Primary PCI for acute myocardial infarction

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Ventricular Fibrillation in Acute Myocardial Infarction

CHAPTER 3.1

Out-of-Hospital Ventricular Fibrillation in Patients with Acute Myocardial Infarction: Coronary Angiographic Determinants

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Abstract

Objective. The study aimed to compare the acute coronary anatomy of patients with acute myocardial infarction (MI) complicated by out-of-hospital ventricular fibrillation (VF) versus patients with acute MI without this complication.

Background. More than half of the deaths associated with acute MI occur out-of-hospital and within one hour of onset of symptoms. The angiographic determinants of out-of hospital VF in patients with acute MI have not been investigated in detail.

Methods. Acute coronary angiographic findings of 72 consecutive patients with acute MI complicated by out-of-hospital VF were compared to 144 matched patients with acute MI without this complication.

Results. Patients with an acute occlusion of the LAD or LCx had a higher risk for out-of-hospital VF compared to patients with an acute occlusion of the RCA (odds ratio and 95% confidence interval respectively 4.82 (2.35-9.92) and 4.92 (2.34-10.39). With regard to extent of coronary artery disease, the location of the culprit lesion in the coronary arteries (proximal versus mid or distal), the flow in the infarct related artery (IRA), the presence or absence of collaterals to the IRA and of chronic occlusions, there were no differences between the two groups.

Conclusions. Acute MI due to occlusion in the LCA is associated with greater risk for out-of-hospital VF compared to the RCA. The location of occlusion within LCA (LAD, LCx, proximal or distal), amount of myocardium at risk for necrosis, and extent of coronary artery disease are not related to out-of-hospital VF.

Introduction

More than half of the deaths associated with acute myocardial infarction (MI) occur out-of-hospital and within one hour of symptom onset (1,2). There is no doubt that early ventricular fibrillation (VF) is the major lethal complication of acute MI (3,4). However the determinants of early ventricular fibrillation or out-of hospital ventricular fibrillation in patients with acute MI have not been investigated in depth (4-6). Nevertheless, a number of suggestions have been derived from either coronary angiography in the setting of thrombolysis studies or at a late phase of acute MI , or from post-mortem examinations. Unfortunately, previous studies reached conflicting conclusions for all the examined determinants: location of the infarction (7-11), identification of the infarct related artery (IRA) (7,10,12-14), infarct size (8-10) and extent of coronary artery disease (7,10,13). Moreover, other determinants such as flow grade in the IRA before reperfusion therapy, collaterals to the IRA, chronic coronary occlusions and proximal or distal location of culprit lesions have not been studied yet. No previous studies have compared coronary anatomy and coronary flow of patients with acute MI complicated by out-of-hospital VF versus a control group of similar patients without out-of-hospital VF. While coronary angioplasty is being increasingly used as the primary treatment for patients with acute MI (15), acute coronary angiography is an unique method to study coronary anatomic and hemodynamic variables during acute MI and before reperfusion therapy. Beside an accepted treatment option, it provides accurate information on infarct location, culprit lesion, presence of chronic occlusions, collateral circulation and initial flow grade in the IRA. It also provides information on amount of myocardium at risk for necrosis (region at risk) and on the extent of coronary artery disease. The latter is evaluated by number of diseased vessels or by jeopardy score (JS, amount of myocardium in “jeopardy”). Therefore the aim of the study is a comparison of coronary anatomy before reperfusion therapy of patients with acute coronary occlusion complicated by out-of-hospital VF versus patients with acute coronary occlusion without out-of-hospital VF. More specifically we studied the precise location of culprit lesion, the extent of coronary artery disease (number of diseased vessels and JS), region at risk, coronary flow grades

in the IRA , presence or absence of collaterals, and of chronic occlusions in a non-infarct related artery.

Methods

Patients and study protocol. In De Weezenlanden Hospital Zwolle and in the University Hospital Gent primary angioplasty is the treatment of choice for complicated and uncomplicated acute MI provided that patients present within 6 hours after symptom onset, have electrocardiographic criteria for acute MI (presence of ST segment elevation of more than 0.1 mV in at least two adjacent leads of a 12 -lead ECG or presence of a presumed new left bundle branch block) and (for acute MI cases complicated by out-of-hospital VF) have a reasonable chance to survive without major neurological sequelae. Between January 1995 and December 1998, 75 survivors of out-of-hospital VF fulfilled these criteria and were candidates for primary angioplasty. Three patients with left bundle branch block had a normal coronary angiogram so that the suspected diagnosis of an acute coronary occlusion and acute MI could not be confirmed. These patients were excluded for analysis. None of the patients received fibrinolytics. In the same period a group of 1,000 acute MI patients without out-of-hospital VF fulfilled the same inclusion criteria and were treated with primary angioplasty. To form a matched control group each patient with out-of-hospital VF (n= 72) was matched with 2 patients out of the latter group. Patients were matched for age (± 5 years), gender, admission hospital (Gent or Zwolle), and primary or secondary admission (referred by a local community hospital after diagnosis of acute MI).

Angiography. All patients were treated intravenously with at least 10,000 Units of heparin and at least 250 mg aspirin and underwent immediate coronary angiography. Right and left coronary angiograms were obtained in multiple projections aiming to start with the non-IRA (based on ECG) in order to visualize collateral circulation to the IRA. Ventriculography was not performed in the acute phase. Angiography of the IRA was repeated after intracoronary administration of nitrates.

Data collection. Two experienced cardiologists who were blinded to angiographic data interpreted all electrocardiograms recorded on admission. The principal angiographic and clinical data were prospectively entered in a database. Coronary stenoses were graded by visually estimating the reduction in luminal diameter (0-49, 50-74, 75-94, 95-99 and 100 %) in the angiographic projection in which the stenosis appeared most severe. Coronary lesions resulting in 75 % reduction in luminal diameter or more by visual estimation were considered significant.

Culprit lesion. A lesion was considered the culprit lesion if it was a fresh occlusion at angiography. A coronary segment was considered occluded if it was subtotally or totally occluded with Thrombolysis in Myocardial Infarction (TIMI) flow grade <3 (16). An occlusion was considered acute if angiography revealed a thrombus at the site of the occlusion or if a guide wire passed easily through the occlusion if angioplasty was attempted. If there was no acute occlusion at angiography the lesion with the most severe reduction of lumen diameter (at least 75%) was assigned as the culprit lesion provided that its localization corresponded with the location of ST segment elevations on the ECG.

