10 VPCs/h^{7,11} to be independent predictors of post AMI sudden death,^{1,4,11} cardiac death,³ major events,² and all-cause mortality.^{7,8,11}

Prognostic Implication of Ventricular Ectopy One Week after Acute Myocardial Infarction

In the present study, heart failure in the coronary care unit and >10 VPCs/h 1 week after AMI were independent predictors of mortality. This is well in agreement with previous studies demonstrating in-hospital >10 VPCs/h and repetitive VPCs to be significantly related to mortality after having adjusted for left ventricular dysfunction.^{7,17-18} Thus, as the risk of dying in the years after myocardial infarction is independently increased by the presence of heart failure and >10 VPCs/h during hospitalization, this must not, as stressed by Bigger,¹⁹ be misinterpreted as an actual interaction between the two variables with respect to mortality.

Prognostic Implication of Ventricular Ectopy One Month after Acute Myocardial Infarction

One month after AMI, the present study demonstrated >10 VPCs/h and increasing resting heart rate to be independent predictors of mortality. It is possible that increasing resting heart rate during daytime indicates latent heart failure, and/or it might also imply autonomic imbalance, reflecting altered sympathovagal neurocardiac reflex regulation, with either increased sympathetic or decreased parasympathetic activity, or both. Experimental studies have demonstrated that autonomic imbalance lowers the threshold for fatal arrhythmias.²⁰⁻²² A recent study displayed a significant increase in mean heart rate and a significant change in autonomic influence on the heart, mainly due to decreased vagal activity, during the last few

minutes preceding the onset of episodes of spontaneous idiopathic ventricular tachycardia.²³

Prognostic Implication of Ventricular Ectopy Sixteen Months after Acute Myocardial Infarction

Sixteen months after infarction, history or clinical findings no longer predicted later mortality, whereas presence of ventricular tachycardia, and to some extent occurrence of more than two types of VPCs, that is, the quality rather than quantity of ventricular ectopy, predicted mortality. This is well in agreement with the study of Rehnqvist *et al.*,² using 6 hours of ECG monitoring 1 year after infarction, which demonstrated that complex ventricular ectopy, that is, repetitive VPCs, multifiform VPCs, and R on T phenomenon, independently predicted mortality the following year.

Development of Frequent and Complex Ventricular Ectopy

The development of frequent and complex ventricular ectopy 16 months after an AMI predicted increased long-term mortality, an observation that has not previously been published. Development of frequent and complex ectopy from 1 week to 1 month after AMI was significantly related to heart failure. This means that patients with heart failure have a higher prevalence of VPCs and a higher risk of developing VPCs, and that further prognostic information is obtained by performing a second Holter monitoring after 1 month.

Ventricular Ectopy and Mortality

For fatal arrhythmias to develop, important prerequisites are triggered activity/after depolarizations, induction of enhanced automaticity, and/or emergence of a substrate for reentrant arrhythmias, characterized by unidirectional block and slow conduction in often damaged/ischemic tissue, as well as appearance of discharging or modulating events such as VPCs or increased heart rate. The susceptibility of the arrhythmia substrate to modulating events may be dependent on an abnormal autonomic tone, for instance, reduced vagal tone which may shorten ventricular refractoriness.²⁴ Any of these elements—abnormal automaticity, presence of an arrhythmogenic substrate, modulating events such as VPCs and autonomic imbalance—may be modified in a circadian manner as well as over the time course of the infarction process. This may explain the fact that the present study demonstrated the prognostic implication of ventricular ectopy in relation to mortality and thus fatal arrhythmias to be different early and late after an AMI.

Conclusion

The present study demonstrated that 1 week and 1 month after an AMI the quantity of VPCs, that is, >10 VPCs/h, predicted mortality, whereas 16 months after an AMI the quality of VPCs, that is, ventricular tachycardia, predicted mortality. Although the present study population was characterized as

stable, without serious angina pectoris or heart failure, and thus with a fairly good post AMI prognosis, occurrence of frequent or complex ventricular ectopy was demonstrated to be a strong and independent predictor of mortality. Thus, Holter monitoring may still be useful in prognostic evaluation during the period after an AMI.

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