Influence of age on the relation between heart rate variability, left ventricular ejection fraction, frequency of ventricular extrasystoles, and sudden death after myocardial infarction

Olusola Odemuyiwa, Thomas G Farrell, Marek Malik, Yaver Bashir, Teri Millane, Tim Cripps, Jan Poloniecki, D Bennett, A John Camm

Abstract

Aims—To examine the influence of age on the prediction of sudden death after acute myocardial infarction based on heart rate variability (HRv), left ventricular ejection fraction (LVEF), and the frequency of ventricular extrasystoles.

Background—Autonomic and left ventricular function and the frequency of ventricular extrasystoles change with age but the influence of age on the prediction of sudden death from these variables has not been examined.

Methods—The 477 patients who had been through an early postinfarction risk stratification protocol and followed up for a mean of 790 days were dichotomised at 60 years of age.

Results—Sudden deaths occurred with similar frequency in both age groups (12 (4.7%) of the 256 patients aged <60 years and seven (3.2%) of the 221 older patients). Sudden death, however, accounted for 52% of all deaths in the young group but only 18.4% of all deaths in the older group ($p < 0.01$). An HRv index of <20 units combined with an average of more than 10 ventricular extrasystoles an hour on Holter monitoring (VE10) had a sensitivity of 50%, a positive predictive accuracy of 33%, and a risk ratio of 18 in the young group ($p < 0.001$) but was not significantly predictive in older patients. The situation was similar when the combination of an LVEF <40% with VE10 was considered. This combination had a sensitivity of 44%, positive predictive accuracy of 36.4%, and a risk ratio of 16.1 in young patients ($p < 0.001$), but was not significantly predictive in older patients. The combination of VE10 with either LVEF <40% or HRv <20 units gave a sensitivity of 75%, positive predictive accuracy of 30%, and a risk ratio of 30 in young patients ($p < 0.001$), but the relation between this combination and sudden death in older patients was not statistically significant.

Conclusion—In postinfarction patients aged <60 sudden death was a more predominant mode of death and was

more reliably predicted from a depressed HRv index, an LVEF <40%, and VE10 than in older postinfarction patients. These findings may have important implications for post-infarction risk stratification and management.

Left ventricular dysfunction and frequent ventricular extrasystoles are associated with an increased risk of sudden death after myocardial infarction.¹² The clinical value of this relation, however, is still questioned partly because it is unclear how these variables cause sudden death. The association between autonomic dysfunction and ventricular fibrillation in animals³ has recently generated interest in the potential of autonomic function tests to predict and explain sudden death in postinfarction patients. Firstly, Kleiger *et al*⁴ showed that depressed heart rate variability was associated with increased all cause mortality after myocardial infarction and La Rovere *et al*⁵ and Farrell *et al*⁶ subsequently showed a correlation between reduced baroreceptor sensitivity and an increased risk of sudden death and ventricular arrhythmias in postinfarction patients.

There is a decline in autonomic function with age in both postinfarction patients and in healthy controls.⁷⁻⁹ Age is also a well recognised determinant of all cause mortality after myocardial infarction.¹⁰⁻¹² But as autonomic function,⁷⁻⁹ ventricular systolic,¹³ and diastolic function,¹⁴⁻¹⁶ and the prevalence of frequent ventricular extrasystoles¹⁷ all change with age, their value as predictors of sudden death may well change with age. We examined the practical implications of this hypothesis by dichotomising 477 serial postinfarction patients at 60 years of age.

Patients and methods

PATIENTS

The study population consisted of 477 patients under the age of 75 years admitted to our institution with acute myocardial infarction. Acute myocardial infarction was diagnosed if two of three criteria were met:

- Characteristic chest pain lasting 30 minutes.
- A sequential rise and fall in plasma concentrations of aspartate transaminase, β hydroxy-

Department of
Cardiological
Sciences, St George's
Hospital, Cranmer
Terrace, London
SW17 0RE
O Odemuyiwa
T G Farrell
M Malik
Y Bashir
T Millane
T Cripps
J Poloniecki
D Bennett
A J Camm

Correspondence to
Dr Olusola Odemuyiwa,
Department of Cardiological
Sciences, St George's
Hospital, Cranmer Terrace,
London SW17 0RE

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butyric dehydrogenase, or creatine kinase with a peak concentration at least twice the upper limit of the reference range of our laboratory. (c) Development of new pathological Q waves or persistent ST-T changes suggestive of non-Q wave infarction.