Coronary anatomy. The coronary arteries were divided into segments according to conventional terminology (17) and the number of significantly diseased coronary arteries was conventionally assigned from 1 to 3 (18). The extent of coronary artery disease was additionally scored using the coronary artery jeopardy score (19). This score provides more information on the amount of myocardium at risk for ischemia than the number of significantly diseased coronary arteries. Briefly, the coronary circulation is devided in six arterial segments: left anterior descending coronary artery (LAD), major anterolateral (diagonal) branch, first major septal perforator, left circumflex coronary artery (LCx), major circumflex marginal branch and the posterior descending artery. Each segment with a 75% or greater luminal diameter reduction is given a score of 1 point. Each segment distal to a segment with a 75 % or greater stenosis is also given 1 point. The maximum number of points is 6. To determine the amount of myocardium at risk for necrosis (region at risk) we scored each angiogram by giving a point to segments that are distal to the infarct culprit segment. Thus, the maximum score is 5 (in case of left main

occlusion).Statistical analysis. Univariate analysis of categorical variables was carried out by a two tailed Fisher's exact test. Descriptive variables with a normal distribution were given by median and the 25-75 percentile. Multivariate analysis for prediction of out-of-hospital VF was carried out using logistic regression analysis (SPSS release 7.5).

Results

Patients. Clinical data of 72 patients with out-of-hospital VF and 144 patients without out-of-hospital VF are summarized in Table 1. Time from symptom onset to collapse is unknown. The median time interval between collapse and angiogram was 135 min (25^{th}-75^{th} percentile: 90-180 min). The median time interval between onset of pain and angiogram of patients without out-of-hospital VF was 202 min (25^{th}-75^{th} percentile: 141-285 min). Both groups (matched as previously described) were comparable for history of coronary artery disease (including angina, coronary angioplasty, and history of a previous MI). In patients with ST segment elevations (n = 211, excluding five patients with left bundle branch block) anterior localization was statistically more frequent in patients with out-of-hospital VF (62.5% vs 37.5%; p = 0.0005).

Left ventricular ejection fraction (LVEF) was documented in 43 patients with and in 122 patients without out-of-hospital VF. LVEF were respectively 42.4.% (SD ±13.8) and 47.3% (SD ±11.9) (p = 0.03). LVEF of patients with acute occlusion of left coronary artery (LCA) with or without out-of-hospital VF were respectively 41.6.% (SD ±14.1) and 44.2 % (SD ±12.8) (p = 0.3). LVEF of patients with acute occlusion of right coronary artery (RCA) with or without out-of-hospital VF were respectively 48.6.% (SD ±11.5) and 51.0 % (SD ± 9.5) (p = 0.7).

Angiographic data of the total population. Angiographic data are summarized in Table 2. The most frequent (48.6%) location of culprit lesion was on the LAD followed by RCA (36.1%). In most of these patients mid or proximal right coronary segments were involved. In all but one of these patients the culprit lesion was located proximal to the posterior descending artery.

Table 1. Clinical characteristics

	Patients with out-of-hospital VF (n = 72)	Patients without out-of-hospital VF (n = 144)	p-Value *
Male	56(77.8%)	112(77.8 %)	1.00
Age	56.3(±10.4)	56.7(±10.3)	0.80
History of CAD ┼	22(31.4%)	61(43.6%)	0.10
History of MI	6(8.6%)	11(7.8%)	1.00
ECG MI location			
Anterior	45 (62.5%)	54(37.5%)	
Non-anterior	22 (30.6%)	90(62.5%)	0.0005╪
Left bundle branch block	5(6.9%)	0(0%)	

* According to two-tailed Fisher's exact test. ┼ CAD =Coronary artery disease= angina, prior MI or percutaneous transluminal coronary angioplasty. MI = myocardial infarction; VF = ventricular fibrillation.

Table 2. Angiographic data of the total study population (n = 216)

	N	%
IRA		
LAD	105	48.6
RCA	78	36.1
LCx	33	15.3
Location of culprit lesion on LAD		
proximal	38	17.6
mid	66	30.6
distal	1	0.5
Location of culprit lesion on RCA		
proximal	30	13.9
mid	33	15.3
distal	15	6.9
Location of culprit lesion on LCx		
proximal	11	5.1
distal	22	10.2
Chronic occlusion*		
LAD	5	2.3
RCA	6	2.8
LCx	8	3.7
TIMI-flow grade		
0	140	64.8
1	19	8.8
2	36	16.7
3	21	9.7
Presence of collaterals to IRA	63	29.2
Vessel disease		
1	126	58.3
2	56	25.9
3	34	15.7
JS (Jeopardy score)		
1	58	26.9
2	40	18.5
3	69	31.9
4	29	13.4
5	12	5.6
6	8	3.7
Region at risk		
≤1	123	57.0
2	46	21.3
3	47	21.8

* One patient had two chronic occlusions. Data presented are number and % of patients. IRA = infarct-related coronary artery; JS = amount of myocardium at risk of ischemia; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; TIMI = Thrombolysis in Myocardial Infarction.

Nineteen of the 216 patients (8.8%) had chronic occlusions in a non-IRA. Flow in the IRA was absent or severely decreased in 90.3% of the patients, however in 9.7% a TIMI 3 flow grade was observed.

Angiographic visible collaterals to the IRA were present in 29.2% of the patients. Although 58.3% of the patients presented with one vessel disease, there was a large variation in the extent of coronary artery disease when expressed by jeopardy score (Table 2). Forty-three % of the patients presented with a moderate (= 2) to large (= 3) region at risk.

