

Predictors of early ventricular fibrillation before reperfusion therapy for acute ST-elevation myocardial infarction

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Background. Early VF accounts for the majority of deaths during the acute phase of acute MI. In patients treated with fibrinolytics, in-hospital VF occurs most frequently with inferior MI. Contrariwise, out-of-hospital VF seems to be associated with anterior wall MI and preinfarction angina (preconditioning) may protect against VF.

Aim. To study clinical characteristics of patients with or without VF before or during reperfusion therapy.

Study design and Methods. From January 1995 until December 2001, we treated 2826 patients for acute MI and reviewed the clinical records of all patients. Patients who developed early VF were classified according to the first episode of VF: either before or during the angioplasty procedure.

Results. VF developed in 219 (8%) patients. Early VF before reperfusion therapy (n=145, 5%) was independently related to anterior MI (RR 2.3 (95% CI 1.53-3.50), p<0.001), absence of preinfarction angina (RR 2.1 (95% CI 1.38-3.24), p=0.001) and Killip class >1 (RR 3.8 (95% CI 2.34-6.10), p<0.001). The majority of patients with VF during angioplasty (n=74, 3%) had inferior MI (61%).

Conclusion. Early VF before reperfusion therapy is independently associated with anterior MI,

absence of preinfarction angina and Killip class >1, whereas the majority of patients with VF during angioplasty have inferior MI. (*Neth Heart J* 2004;12:7-12.)

Key words: ventricular fibrillation, myocardial infarction, preconditioning, angina, heart failure

Early ventricular fibrillation (VF) accounts for the majority of deaths in patients with acute myocardial infarction (MI).¹⁻³ The mechanisms of primary VF, that is VF in the first 24 hours of an acute MI, seem to be multifactorial in origin and data have been inconclusive and sometimes contradictory.³⁻¹⁰ In particular in patients treated with thrombolysis, in-hospital VF has been shown to be related to inferior MI.^{10,11} Contrariwise, VF before hospital admission has been shown to be related to anterior wall MI in survivors of out-of-hospital cardiac arrest.⁸ The mechanisms of early VF before and during hospital admission are not understood but VF during fibrinolysis is considered to be related to, amongst other factors, reperfusion.¹¹ Furthermore, preinfarction angina, as a surrogate for preconditioning, may have a protective effect against early VF.¹²⁻¹⁴ It probably induces a kind of preconditioning of the myocardium and may therefore protect against VF during acute ischaemia, as has been shown in animal experiments.^{13,15,16}

Therefore, we sought to investigate clinical characteristics of patients with or without early VF before reperfusion therapy by primary angioplasty and patients with or without VF during the angioplasty procedure in a large consecutive cohort of acute MI patients. We studied these two modes of early VF with the objective to find predictors of early VF before reperfusion therapy. Furthermore, we studied patients who developed VF for the first time during the PCI procedure.

Methods

Patients and study protocol

Between January 1995 and December 2001, 2689 patients were admitted to our hospital with acute MI

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Table 1. Clinical characteristics of 2628 patients with and without VF before reperfusion therapy.

	VF before reperfusion therapy		p value
	No (n=2483) (95%)	Yes (n=145) (5%)	
Male (%)	1896 (76)	120 (83)	0.08
Age >60 years (%)	1334 (54)	65 (45)	0.04
Anterior infarction (%)	1205 (49)	96 (66)	<0.001
Previous coronary event (%)	386 (15)	19 (13)	0.43
Family history (%)	985 (40)	57 (39)	0.93
Hypertension (%)	675 (27)	29 (20)	0.06
Diabetes (%)	273 (11)	10 (7)	0.12
Hypercholesterolaemia (%)	479 (19)	25 (17)	0.54
Smoking (%)	1162 (47)	71 (49)	0.61
Killip >1 (%)	193 (8)	35 (24)	<0.001
Preinfarction angina*	664 (44)*	32 (27)*	<0.001

VF=ventricular fibrillation. *Preinfarction angina was documented in 1500 (60%) patients without VF before reperfusion therapy and in 115 (80%) patients with VF before reperfusion therapy.

and underwent acute coronary angiography with a view to performing coronary angioplasty.