Only patients admitted straight from home and who survived the acute phase of myocardial infarction were enrolled in the study and studied prospectively.

EVALUATION

As part of the risk stratification protocol, the patients' historical and clinical data on admission were recorded and following tests were performed between five and 11 days after infarction:

(a) Ambulatory 24 hour electrocardiographic recordings with a Reynolds Tracker two channel recorder (leads II and CM5). We used the Pathfinder 3 system, an operator-computer interactive device, for arrhythmia recognition and grading ventricular frequency.

(b) Patients performed a symptom limited treadmill exercise test with the Bruce protocol just before discharge from hospital. Exercise-induced ST segment depression, angina, or ventricular tachycardia; a rise in systolic blood pressure of less than 30 mm Hg; or an inability to complete the first stage of the protocol were indications for predischARGE left ventriculography and selective coronary angiography. Left ventricular ejection fraction (LVEF) was calculated from the ventricular silhouettes at end systole and end diastole in the right anterior oblique view by a digitising personal computer program (MAC angio computer package) based on the formula of Sandler and Dodge.¹⁸ In those patients who did not undergo coronary angiography, radionuclide angiograms were performed in the supine position and the LVEFs were calculated by the multiple gated method performed in the 45° left anterior oblique projection.¹⁹

FOLLOW UP

All patients were followed up in a special infarct clinic. Follow up visits were made three to four weeks after discharge from hospital, then at three months, and subsequently every year or more frequently when clinically indicated. Treatment was at the discretion of

the patient's physician. β Blockers and anti-arrhythmic therapy were not routinely prescribed. The main endpoint was sudden death, which was classified by OO and TF without knowledge of the risk stratification results. Sudden death was defined as death within an hour of the onset of new symptoms: it included instantaneous deaths, deaths during sleep, and unwitnessed death, provided these occurred within an hour of the patient last being seen.²⁰ It was confirmed by examination of the case records, by the results of necropsy when available, and by interviewing the relatives or the general practitioner.

ANALYSIS

A heart rate variability index (HRv) was calculated by digitising the 24 hour electrocardiographic recording off line and transferring it to a personal computer (IBM PC-AT). Each beat was then classed as normal or aberrant based on the matching pairs principle. An HRv was calculated for each patient.^{21,22} The frequency distribution of durations of normal to normal RR intervals was constructed. Measured values of HRv were then obtained in technical units by measuring the baseline width of the distribution curve. This method of triangular interpolation of the frequency distribution of the normal to normal interval duration, which has been explained in more detail elsewhere,^{23,24} is not affected by low levels of noise and artefact, whereas the widely used methods based on the standard deviation of normal to normal interval durations require the long term electrocardiogram to be clear of artefacts.²¹

To show the strength of associations we selected a LVEF cut off of 40%. Previous studies have shown a close association between a frequency of ventricular extrasystoles of ≥ 10 per hour (VE10) and sudden death.^{1,2} A cut off point of 20 baseline width units was selected for the HRv because our previous study had shown that this value best distinguished patients with arrhythmic events from those without.²⁴ The population was divided at the age of 60 because this gave nearly the same number of patients and the same rates of sudden death in each group.

The HRv was calculated in 418 patients; left ventricular angiography carried out in 436 patients; and 409 patients had data for both. Predictive characteristics were calculated for the appropriate subtotals.

The χ^2 test with Yates' correction and *t* tests was used to determine the significance of the differences between proportions and means respectively. A value of *p* < 0.05 was considered to be significant.