Univariate analysis of angiographic data. The infarct artery in patients with out-of-hospital VF was LAD , LCx or RCA in respectively 65.3% , 19.4% and 15.3% (Table 3). This distribution was significantly different from patients without out-of-hospital VF (respectively 40.3%, 13.2% and 46.5%; $p < 0.001$). Patients with an acute occlusion on the LAD or LCx had a higher risk for out-of-hospital VF compared to patients with an acute occlusion on the RCA (odds ratio and 95% confidence interval respectively 4.82 (2.35-9.92) and 4.92 (2.34-10.39) (Table 4). Patients with an acute occlusion of the LAD had comparable risk for out-of-hospital VF when compared to patients with occlusion of LCx (odds ratio and 95% confidence interval: 1.10 (0.50-2.42)). The distribution of regions at risk differs between both groups ($p = 0.01$) (Table 3). However in patients with occlusion on the LCA, the region at risk ($\leq$ 1, 2 and 3) was not associated with out-of-hospital VF (Table 5). With regard to the extent of coronary artery disease (expressed by number of diseased vessels or by jeopardy score) , the location of the culprit along the coronary arteries (proximal versus mid or distal), the flow in the IRA, the presence or absence of collaterals to the IRA and of chronic occlusions, there were no differences between the two groups (Table 3).

Multivariate analysis. Logistic regression analysis was performed to detect those that are independently associated with out-of-hospital VF. Forward analysis retained four significant variables (Table 6). Acute occlusion of LAD and LCx are both significantly associated with out-of-hospital VF. TIMI 0 flow in the IRA or presence of an additional (chronic) occlusion in a non-IRA are both of borderline significance as predictors of out-of-hospital VF.

Table 3. Univariate analysis of angiographic data

	Patients with out-of-hospital VF (n = 72)	Patients without out-of-hospital VF (n = 144)	p-Value *
IRA			< 0.001
LAD	47(65.3%)	58(40.3%)	
RCA	11(15.3%)	67(46.5%)	
LCx	14(19.4%)	19(13.2%)	
RCA versus LAD or LCx	11(15.3%)	67(46.5%)	< 0.001
Location of culprit lesion			
Proximal	25(34.7%)	54(37.5%)	0.77
Chronic occlusion	9 (12.5%)	9(6.3%)	0.13
TIMI-flow grade = 0	53(73.6%)	87(60.4%)	0.07
Presence of collaterals to IRA	23(31.9%)	40(27.8%)	0.53
Vessel disease			0.45
1	44(61.1)	82(56.9)	
2	15(20.8)	41(28.5)	
3	13(18.1)	21(14.6)	
JS (Jeopardy score)			0.30 (0.23) ┼
1	13(18.1)	45(31.3)	
2	14(19.4)	26(18.1)	
3	29(40.3)	40(27.8)	
4	10(13.9)	19(13.2)	
5	3(4.2)	9(6.3)	
6	3(4.2)	5(3.5)	
Region at risk			0.01 (0.07) ┼
≤1	32(44.4)	91(63.2)	
2	23(31.9)	23(16.0)	
3	17(23.6)	30(20.8)	

* According to two-tailed Fisher's exact test. ┼ chi-square test for linear trend. Data presented are number (%) of patients. JS = amount of myocardium at risk of ischemia; IRA = infarct-related coronary artery; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; TIMI = Thrombolysis in Myocardial Infarction; VF = ventricular fibrillation.

Table 4. Location of culprit lesion : Univariate analysis

	Patients with out-of-hospital VF (n = 72)	Patients without out-of-hospital VF (n = 144)	Odds ratio (95% confidence interval)	p-Value
LCA/RCA	61/11	77/67	4.82 (2.35-9.92)	0.00001
LAD/RCA	47/11	58/67	4.94(2.34-10.39)	0.00001
LCx/RCA	14/11	19/67	4.49(1.75-11.49)	0.002
LAD/LCx	47/14	58/19	1.10(0.50-2.42)	0.84
proximal LAD/ distal LCx	15/10	23/12	0.78(0.27-2.26)	0.79

Data presented are number of patients. LAD = left anterior descending artery; LCA = left coronary artery; LCx = circumflex artery; RCA = right coronary artery; VF = ventricular fibrillation.

Table 5. Region at risk in patients with acute occlusion on LCA: Univariate analysis

	Patients with out-of-hospital VF (n = 61)	Patients without out-of-hospital VF (n = 77)	p-Value *
Region at risk			0.37
≤1	21(34.4)	24(31.2)	
2	23(37.7)	23(29.9)	
3	17(27.9)	30(39.0)	

* Pearson chi-square test. LCA = left coronary artery; LVEF = left ventricular ejection fraction ; VF = ventricular fibrillation.

Table 6. Multivariate analysis: Angiographic predictors of out-of-hospital VF

	B-coefficient	SE	p-Value
Culprit on LAD	-0.8725	0.1989	0.0001
Culprit on LCx	-0.8406	0.2504	0.0008
TIMI flow grade = 0	-0.3589	0.1690	0.03
Chronic occlusion	-0.6018	0.2785	0.03
Constant	0.1626	0.3283	0.6

B = beta; IRA = infarct-related coronary artery; LAD = left anterior descending artery; LCx = Left circumflex artery; SE = standard error; TIMI = Thrombolysis in Myocardial Infarction; VF = ventricular fibrillation.

Stepwise addition of any other angiographic variable, such as region at risk, jeopardy score, proximal versus distal occlusion was performed and none of them showed an association with out-of-hospital VF, independent of the former four variables.

Discussion

This is the first study in patients with acute MI complicated with out-of-hospital VF in which acute coronary anatomy is compared to a control group of patients with acute MI not complicated with out-of-hospital VF. All patients, including those without out-of-hospital VF were treated within the same time period and selected according to the same electrocardiographic criteria and all underwent the same angiographic study protocol.

Acute occlusion of left coronary artery. Our major finding is the increased risk of out-of-hospital VF with acute occlusion on the LCA (LAD or LCx) when compared to acute occlusion of RCA. This strong association persists even after multivariate adjustment for other anatomic variables such as JS or region at risk which illustrates that this association is independent of infarct size or of amount of myocardium at risk for necrosis and that it is independent of the extent of coronary artery disease when it is expressed by number of diseased vessels or by jeopardy score. For example, proximal LAD occlusion, which is associated with a large amount of myocardium at risk for necrosis, has no significantly larger risk for out-of-hospital VF than for example occlusion on the distal LCx (Table 4). Both occlusions however have a significantly higher risk for out-of-hospital VF than occlusion on RCA. This finding is in contradiction to earlier hypotheses derived on theoretical grounds, that acute occlusions of the RCA, which usually supplies the conduction system, are more prone to life threatening arrhythmia's (20). This theoretical prediction was in concert with observations of Davies et al. in sudden ischemic death (21). Later studies however found inconsistent associations of early ventricular fibrillation and IRA (7-14), but some included few or no patients