Acute myocardial infarction

Patients had symptoms of acute MI lasting longer than 30 minutes and presented within six hours, accompanied by an electrocardiogram with ST-segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads before acute angiography.

Patients with ventricular fibrillation

Patients with out-of-hospital resuscitation and VF before arrival of the ambulance were excluded from this analysis. These patients have been described before.⁸ All patients who developed VF from the moment of arrival of the ambulance in the acute phase of MI up to or during primary angioplasty were considered to have VF and qualified for this analysis.

Patients were categorised into two groups according to the first episode of VF: before the angioplasty procedure and during the angioplasty procedure.

Clinical data

Baseline clinical data were collected prospectively in a dedicated database.¹⁷ Clinical variables included age, gender, infarct location, risk factors for cardiovascular disease and Killip class at presentation. Preinfarction angina was defined according to other studies^{14,18,19} as in our previous report¹² by the presence of at least one episode of chest pain occurring in the 72 hours preceding the acute MI. If presence or absence of chest pain was not documented in the patient's record, we considered this parameter to be unknown and therefore missing. All patients' records were reviewed to ensure the proper distinction between patients with

VF before and during the angioplasty procedure and presence or absence of preinfarction angina.

Statistical analysis

The primary objective was to study differences between the patients with versus those without VF before reperfusion therapy by primary angioplasty to find predictors of early VF before reperfusion therapy. A second objective was to study the differences between the patients with versus those without a first episode of VF during the angioplasty procedure. A chi-square statistic was calculated to test differences between proportions. Fisher's exact test was used if there was an expected cell value of less than 5. P values <0.05 were considered to be significant. We performed multivariate analysis to find independent predictors of VF before angioplasty with variables that were significantly differently distributed ($p < 0.05$) between patients with and without VF before angioplasty. Multivariate analysis was carried out using logistic regression analysis (SPSS release 10.0).

Results

During the observation period, 2628 patients with ST-elevation acute MI fulfilled the entry criteria for this study and were admitted to our hospital. In 219 (8%) patients, acute MI was complicated by VF. In 145 (5%) patients the first episode of VF occurred before the angioplasty procedure and in 74 (3%) patients the first episode of VF occurred during the angioplasty procedure.

Ventricular fibrillation before angioplasty

Patients with and without VF before angioplasty showed a similar pattern of risk factors for cardio-

Table 2. Clinical characteristics of 2483 patients with and without VF during reperfusion therapy.

	VF during reperfusion therapy		p value
	No (n=2409) (97%)	Yes (n=74) (3%)	
Male (%)	1844 (76)	52 (70)	0.211
Age >60 years (%)	1290 (53)	44 (59)	0.31
Anterior infarction (%)	1176 (49)	29 (39)	0.10
Previous coronary event (%)	373 (15)	13 (18)	0.633
Family history (%)	960 (40)	25 (34)	0.29
Hypertension (%)	657 (27)	18 (24)	0.57
Diabetes (%)	264 (11)	9 (12)	0.74
Hypercholesterolaemia (%)	469 (19)	10 (13)	0.20
Smoking (%)	1125 (47)	37 (50)	0.57
Killip >1 (%)	184 (8)	9 (12)	0.15
Preinfarction angina*	636 (44)*	28 (47)*	0.70

VF=ventricular fibrillation. *Preinfarction angina was documented in 1440 (60%) patients without VF before reperfusion therapy and in 60 (80%) patients with VF during reperfusion therapy.

vascular disease. Four variables showed a significantly different distribution over both groups. Firstly, less patients with VF before angioplasty were older than 60 years of age, when compared with patients without VF before angioplasty (45% vs. 54%, $p=0.04$). Patients with VF before angioplasty had an anterior MI more often compared with patients without VF before angioplasty (66% vs. 54%, $p<0.001$). In the patient group with VF before angioplasty, presence or absence of preinfarction angina was documented in 118 (81%) patients and in the patient group without VF before angioplasty, presence or absence of preinfarction was documented in 1500 (60%) patients. Patients with VF before angioplasty had significantly less (one or more) documented episodes of preinfarction angina, when compared with patients without VF before angioplasty (27% vs. 44%, $p<0.001$). There were more patients with Killip class >1 at presentation in the patient group with VF before angioplasty, compared with patients without VF (24% vs. 8%, $p<0.001$). Clinical characteristics of patients with and without VF before angioplasty are shown in table 1.