Results

There were 343 (71.9%) men and 134 (28.1%) women aged between 26 and 75 (mean (SD), 57.6 (9.4) years. Of the 477 patients, 221 were 60 or older and 256 were younger than 60. A higher proportion of older patients (20.4%) than younger patients (8.2%) had a history of previous infarction (*p* < 0.001) but more

Table 1 Clinical and historical characteristics and distribution of prognostic variables

	<i>Age < 60 (n = 256)</i>	<i>Age ≥60 (n = 221)</i>	<i>p Value</i>
<i>Clinical and historical characteristics (n (%))</i>			
Past MI	21 (8.2)	45 (20.4)	<i>p</i> < 0.001
Anterior MI	120 (46.9)	98 (44.3)	
Non-Q wave MI	103 (40.2)	75 (34.0)	<i>p</i> < 0.001 <i>p</i> < 0.05
Streptokinase	112 (43.8)	94 (42.5)	
Aspirin	119 (46.5)	109 (49.3)	
β blockers on discharge	110 (43.0)	58 (26.2)	
Revascularisation	66 (25.8)	39 (17.7)	
<i>Distribution of prognostic variables</i>			
Age (y (SEM))	51.1 (0.43)	66 (0.25)	<i>p</i> < 0.001
HRv < 20 (no (%))	40 (17.9)	63 (32.3)	
HRv (mean (SEM))	28.8 (0.71)	24.8 (0.8)	<i>p</i> < 0.0001
LVEF < 40% (n(%))	51 (21.9)	62 (30.5)	<i>p</i> < 0.05
LVEF (mean (SEM))	51.8 (0.9)	47.5 (1.1)	<i>p</i> < 0.004
VE10 (n(%))	38 (17.0)	55 (28.2)	<i>p</i> < 0.01

MI, myocardial infarction; HRv < 20, heart rate variability under < 20 units; LVEF, left ventricular ejection fraction; VE10, ventricular extrasystoles of 10 or more per hour.

Table 2 Relation between clinical variables and sudden death (n (sudden deaths))

	Age < 60	Age ≥ 60
Past MI	21 (3)	45 (1)
Anterior MI	120 (4)	98 (5)
Non-Q-wave MI	103 (6)	75 (2)
Streptokinase	112 (2)	94 (2)
Killip >2	10 (0)	32 (4)
Congestive failure	12 (1)	33 (2)
β blockers on discharge	110 (1)	58 (1)
HRv < 20 units	40 (6)	63 (5)
LVEF < 40%	51 (5)	62 (2)
VE10	38 (6)	55 (2)
HR > 80/min	202 (7)	168 (5)

See footnote to table 1 for abbreviations.

younger (43%), than older patients (26.2%) were discharged on β blockers ($p < 0.01$). Tables 1 and 2 show the other major historical and clinical characteristics.

ALL CAUSE MORTALITY AND SUDDEN DEATH RATES

The mean follow up period was 790 (range 490–1412) days during which there were 61 (12.8%) deaths, made up of 23 (9%) of the 256 younger patients and 38 (17.2%) of the 221 older patients ($p < 0.02$). There were 19 (4%) sudden deaths, made up of 12 (4.7%) of 256 in the young group, and seven (3.2%) of the 221 older patients (NS). Therefore, 12 (52%) of the 23 deaths in the young group and seven (18.4%) of the 38 deaths in the older group were sudden ($p < 0.01$).

TIMING OF SUDDEN DEATHS

Sudden deaths in younger patients occurred between seven and 373 days after infarction; seven (58.3%) occurred within 30 days of infarction. The sudden deaths in older patients occurred between 18 and 439 days of infarction with three (42%) occurring within 30 days of infarction.