with out-of-hospital VF or had no angiographic data (7,10-12). Others studies did not specifically address acute MI complicated with out-of-hospital VF and possibly included a heterogeneous group of patients with cardiac arrest (13,14). Protection of myocardium against orthosympathetic stimuli, for instance by betablockers, is known to increase the threshold for development of ventricular fibrillation (22) or ventricular tachycardia (23) in the early phase of acute MI. In experimental models of early ventricular fibrillation by exercise induced myocardial ischemia in conscious dogs with a healed MI, heart rate variability, autonomic function and baroreflex sensitivity have been studied (24). These studies associated decreased incidence of sudden death with high vagal tone and vagal reflexes. Moreover, vagal stimulation reduced incidence of early ventricular fibrillation in the same model (25). Sinus bradycardia is particulary frequent in patients with inferior and posterior infarction (26, 27). The cause of the vagotonia and resultant sinus bradycardia and hypotension appears to be stimulation of cardiac vagal afferent receptors (which are more common in the inferioposterior than the anterior or lateral portions of the left ventricle) with resulting efferent cholinergic stimulation of the heart. The phenomenon is a manifestation of the Bezold-Jarisch reflex (28). A possible hypothesis, generated by our data, is that vagal tone in patients with acute occlusion of RCA protects against early ventricular fibrillation during acute MI.

Amount of myocardium at risk of necrosis. A second finding is the relation between out-of-hospital VF and size of region at risk (Table 3). In large studies of patients hospitalized for acute MI, early ventricular fibrillation is associated with final infarct size (8,9). In patients with out-of-hospital VF no such relation with infarct size has been studied. In our study this association disappears after adjustment for site of occlusion (RCA or LCA). Patients with occlusion on LCA have on average a larger region at risk. Within this group, region at risk is no more associated with out-of-hospital VF (Table 5). For example, patients with occlusion of proximal LAD have an equivalent risk for out-of-hospital VF compared to patients with occlusion of distal LCx (Table 4).

Consequently, the association of region at risk with out-of-hospital VF in our study population is a confounding effect of occlusion of LCA and region at risk is not an independent risk factor for out-of-hospital VF.

Extent of coronary artery disease. The third finding is the absence of association of out-of-hospital VF with extent of coronary artery disease. Distribution of jeopardy scores is not significantly different in both groups. Our findings are in accordance with data found at autopsy in victims of out-of-hospital cardiac arrest where extent of coronary artery disease did not differ significantly from that found in patients with stable angina or previous infarction (29). These autopsy studies face the difficulty to identify acute MI in these victims. Presence of an acute MI or an unstable coronary artery in victims of sudden death varies between 20 and 90% (30). A possible explanation for these discrepancies lies in varying autopsy techniques to find an acutely occluded segment and to describe the extent of coronary artery disease (13). Kyriakidis et al. (10) reported an association of in-hospital primary VF with the extent of coronary artery disease, expressed by the Gensini score (31), in a small number of patients. In our study we used two previously validated measurements of extent of coronary artery disease, the number of diseased vessels (18) and the jeopardy score (19). Both were not associated with out-of-hospital VF.

Study limitations. Although this is to our knowledge the largest comparative angiographic study of patients with acute MI and out-of-hospital VF the study is still somewhat limited by the moderate number of patients. As a consequence relativly small effects of region at risk or extent of coronary artery disease cannot be excluded with certainty.

The second limitation is potential selection bias. Only successfully resuscitated victims who presented with ST segment elevation or left bundle branch block were studied. The coronary anatomy of the successfully resuscitated victims could be different from the victims in whom the resuscitation was not successful (for example occlusion of left main coronary segment). Autopsy studies of non-survivors should be performed but these studies face the difficulty to diagnose

acute MI in its early phase as well as its arrhythmic complications.

The major finding of this study (association of out-of-hospital VF with occlusion on LCA) cannot be explained by selection bias because patients with occlusion of RCA complicated by out-of-hospital VF have theoretically an equal chance to survive resuscitation compared to patients with occlusion of the LCA.

The third limitation is the lack of information on pre-existent LVEF. This information is only available in a prospective study design. For obvious reasons such studies are very difficult to perform. We determined LVEF during hospitalization in the majority of patients. After adjustment for occlusion site (RCA or LCA) LVEF was not related to out-of-hospital VF.

Conclusions

Acute MI related to the LCA is associated with greater risk for out-of-hospital VF compared to RCA. The location of occlusion within LCA (LAD, LCx, proximal or distal) , amount of myocardium at risk for necrosis, and extent of coronary artery disease are not related to out-of-hospital VF. Presence of a chronic occlusion in a non-IRA or complete absence of antegrade coronary flow in the infarct related artery are possibly additional independent determinants of out-of-hospital VF. These data, obtained by acute angiography, offer new insights into the mechanisms by which acute coronary artery occlusion induces sudden cardiac death and strongly support the hypothesis that vagal reflex during MI is protective against early VF.

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CHAPTER 3.2

Preinfarction Angina Protects Against Out-of-Hospital Ventricular Fibrillation in Patients with Acute Occlusion of Left Coronary Artery

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Abstract

Objectives. The study aimed to compare the acute coronary anatomy of patients with acute myocardial infarction (MI) complicated by out-of-hospital ventricular fibrillation (VF) versus patients with acute MI without this complication.

Background. More than half of the deaths associated with acute MI occur out-of-hospital and within one hour of symptom onset . In animal studies preconditioning protects against VF during acute coronary occlusion. In humans preinfarction angina (PA), which can serve as a marker for preconditioning reduces infarct size but the protective effect on early VF in patients with acute MI has not been investigated.

Methods. Preinfarction angina status and acute coronary angiographic findings of 72 consecutive patients with acute MI complicated by out-of-hospital VF were compared to 144 matched patients with acute MI without this complication.