Patients with ventricular fibrillation during angioplasty

There were no significant differences in baseline characteristics between patients with a first episode of VF during angioplasty and patients without VF (table 2). The majority of patients with VF during angioplasty had inferior MI (61%), but this difference was not significant compared with patients without VF. In the patient group with VF during angioplasty, presence or absence of preinfarction angina was documented in 60 (81%) patients and in the patient group without VF, presence or absence of preinfarction angina was

documented in 1440 (60%) patients. The distribution of episodes of preinfarction angina was similar when patients with VF during angioplasty were compared with patients without VF (47% vs. 44%, $p=0.70$). There was an equal proportion of documentation of presence or absence of preinfarction angina between the patients with VF during the angioplasty procedure and the patients with VF before the angioplasty procedure (81% vs. 80%). Clinical characteristics of patients with VF during the angioplasty procedure and patients without VF are shown in table 2.

Independent predictors of ventricular fibrillation before reperfusion therapy by primary angioplasty

We performed logistic regression analysis using dichotomous variables that were significantly different ($p<0.05$) in univariate analysis between the patients with VF before angioplasty and patients without VF before angioplasty to analyse their independent value in a multivariate model. Therefore we analysed the following variables: age >60 years, anterior infarction, presence of preinfarction angina and Killip class >1. This analysis revealed that anterior MI, absence of preinfarction angina and Killip class >1 were independent predictors of the development of VF in the early phase of an acute MI (table 3).

Discussion

To our knowledge this is the first study of early VF in relation to the timing of the first episode of VF before or during primary angioplasty. In 219 (8%) patients, acute MI was complicated by VF, in agreement with other large STEMI trials.¹¹ In 145 (5%) patients the first episode of VF occurred before the PCI procedure and in 74 (3%) patients the first episode of VF occurred

Table 3. Odds ratios for ventricular fibrillation before reperfusion therapy, taken from the multiple logistic regression analysis.

	Predictors of ventricular fibrillation before reperfusion therapy		
	OR	(95% CI)	p value
Killip >1	3.8	(2.34-6.10)	<0.001
Anterior myocardial infarction	2.3	(1.53-3.50)	<0.001
Absence of preinfarction angina	2.1	(1.38-3.24)	0.001
Age >60	1.4	(0.97-2.11)	0.07

during the PCI procedure. Our principle finding is that early VF is independently associated with anterior MI, absence of preinfarction angina and Killip class >1 at presentation. In contrast, the majority of patients with VF during angioplasty had inferior MI.

Patients with VF before angioplasty were somewhat younger compared with patients without VF before angioplasty. Risk factors for cardiovascular disease showed a similar pattern in patients with and without VF before reperfusion therapy. More patients with VF before angioplasty had anterior wall MI, absence of preinfarction angina and Killip class >1 at presentation, when compared with patients without VF before angioplasty.

Anterior versus inferior wall myocardial infarction

Primary VF is triggered by acute ischaemia in combination with an elevated sympathetic tone due to total occlusion of a coronary artery.^{20,21} Sudden cardiac death has been associated with a higher sympathetic tone^{22,23} and β -blocking agents reduce the incidence of sudden death.^{24,25} In animal experiments, vagal stimulation or sympathetic inhibition reduces the threshold to VF.²⁶ Inferior acute MI is frequently accompanied by a strong vagal reaction and subsequent bradycardia.^{27,28} Since vagal stimulation seems to protect the myocardium against VF, it is possible that this may lead to a relative protection from VF in patients with inferior MI and a higher frequency of VF in anterior MI before intervention.