Table 3 Relation of HRv and VE10 to sudden death

	n	Sd	sens	ppa	rr	(95% CI)	p Value
<i>All patients (n = 418), sudden deaths = 14 (3.3%)</i>							
HRv < 20	103	11	78.6	10.7	11.0	(3.2 to 39.3)	<0.001
VE10	93	8	57.0	8.6	4.7	(3.1 to 24.1)	<0.01
HRv < 20 + VE10	35	5	36.0	14.3	6.1	(2.2 to 17.3)	<0.01
<i>Patients aged < 60 (n = 223), sudden deaths = 8 (3.6%)</i>							
HRv < 20	40	6	75.0	15.0	13.7	(2.9 to 65.4)	<0.001
VE10	38	6	75.0	15.8	15.4	(3.2 to 73.0)	<0.001
HRv < 20 + VE10	12	4	50.0	33.0	17.6	(5.0 to 62.2)	<0.001
<i>Patients aged ≥ 60 (n = 195), sudden deaths = 6 (3.1%)</i>							
HRv < 20	63	5	83.3	7.9	10.5	(1.3 to 88.2)	<0.05
VE10	55	2	33.0	3.6	2.6	(0.5 to 13.9)	NS
HRv < 20 + VE10	23	1	16.7	4.3	1.4	(0.2 to 11.5)	NS

Sd, sudden deaths; ppa, positive predictive accuracy; rr, risk ratio; sens, sensitivity.

Table 4 Relation of EF < 40 and VE10 to sudden death

	n	Sd	Sens	ppa	rr	(95% CI)	p Value
<i>All patients (n = 436), sudden deaths = 15 (3.4%)</i>							
LVEF < 40	113	7	46.7	6.2	2.5	(1.0–6.8)	NS
LVEF < 40 + VE10	37	5	33.0	13.5	5.4	(2.0–14.3)	<0.01
<i>Patients aged < 60 (n = 233), sudden deaths = 9 (3.9%)</i>							
LVEF < 40	51	5	55.6	9.8	4.5	(1.3–16.0)	<0.05
LVEF < 40 + VE10	11	4	44.4	36.4	16.1	(3.9–69.4)	<0.001
<i>Patients aged ≥ 60 (n = 203), sudden deaths = 6 (2.9%)</i>							
LVEF < 40	62	2	33.3	3.2	1.1	(0.2–6.0)	NS
LVEF < 40 + VE10	26	1	16.7	3.8	1.4	(0.2–11.2)	NS

For abbreviations see footnotes to tables 1 and 3.

RELATION BETWEEN AN HRV INDEX < 20 UNITS AND SUDDEN DEATH

An HRv index < 20 units was found in 40 (17.9%) of the young patients: six (15%) of these 40 compared with two (1%) of the 183 patients with HRv > 20 units died suddenly ($p < 0.001$). An HRv < 20 units was found in 63 (32.3%) of the older patients: five (7.9%) of these 63 compared with one (1%) of the 132 older patients with HRv > 20 units died suddenly ($p < 0.05$) (table 3).

RELATION BETWEEN A LOW LVEF AND SUDDEN DEATH

An LVEF < 40% was found in 51 (21.9%) of the 233 younger patients: five (10%) of these 51 compared with four (2%) of the 182 patients with EF ≥ 40% died suddenly ($p < 0.05$). An EF < 40% was found in 62 (30.5%) of the 203 older patients: two (3.2%) of these 62 compared with four (2.8%) of the 141 patients with EF ≥ 40% died suddenly (NS) (table 4).

RELATION BETWEEN VE10 AND SUDDEN DEATH

Thirty eight (17%) of 223 young patients had VE 10: six (15.8%) of these 38 died suddenly compared with two (1%) of the remaining 185 patients ($p < 0.001$). VE10 was found in 55 (28.2%) of the older patients: two (3.6%) of these 55 patients and four (2.9%) of the remaining patients died suddenly (NS) (table 3).

RELATION BETWEEN THE COMBINATION OF VE10 AND HRV AND SUDDEN DEATH

A low HRv and VE10 were combined in 12 (5.4%) of the young patients: four (33%) of these 12 patients died suddenly compared with four (1.6%) of the remaining patients ($p < 0.001$). The relation between these variables and sudden death in older patients was not statistically significant (table 3).