Results. Data on PA status was documented in 68 of the 72 patients with VF (94.4%) and in 139 of the 144 controls (96.5%). PA is associated with lower risk for VF (odds ratio 0.43 , 95% confidence interval 0.22-0.87). In patients with acute occlusion on left coronary artery (n=135, LCA) the risk reduction is pronounced (odds ratio 0.26, 95% confidence interval 0.10-0.65) whereas in patients with acute occlusion on the RCA (n=72) there is no significant relation between PA and VF (odds ratio 3.48 , 95% confidence interval 0.79-15.25). The protective effect of PA on VF was not observed in patients with acute occlusion on RCA. In patients with acute occlusion on LCA the protective effect is observed in patients with and without presence of collaterals (odds ratios respectively 0.13 , 95% confidence interval 0.03-0.60 and 0.32 , 95% confidence interval 0.10-1.05) and in patients with or without flow in the infarct related coronary artery (odds ratios respectively 0.11 , 95% confidence interval 0.01-0.94 and 0.36 , 95% confidence interval 0.12-1.07).

Conclusions. This is the first study in humans which addressed the effect of preinfarction angina (as a marker of preconditioning) on ventricular fibrillation during acute coronary occlusion. Preinfarction angina protects against out-of-

hospital ventricular fibrillation in patients with acute occlusion of the left coronary artery. This protection is independent of presence of collaterals or flow in the infarct related coronary artery or extent of coronary artery disease. The protective effect of PA on VF is not observed in patients with acute occlusion on RCA.

Introduction

When the heart is subjected to a transient nonlethal period of ischemia, it quickly adapts itself to become resistant to infarction from a subsequent ischemic insult. This adaptation is called preconditioning . In animal experiments preconditioning both reduces myocardial infarct size and protects against life-threatening ventricular arrhythmias (1-3). Although protective effects of preconditioning are clearly demonstrated in humans (4), for both logistic and ethical reasons, no clinical study can meet the strict conditions of experimental studies on preconditioning with infarct size or life-threatening arrhythmias as the end-point. Clinical studies on infarct size have demonstrated that PA can serve as a "marker" for preconditioning (2, 5) and reduces infarct size (5-7). To our knowledge the effect of preconditioning or PA on life-threatening arrhythmias during early phase of AMI has not been studied in humans. It is expected that as the mechanism of preconditioning is more thoroughly understood, pharmacological preconditioning will become practical for clinical use (8,9). Since the most important cause of death associated with acute myocardial infarction (AMI) is early and out-of-hospital ventricular fibrillation (VF) it would be a key question if preconditioning or PA also can protect against this lethal complication. We previously reported a large case-control study of survivors of out-of-hospital VF related to acute coronary occlusion (10), In the present study we use this setting to test the hypothesis that PA protects against early VF during AMI. Since we demonstrated that patients with acute occlusion of the left coronary artery (LCA) have a significantly higher risk for early VF compared to patients with acute occlusion of right coronary artery (RCA) we further subanalysed retrospectively the effect of PA according to the site of occlusion.

Methods

In De Weezenlanden Hospital Zwolle and in the University Hospital Ghent primary angioplasty is the treatment of choice for complicated and uncomplicated AMI provided that patients present within 6 hours after symptom onset, have electrocardiographic criteria for AMI (presence of ST segment elevation of more than 0.1 mV in at least two adjacent leads of a 12 -lead ECG or presence of a presumed new left bundle branch block) and (for AMI cases complicated by out-of-hospital VF) have a reasonable chance to survive without major neurological sequelae. Between January 1995 and December 1998, 72 survivors of out-of-hospital VF fulfilled these criteria and were candidates for primary angioplasty. Clinical and angiographic data were compared to 144 controls matched for age, gender, admission hospital (Gent or Zwolle) and primary or secondary admission (referred by a local community hospital after diagnosis of acute MI) as previously reported (10). In summary, univariate analysis showed that patients with an acute occlusion on the left coronary artery (LCA)(left anterior descending artery or circumflex artery) had a higher risk for out-of-hospital VF compared to patients with an acute occlusion on the right coronary artery (RCA) (odds ratio and 95% confidence interval respectively 4.82 (2.35-9.92) and 4.92 (2.34-10.39)). Multivariate analysis showed that only acute occlusion of LCA was significantly associated with out-of-hospital VF. Flow grade in the infarct related artery (IRA) or presence of an additional (chronic) occlusion in a non-IRA were both of borderline significance as predictors of out-of-hospital VF. In the present study we further specify preinfarction angina status and medication. According to previous studies (5, 11-13) preinfarction angina is defined by the presence of at least one period of chest pain occurring in the four weeks preceding the AMI. These data were entered prospectively for the patients of De Weezenlanden Hospital (n= 150) and were retrospectively collected by reviewing the medical records for the patients of University Hospital Gent (n=66).

Statistical analysis. Univariate analysis of categorical variables was carried out by a two tailed Fisher's exact test. Descriptive variables with a normal distribution were

given by mean and standard deviation. Tests for heterogeneity of subgroups were carried out by Breslow-Day test .

Results

Relation between PA and VF.

Data on PA status was documented in 68 of the 72 patients with VF (94.4%) and in 139 of the 144 controls (96.5%). Patients with undocumented PA status were excluded for further analysis. PA is associated with lower risk for VF (odds ratio 0.43 , 95% confidence interval 0.22-0.87). PA was present in 19.1% of patients with VF compared to 35.3% in controls (p = 0.02)) (Table 1). Relation between PA and VF according to the site of acute coronary occlusion.

In patients with acute occlusion of LCA (n=135) PA protected against VF (odds ratio 0.26, 95% confidence interval 0.10-0.65)(Table 2, Fig 1). In patients with acute occlusion of RCA (n=72) PA was not significantly associated with VF (odds ratio 3.48, 95% confidence interval 0.79-15.25). The effect of PA on VF differed significantly according to the site of occlusion (Breslow –Day test for heterogeneity : p=0.002, Table 2, Fig 1).

Relation between PA and clinical characteristics or coronary anatomy during the acute phase of MI.

PA was not related to age, sex, history of PTCA or MI in either controls or VF patients. (Table 3). The preinfarction use of betablocker or aspirin was unknown in 7 patients. Of the patients with known preinfarction medication few were treated with betablocker before the onset of MI, respectively 7.4% of VF patients and 11.5% of controls (p = 0.47, Table 1) and use of betablocker was not associated with PA in both VF patients and controls (Table 3). Also, few patients were treated with aspirin before the onset of MI, respectively 5.9% of VF patients and 10.1% of controls (p=0.43, Table 1) and use of aspirin was associated with PA in controls (p=0.04) but not in VF patients (Table 3). PA was not associated with proximal

coronary occlusion (n = 77), presence of a chronic occlusion (n=16), multivessel disease (n=77) or jeopardy score >3 (n=46) (Table 3).