In contrast, inferior MI appears to more arrhythmogenic during mechanical reperfusion. Gacioch and Topol²⁹ described sudden clinical deterioration with VF during angioplasty in patients with right coronary artery related acute MI, which seemed to be haemodynamically stable at hospital admission. Complications during angioplasty for acute MI, especially VF, occur more frequently when procedures are performed in the right coronary artery compared with the left coronary artery, whereas shock is more frequently seen in left coronary artery related acute MI.³⁰ When VF occurs during fibrinolysis it is usually related to inferior acute MI.^{9,11} Although the mechanisms are not well understood, reperfusion seems to play an important role in developing VF. This has been studied in various trials including pre- and in-hospital trials with acute

MI patients treated with fibrinolytics.¹¹ However, in these trials the period before the administration of the fibrinolytic agent has not been studied separately, in particular with regard to the location of acute MI site and the first episode of VF. The Bezold-Jarisch reflex,³¹ particularly seen in patients with inferior STEMI and known for its extreme vagal stimulation, will play a role in the (para)sympathetic balance during PCI and may influence the occurrence of VF before or during PCI. However, this reflex is still poorly understood physiologically and its relevance is therefore unknown.

On the basis of our study, we hypothesise that patients with inferior MI are relatively protected from VF before reperfusion therapy due to the vagal response. However, in inferior MI the myocardium is more susceptible to VF during reperfusion therapy.

Preinfarction angina

In animal experiments,^{13,15,16} preconditioning has been shown to protect against VF due to acute ischaemia. We previously reported, from a cohort of out-of-hospital VF survivors with acute MI, that preinfarction angina, as a surrogate for preconditioning, seemed to protect against VF.¹²

Our data show that preinfarction angina protects the patient from developing VF before reperfusion. These findings may be important as pharmacological interventions can inhibit or stimulate preconditioning.³² The use of sulphonureas in diabetics, an especially high-risk patient group for acute MI, has been shown to inhibit preconditioning pathways as has the use of methylxantines.^{33,34} On the other hand, adenosine α_1 -receptor agonists and K^+ -ATP channel openers may stimulate preconditioning.³⁴ Our multivariate analysis shows that the absence of preinfarction angina (or preconditioning) is an independent risk factor for VF in the early phase of acute MI. In animals, preconditioning has been shown to protect against reperfusion-induced ventricular arrhythmias^{35,36} but in our patients with VF during angioplasty we could not find a protective effect of preinfarction angina against VF during angioplasty.

Heart failure

Secondary VF in acute MI is defined as VF usually occurring 48 hours or later after acute MI and is usually

due to severe heart failure.³ More patients with early VF before angioplasty had Killip class >1 at presentation compared with patients without VF before angioplasty. To find independent predictors of early VF before angioplasty, we performed multivariate analysis including: infarct location, preinfarction angina, Killip class and age. This analysis revealed that except for age, they were all independent predictors of early VF before angioplasty or reperfusion. Moreover, in multivariate analysis it was the strongest predictor of VF before reperfusion therapy. Heart failure therefore seems to be a risk factor for both primary as secondary VF.

Limitations

The first limitation of our study is potential selection bias, as is the case with all studies on early VF in humans with acute myocardial infarction. The patient group with VF before angioplasty does not include patients with early VF in whom resuscitation was not successful. However, there are no data suggesting that patients with VF and anterior myocardial have a higher rate of successful resuscitation than patients with inferior MI, and it does not seem plausible.

The second limitation is the possibility of information bias. In patients with VF, both before and during the angioplasty procedure, there was a higher incidence of documentation of preinfarction angina, when compared with patients without VF. This may be due to the fact that the patient had experienced a serious complication leading to a more thorough analysis of symptoms before the acute event by the patient and the physician and therefore to a more detailed documentation by the physician. However, the patient group without VF is so large that it gives a reliable representation of the presence or absence of preinfarction angina in this group and the incidence of preinfarction angina in these patients is comparable with other reports. This makes information bias an unlikely explanation of our findings.

Conclusions

VF before reperfusion therapy is usually related to acute anterior MI, while the majority of patients with VF during primary angioplasty have inferior MI. Preinfarction angina, as a surrogate for preconditioning, protects against early VF, whereas heart failure increases the risk of early VF during the initial hours of ST-elevation MI. It would be of interest to study the effect of a (pharmacological) intervention during transportation to the catheterisation laboratory for PCI in STEMI patients with a higher risk for early VF. ■

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