RELATION BETWEEN SUDDEN DEATH AND THE COMBINATION OF A LOW LVEF AND VE10

An LVEF < 40% was combined with VE10 in 11 (4.7%) of the young patients: four (36.4%) of these died suddenly compared with five (2.3%) of the remaining patients ($p < 0.001$). The relation between this combination of variables and sudden death in the older group did not reach statistical significance (table 4).

RELATION BETWEEN SUDDEN DEATH AND THE COMBINATION OF VE10 WITH LOW HRV OR LOW LVEF

A combination of VE10 with either a low HRv or an LVEF < 40% was found in 20 (9.1%) of the 236 young patients: six (30%) of these 20 died suddenly compared with two (1%) of the remaining patients ($p < 0.001$) (table 5). The relation between this combination of variables and sudden death did not reach statistical significance in the older group.

Discussion

We have shown that sudden death is a commoner mode of death and is more reliably

Table 5 Relation of LVEF and HRv to sudden death (Sd)

	n	Sd	Sens	ppa	rr	(95% CI)	p Value
<i>All patients (n = 409), sudden deaths = 14 (3.4%)</i>							
HRv + EF	42	5	35.7	11.9	4.9	(1.8–14.0)	<0.01
HRv/EF	174	13	92.8	7.5	17.6	(2.3–131.6)	<0.001
HRv/EF + VE10	52	7	50.0	13.5	6.9	(5.0–36.6)	<0.001
<i>Patients aged < 60 (n = 219), sudden deaths = 8 (3.7%)</i>							
HRv + EF	12	3	37.5	25.0	10.4	(2.6–41.3)	<0.01
HRv/EF	79	8	100.0	10.0	—	—	<0.001
HRv/EF + VE10	20	6	75.0	30.0	30.0	(16.5–138.4)	<0.001
<i>Patients aged > 60 (n = 190), sudden deaths = 6 (3.2%)</i>							
HRv + EF	30	2	33.0	6.7	2.7	(0.5–14.2)	NS
HRv/EF	95	5	83.3	5.3	5.0	(2.0–49.4)	NS
HRv/EF + VE10	32	1	16.7	3.1	1.0	(0.1–8.2)	NS

See footnotes to tables 1 and 3 for abbreviations.

predicted in younger than in older postinfarction patients by heart rate variability, frequency of ventricular extrasystoles, and to a lesser extent the left ventricular ejection fraction. Our first finding is consistent with previous reports. Vismara *et al*²⁵ who found that 36% of the deaths in postinfarction patients aged under 50 years but only 16% of the deaths in older patients were sudden. According to Daly *et al* 46% of deaths in 551 young men who survived unstable angina or acute myocardial infarction were sudden and the proportion of sudden deaths was inversely related to age at initial attack.²⁶

The rates of sudden death (4%, 5.4%, and 4.5%) in our study and in the MILIS and BHAT studies are similar.^{1,2} The higher proportion of patients with VE10 in our study (22%), however, compared with 15% and 13% reported by the MILIS and BHAT studies may be due to differences between the studies in criteria for patient recruitment, in the timing of Holter monitoring, and in the proportion of older patients.^{1,2} The positive predictive accuracy of VE10 for sudden death in the present study of 8.6% was, nevertheless, close to the 10% and 9% reported by the MILIS and BHAT studies.^{1,2}

The BHAT study found a direct relation between the frequency of ventricular extrasystoles and age; but the implications of this finding for risk stratification were not considered.³ We found VE10 to be a more reliable predictor of sudden death in the younger patients (table 3). The combination of low HRv with VE10 was present in 8.5% of our patients and was also a much better predictor in the younger group (table 3).

An LVEF < 40% had a positive predictive accuracy for sudden death of 6.2% in our study and of 10% in the MILIS study.¹ In a report in 1977 by Schulze *et al*,²⁷ 55% of the patients (compared with 26% in our study) had an LVEF < 40%, a finding that had a positive predictive accuracy of 18%. In the study by Schulze *et al* all the sudden deaths occurred in patients with an LVEF < 40%. But a rate of 14.7% for sudden deaths in patients taking quinidine or procainamide, compared with 6.4% in those not taking antiarrhythmic drugs, indicates that the relation between LVEF < 40% and sudden death may have been reinforced by the concomitant arrhythmogenic effect of antiarrhythmic therapy in patients with low ejection fractions.