Table 1. Univariate analysis of patients with and without out-of-hospital VF

	Patients with out-of-hospital VF (n = 68)	Patients without out-of-hospital VF (n = 139)	p-Value *
Male	53(77.9%)	109(78.4%)	1.00
Age	56.0(±10.2)	56.7(±10.3)	0.66
Preinfarction angina	13(19.1%)	49(35.3%)	0.02
History of MI	6(8.8%)	11(8.0%)	1.00
History of PTCA	3(4.4%)	7(5.1%)	1.00
Medication prior to MI			
Unknown	3(4.4%)	4(2.9%)	
Betablocker	5(7.4%)	16(11.5%)	0.47
Aspirin	4(5.9%)	14(10.1%)	0.43

* According to two-tailed Fisher's exact test. Data presented are number (%) of patients or mean ± standard deviation. MI = acute myocardial infarction, PTCA= percutaneous transluminal coronary angioplasty, VF = ventricular fibrillation.

Table 2. Effect of preinfarction angina on out-of-hospital VF depends on site of occlusion.

	Out-of-hospital VF n = 68	No Out-of-hospital VF n = 139	Odds ratio (95% confidence interval)
Occlusion on LCA (n=135)			
With PA	7	26	0.26 (0.10-0.65)
Without PA	52	50	
Occlusion on RCA (n=72)			
With PA	6	23	3.48 (0.79-15.25)
Without PA	3	40	

LCA= left coronary artery, RCA= right coronary artery, PA = preinfarction angina VF = ventricular fibrillation; Breslow-Day test for heterogeneity: P= 0.002)

However, PA was associated with presence of collaterals to the IRA (p = 0.005) and presence of antegrade flow (TIMI grade 1 or more) in the IRA (p = 0.05) of control patients but not of VF patients (Table 3). Also in the subgroup of controls without preinfarction treatment with apirin (n= 125) , PA was associated with presence of collaterals (p = 0.005) but not with flow in the infarct related artery (p = 0.11).The LCA was the infarct related artery in 95% of patients who had VF without PA whereas in all other groups (VF patients with PA and controls with or without PA) the LCA was the infarct related artery in respectively 53.8%, 53.1% and 55.6%.

Table 3. Clinical and angiographic characteristics of patients with preinfarction angina

	Out-of-hospital VF			Controls		
	PA (n=13)	No PA (n=55)	p-value	PA (n=49)	No PA (n=90)	p-value*
Male	10(76.9%)	43(78.2%)	1.00	39(79.6%)	70(77.8%)	1.00
Age						
History MI or PTCA	1(7.7%)	6(10.9%)	0.40	7(14.3%)	8(8.9%)	1.00
Beta-blocker ┼	2(18.2%)	3(5.6%)	0.20	8(16.3%)	8(9.3%)	0.27
Aspirin ┼	0	4(7.4%)	1.00	9(18.4%)	5(5.8%)	0.04
Culprit on LCA	7(53.8%)	52(94.5%)	0.001	26(53.1%)	50(55.6%)	0.86
Proximal occlusion	7(53.8%)	16(29.1%)	0.11	18(36.7%)	36(40.0%)	0.72
Chronic occlusion	3(23.1%)	4(7.3%)	0.12	3(6.1%)	6(6.7%)	1.00
TIMI score >0	3(23.1%)	14(25.5%)	1.00	25(51.0%)	30(33.3%)	0.05
Collaterals	5(38.5%)	17(30.9%)	0.60	21(42.9%)	17(18.9%)	0.005
Multivessel disease	7(53.8%)	19(34.5%)	0.22	22(44.9%)	39(43.3%)	0.86
Jeopardy score >3	4(30.8%)	10(18.2%)	0.45	11(22.4%)	21(23.3%)	1.00

* According to two-tailed Fisher's exact test. ┼Patients with undocumented preinfarction medication (n = 7) are excluded in this analysis ; MI = acute myocardial infarction, PA= preinfarction angina, PTCA= percutaneous transluminal coronary angioplasty, TIMI = Thrombolysis in myocardial infarction,VF = ventricular fibrillation.

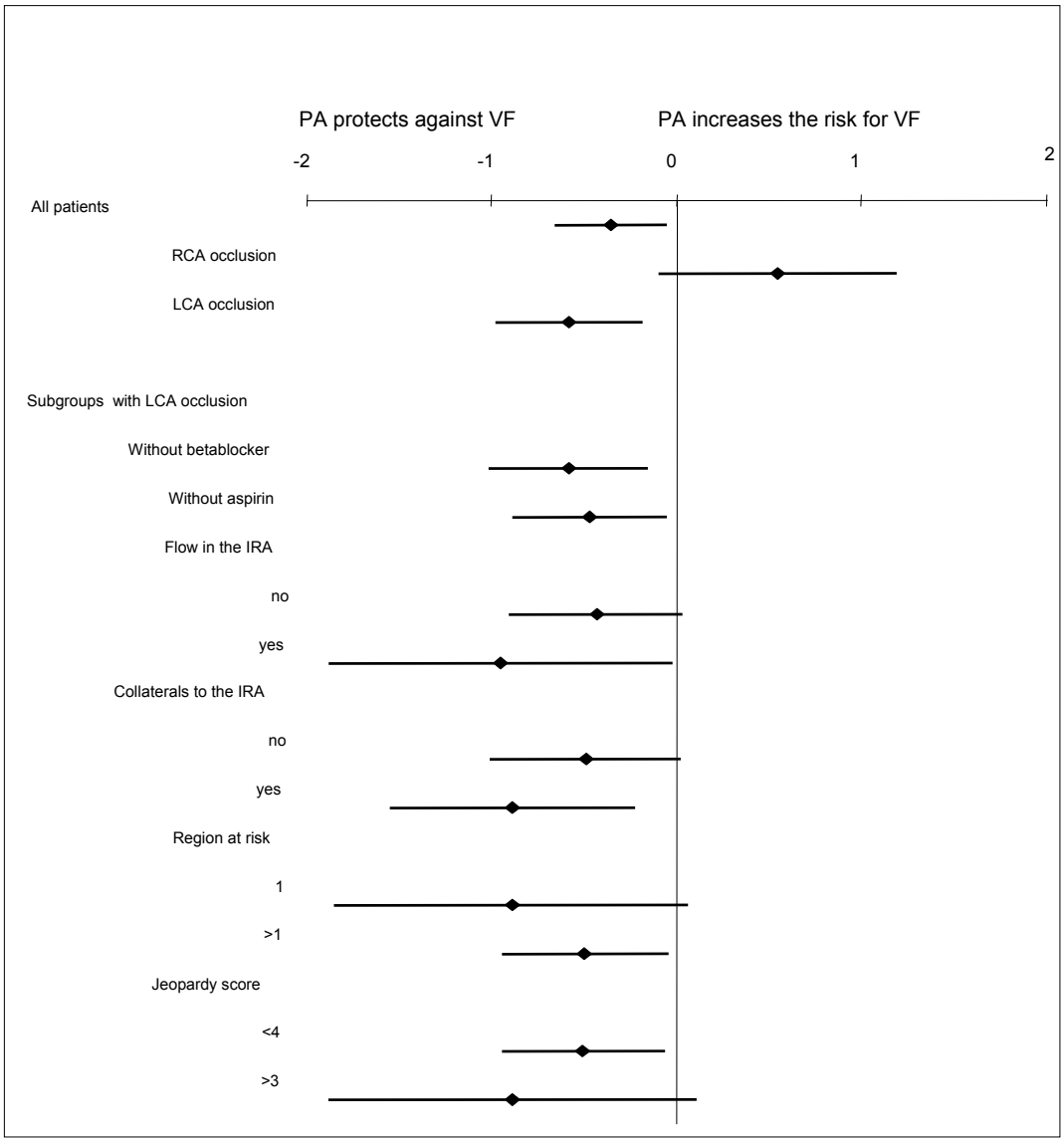
Relation of preinfarction angina to out-of-hospital VF in subgroups of patients with occlusion of LCA (Fig 1).

135 patients (59 survivors of out-of-hospital VF and 76 controls) presented with an acute occlusion on LCA. Patients with PA had lower risk of VF compared to patients without PA (odds ratio 0.26, 95% confidence interval 0.10-0.65) (Figure 1). PA also reduces the risk of VF in predefined subgroups of patients with occlusion of LCA . The protective effect of PA on VF is observed in patients with or without collaterals to the IRA, in patients with or without antegrade flow in the IRA, in patients with small or large area at risk (respectively region at risk = 1 and region at risk >1) and in patients with and without extensive coronary artery disease (respectively jeopardy score > 3 or <4). The protective effect was also present in patients who were not treated with betablocker or aspirin before the onset of MI.

Discussion

In this case-control study we confirm our hypothesis that PA protects against early VF during AMI (odds ratio 0.43 , 95% confidence interval 0.22-0.87). Absence of PA is significantly associated with early VF. Moreover we found the protective effect of PA to depend on the site of occlusion. In patients with acute occlusion of the LCA there is a strong protective effect of PA on VF (odds ratio 0.26, 95% confidence interval 0.10-0.65). In patients with acute occlusion of the RCA we found no protective effect of PA on VF. To our knowledge this is the first study that tests the hypothesis that PA protects against VF during early phase of MI in humans. Patients with angina during 48 hours preceding their AMI have lower rates of in –hospital VF following thrombolytic treatment (14, 15). Previous studies have inconsistently shown a protective effect of preconditioning on the occurrence of complex ventricular premature beats during acute coronary occlusion in the setting of PTCA (16) or during ST segment elevation in patients with variant angina (17). Animal experiments have confirmed that preconditioning protects against VF

Figure 1. Effect of preinfarction angina on out-of-hospital VF in subgroups of patients with occlusion on left coronary artery. IRA= infarct related coronary artery



during acute coronary occlusion (3, 18-21). The confirmation of this protective effect during acute coronary occlusion in humans invites for further research as early VF is the major cause of death in patients with AMI. The case-fatality of AMI is still between 25 and 55%, the proportion of out-of-hospital death varies between 67 and 91% (inversely related with age) (22) and out-of-hospital death during AMI is mainly related to early VF (23). Moreover, nowadays preconditioning can also be simulated or inhibited by pharmacological interventions in humans (9, 24). For instance, sulphonureas for patients with diabetes or methylxanthines inhibit the preconditioning pathways and therefore could be deleterious in patients who are at risk for AMI. The increased mortality from cardiovascular causes observed in diabetic patients on sulphonylureas in the UGDP trial and the worse outcome at the time of AMI (25) might be due to blockade of preconditioning (4) Otherwise, preconditioning mechanisms can pharmacologically be simulated by adenosine A1-receptor agonists and K^{+} *atp* channel openers (2-4) The protective effect of PA can theoretically be mediated by preconditioning mechanisms, formation of collaterals or by better preservation of antegrade flow in the IRA. (24) Subgroup analysis (Figure 1) indicates that the protection against VF does not depend on presence of collaterals or antegrade flow rate in the IRA. Therefore our data strongly support animal (3, 18-21) and human (16, 17) studies in which preconditioning exerted an antiarrhythmic effect during prolonged coronary occlusion. The significantly different effect of PA on VF in patients with acute occlusion of the RCA is an unexpected finding. Only 9 of the 68 patients with out-of-hospital VF presented with acute occlusion in RCA. No or even opposite effect of PA on VF in these patients (odds ratio 3.48 , 95% confidence interval 0.79-15.25) has to be confirmed in larger studies. To our knowledge this finding was not reported in animal experiments. One hypothesis to explain this finding is that PA attenuates the vagal reflexes associated with occlusion of right coronary artery and therefore aborts the vagal mediated protection against VF during acute occlusion of RCA. Inferior wall infarctions induce vagal reflexes more often than infarctions located at other sites (26) and vagal tone protects against VF during AMI (27-29). Brief periods of ischemia attenuate extreme autonomic reactions (30) and patients with angina

have attenuated vagal tone (31) and have less severe bradyarrhythmias compared to those without PA (32). Therefore PA might abort the vagal mediated protection against VF that specifically occurs during occlusion of RCA.