In the MILIS study 40 (7.5%) patients had both VE10 and a low LVEF.¹ This subgroup was older than the other subgroups of patients and contained 24% of all the sudden deaths. If, however, older patients are more likely than younger patients to have frequent ventricular extrasystoles and to have had a previous infarction (and thus low LVEFs) the predictive characteristics of these variables may have been different in the younger members of this high risk subgroup. In our study about 5% of young patients had a low LVEF and VE10 and this combination had a sensitivity of 44% and a positive predictive accuracy of 36%. We also found that the combination of VE10 and a depressed HRv and the combination of VE10 with an LVEF < 40%, though they had similar predictive characteristics, identified different patients at high risk of sudden death (tables 3 and 4). Even more striking was that the combination of VE10 with either low HRv or an LVEF < 40% had a sensitivity of 75% and a positive predictive accuracy of 30% in young patients, and values of only 17% and 3% in the older group (table 5).

Our results may reflect the inadequacies of present techniques. Thus even if all the sudden deaths were due to autonomic dysfunction, the degree to which depressed heart rate variability accurately reflects this dysfunction seems to decline with age. This may be due to a considerable age related divergence between the effects of autonomic dysfunction on the sinus node and on the electrophysiology of the myocardium.

Our findings may also be the result of a decline with age in the proportion of sudden deaths caused by autonomic dysfunction. There are several possible mechanisms for this proposition:

- If the predisposition to ventricular fibrillation is brought about by the change in autonomic tone, rather than absolute autonomic level, older patients may experience less severe changes in sympathovagal balance after myocardial infarction than younger patients.
- Sympathetic denervation is associated with adrenergic hypersensitivity and an increased predisposition to ventricular fibrillation in dogs.²⁸ Preconditioning ischaemia prevents this sympathetic denervation. Subclinical ischaemia caused by more severe coronary disease and to decreased myocardial compliance²⁸ may have a similar protective effect in older patients. Also young patients have higher β receptor density and activity and less myocardial fibrosis than older patients^{29,30} and may therefore be either more likely, for the same degree of sympathovagal imbalance, to reach the rapid rates at which ventricular tachycardia deteriorates into ventricular fibrillation or to reach such rates more quickly.³¹
- The relative importance of thromboembolic, rheological, ischaemic, and haemodynamic causes of sudden death increases with age.³²

CLINICAL IMPLICATIONS

Whatever their explanation, our results indicate that it is not correct to assume

physiological homogeneity in a postinfarction population. Such an approach will lead to young patients at higher risk of sudden death being overlooked and many older patients receiving inappropriate treatment.

LIMITATIONS OF THE STUDY

The dichotomy point of 60 years seems arbitrary and its physiological significance is unclear. It was chosen, however, because it provided nearly the same proportion of patients and the same rates of sudden death in each group. The relations between heart rate variability, frequency of ventricular extrasystoles, and sudden death remained significant even in patients younger than 55, among whom there was a sudden death rate of only 2.4%. Our use of VE10 as a prognostic variable was based on the results of previous studies,^{1,2} but this variable may need to be refined: ventricular extrasystoles caused by increased sympathetic activity may have different prognostic implications from those triggered by increased wall stress. The LVEF may be refined by considering diastolic function and abnormalities of wall motion.

Only two of the 12 young and one of the seven older patients who died suddenly were taking β blockers but because β blocker therapy was uncontrolled its effect on our results is difficult to determine. The rates of sudden death may have been lower had more patients ≥ 60 received β blockers.³³ The effect of thrombolytic therapy on our results and the effect of the difference in the proportion of young and old patients who had surgery or angioplasty is also unknown.

Nevertheless, we have shown that age influenced the prediction of sudden death after myocardial infarction based on autonomic function tests, left ventricular ejection fraction, and the frequency of ventricular extrasystoles. If confirmed, our findings could have significant implications for postinfarction risk stratification and management.

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