The major limitation of retrospective studies of survivors of out-of-hospital VF is the possibility of information bias. In survivors of out-of-hospital VF the presence of PA is could be underreported due to retrograde anamnesia or due the possible lower sensitivity of heteroanamnesis for the detection of PA. However, it is very unlikely and there are no theoretical grounds that underrapportation of PA occurs significantly more frequently in VF patients with occlusion of LCA compared to VF patients with occlusion of RCA. We found a significantly different effect according to the site of occlusion. Therefore, the lower presence of PA in survivors of out-of-hospital VF with occlusion of LCA can not be completely explained by underrapportation of PA. The second limitation is the relative low number of patients. Although this is the largest consecutive series of survivors of out-of-hospital VF with angiography during AMI there are too few patients to study the effect of time-interval between last period of PA and onset of MI.

The third limitation of this study is the potential selection bias. Every study on early VF in humans with AMI is threatened by potential selection bias. The study group (early VF) does not include patients with early VF in whom resuscitation was not successful. The control group does not include victims of AMI complicated by sudden cardiac death not related to early VF (asystole, severe bradyarrhythmias and electromechanical dissociation). In order to explain our first finding (PA protects against VF) by selection bias only, one had to assume that PA reduces the success rate of resuscitation for VF. To the best of our knowledge there are no data supporting this assumption. Moreover, in our study, presence of PA was not associated with more severe CAD (jeopardy score, number of diseased vessels) or larger region at risk for infarction. On the contrary it was associated with more

collaterals and better flow in the IRA. Therefore effect of selection bias on our first finding is very unlikely. In order to explain our second finding (the effect of PA on VF differs according to the site of occlusion) by selection bias only one had to assume that PA increases the success rate of resuscitation for VF in patients with occlusion on RCA. Although there are no data directly supporting this assumption, it is known that PA in patients with RCA occlusion protects against right ventricular infarction and is associated with lower in-hospital mortality (32). Therefore effect of selection bias on our second finding cannot be excluded.

Conclusion

This is the first study in humans which addressed the effect of preinfarction angina on ventricular fibrillation during acute coronary occlusion. Preinfarction angina protects against out-of-hospital ventricular fibrillation in patients with acute occlusion of the left coronary artery. This protection is independent of presence of collaterals or flow in the infarct related coronary artery or extent of coronary artery disease. The protective effect of PA on VF was not found in patients with acute occlusion on RCA.

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CHAPTER 3.3

Predictors of Early Ventricular Fibrillation Before Reperfusion Therapy for Acute ST Elevation Myocardial Infarction

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Submitted

Abstract

Objectives. To study clinical predictors of early ventricular fibrillation (VF) in acute myocardial infarction (MI).

Background. Early VF accounts for the majority of death during the acute phase of acute MI and seems to be multifactorial and data about predictors have been sometimes contradictory. In patients treated with fibrinolytics, in-hospital VF most often occurs with inferior MI. Contrariwise, out-of- hospital VF seems to be associated with anterior wall MI and preinfarction angina (preconditioning) may protect against VF. We studied clinical characteristics of patients with or without early VF before or during reperfusion therapy by primary angioplasty.

Methods. From January 1995 until December 2001, we treated 2826 patients for acute MI and reviewed clinical records of all patients who developed early VF and classified the patients 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), whereas 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.

Introduction

Early ventricular fibrillation (VF) accounts for the majority of deaths in patients with acute myocardial infarction (MI) (1,2,3). 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, amongst other factors, to 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.

Methods

Patients and study protocol. Between January 1995 and December 2001, 2689 patients were admitted to our hospital with acute MI and underwent acute coronary angiography with a view to perform coronary angioplasty.

Acute myocardial infarction.

Patients had symptoms of acute MI lasting longer than 30 minutes and presented within 6 hours, accompanied by an electrocardiogram with ST-segment elevation of

more than 1 mm (0.1 mV) in two or more contiguous leads either 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 before or during primary angioplasty were considered to have VF and qualified for this analysis. Patients were categorized in 2 groups according to the first episode of VF, either before the angioplasty procedure or during the angioplasty procedure.

Clinical data.

Baseline clinical data were collected prospectively in a dedicated database (17). Clinical variables were amongst others, 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 report (12) 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 patients' 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 without VF before reperfusion therapy by primary angioplasty to find predictors of early VF before reperfusion therapy. Secondly, to study the differences between the patients with versus 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 different 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 cardiovascular disease (family history, hypertension, incidence of diabetes, hypercholesterolaemia or smoking). Four variables showed a significant different distribution over both groups. Firstly, less patients with VF before angioplasty were older than 60 years of age, when compared to patients without VF before angioplasty (45% vs. 54%, p=0.04). Patients with VF before angioplasty had more often an anterior MI, compared to 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 to 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 to patients without VF (24% vs. 8%, p<0.001). Clinical characteristics of patients with and without VF before angioplasty are shown in Table 1.

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

	VF BEFORE REPERFUSION THERAPY		
	NO (n=2483) (95%)	YES (n=145) (5%)	p-value
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.

Patients with ventricular fibrillation during angioplasty

There were no significant differences in base line 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 to 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 to 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.

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

	VF DURING REPERFUSION THERAPY		
	NO (n=2409) (97%)	YES (n=74) (3%)	p-value
Male (%)	1844 (76)	52 (70)	0.211
Age >60 years (%)	11176 (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.

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

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 analyze their independent value in a multivariate model. Therefore we analyzed 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. 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 to 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 to patients without VF before angioplasty.

Anterior versus Inferior Wall Myocardial Infarction

Primary VF is triggered by acute ischemia 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 beta-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.

On contrast, inferior MI appears to more arrhythmogenic during mechanical reperfusion. Gacioch and Topol (29) described sudden clinical deterioration with VF during angioplasty in patients with right coronary artery related acute MI, that 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 to 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. On the basis of our study, we hypothesize 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 described, in 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 shows that preinfarction angina protects the patient from developing VF before reperfusion. These findings may be important as pharmacological interventions can inhibit or stimulate preconditioning (31).

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 (32,33). On the other hand, adenosine A1-receptor agonists and K+ atp channel openers may stimulate preconditioning (33). 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 ventricular arrhythmias (34,35) 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, occurring usually after 48 hours after acute MI and is usually due to severe heart failure (3). In more patients with early VF before angioplasty had Killip class > 1 at presentation, when compared to 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 they were all, except for age, 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 infraction. 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, and it seems not plausible, that patients with VF and anterior myocardial have a higher rate of successful resuscitation than patients with inferior MI.

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 to 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 to 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.

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