Atrial fibrillation after but not before primary angioplasty for ST-segment elevation myocardial infarction of prognostic importance

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Abstract

Aim In patients with ST-segment elevation myocardial infarction (STEMI), it is uncertain whether atrial fibrillation has prognostic implications. There may be a difference between atrial fibrillation before and after reperfusion therapy.

Methods and results In patients with STEMI treated with primary percutaneous coronary intervention (PCI), ECGs were analysed before and after primary PCI. Of the 1623 patients with electrocardiographic data before primary PCI, 53 patients (3.3%) had atrial fibrillation. Patients with atrial fibrillation were older, were more often female, and less often had anterior MI location. Of the 1728 patients with electrocardiographic data after primary PCI, 52 patients (3.0%) had atrial fibrillation. Atrial fibrillation was more common in older patients and in those with Killip class >1. Also patients with occlusion of the right coronary artery or TIMI flow 0 before primary PCI more commonly had AF after the procedure. Not successful reperfusion was also associated with a higher incidence of AF after primary PCI. Although both atrial fibrillation before and after primary PCI were associated with increased mortality, multivariable analyses, adjusting for differences in age, gender and Killip class on admission, revealed that atrial fibrillation after PCI (OR 3.69, 95% CI 1.87–7.29) but not before PCI (OR 1.86, 95% CI 0.89–3.90) was independent and statistically significantly associated with long-term mortality.

Conclusion In patients with STEMI, atrial fibrillation after but not before primary PCI has independent prognostic implications. Possibly, atrial fibrillation after the PCI is a symptom of failed reperfusion and a sign of heart failure.

Keywords Primary coronary angioplasty · Myocardial infarction · Atrial fibrillation

Introduction

Atrial fibrillation (AF) is a commonly encountered arrhythmia in patients with acute myocardial infarction (AMI) with an overall incidence of 5–22% [1–9]. The predictive value of AF in diverse forms of ACS has been extensively studied. These observations stressed the importance of the time of the onset, the duration and the recurrence rate of AF to identify patients in increased risk of adverse events [4, 6, 10, 11]. The incremental predictive value of AF, however, has remained a matter of discussion given the large overlap between factors increasing the risk of developing AF and other cardiovascular adverse events. Furthermore, most of these results are provided by studies conducted in the thrombolysis or pre-thrombolysis era, and little is known about the impact of AF on cardiovascular risk in patients undergoing primary PCI for ST-segment elevation MI (STEMI) [4]. Besides, the majority of studies on this subject are substudies of clinical trials and due to specific exclusion criteria, characteristics of the patient samples studied are different from the average patient hospitalised with a myocardial infarction. Our aim was to investigate the predictive value of AF with regard to its time of onset (i.e. before or after reperfusion therapy) in patients undergoing primary PCI for

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STEMI and to identify predictors for development of AF in STEMI patients.

Methods

Patients

Between April 1997 and December 2002, 2134 patients with symptoms consistent with acute MI of >30 min duration, presenting within 24 h after the onset of symptom and with a ST-segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads on the electrocardiogram, were admitted. All patients were treated with an invasive approach, with primary PCI performed with standard techniques if the coronary anatomy was suitable for PCI. Angiographically successful reperfusion was defined as TIMI flow grade 3, in combination with a myocardial blush grade 2 or 3. Additional treatment consisted of intravenous heparin, nitroglycerin and aspirin. After sheath removal, low-molecular-weight heparin was given for 1 to 3 days. Follow-up data were collected up to 18 months after randomisation via the registry office, the general practitioner, or via direct contact with the patient or his relatives by telephone. The research protocol was reviewed and approved by the medical ethics committee of our hospital, and patients were included after informed consent.

Measurements

Electrocardiography (ECG) was performed at admission (first ECG), and at 3 h after PCI (second ECG), according to the protocol. All ECGs were analysed as pairs by an independent core laboratory (DIAGRAM BV, Zwolle, the Netherlands) and graded for ST-segment elevation resolution by two investigators who were unaware of the clinical data, angiographic findings, and outcome.

Statistical analysis

Differences between group means at baseline were assessed with the two-tailed Student's *t*-test. Chi-square analysis or Fisher's exact test was used to test differences between proportions. Survival was calculated by the Kaplan-Meier product-limit method. The log-rank test was used to evaluate differences in survival curves. The Cox proportional-hazards regression model was used to calculate relative risks adjusted for differences in baseline characteristics. To predict the independent association between atrial fibrillation and clinical characteristics, multivariable logistic regression analysis was performed. Statistical significance was considered a two-tailed *p* value <0.05. The Statistical Package for

the Social Sciences (SPSS Inc., Chicago, IL, USA) version 10.1 was used for all statistical analysis.

Results

Of the included 2134 patients, electrocardiographic data were available in 1623 patients (76%) before the primary PCI, and in 1728 patients (81%) after the primary PCI. Paired ECGs were available for 1472 patients. The mean age of the 2134 patients was 60.7 years (range 24–89) and there were 475 females (22%).

Atrial fibrillation before primary PCI

Of the 1623 patients with electrocardiographic data before primary PCI, 53 patients (3.3%) had atrial fibrillation. Differences between patients with and without atrial fibrillation before primary PCI are summarised in Table 1. Patients with atrial fibrillation were older, were more often female and less often had anterior MI location. Independent predictors of AF before PCI were age (OR 1.04/years, 95% CI 1.03–1.07), Killip class >1 (OR 4.7, 95% CI 2.38–9.36), and inferior infarct location (OR 2.39, 95% CI 1.3–4.38).

Table 1 Baseline characteristics of 1623 patients with data on atrial fibrillation before primary PCI

Characteristic	AF (<i>n</i> =53)	SR (<i>n</i> =1570)	<i>p</i> -value
Age, years (mean ± SD)	66±11.2	60.5±11.3	0.001
Men	66	78	0.03
Previous MI	9.4	9.7	0.95
Previous PCI	2	4.5	0.36
Previous CABG	0	2	0.30
History of stroke	2	3	0.67
Diabetes mellitus	8	11	0.45
Hypertension	25	28	0.60
Currently smoker	43	53	0.19
Hypercholesterolaemia	17	21	0.46
Killip class>1	25	6	0.001
Family history	40	40	0.92
Anterior MI	30	49	0.009
Multi-vessel disease	60	53	0.28
Occlusion of LAD	30	45	0.04
Occlusion of RCA	47	34	0.06
TIMI 0 flow before PCI	57	60	0.59
Collaterals	6	9	0.38
Successful reperfusion ^a	79	88	0.06

Data are mean (standard deviation) or% unless otherwise indicated. *MI* myocardial infarction. *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *LAD* left anterior descending, *RCA* right coronary artery. ^a Successful reperfusion denotes TIMI 3 flow and blush grade 2 or 3

Atrial fibrillation after primary PCI

Of the 1728 patients with electrocardiographic data after primary PCI, 52 patients (3.0%) had atrial fibrillation. Differences between patients with and without atrial fibrillation after primary PCI are shown in Table 2. Atrial fibrillation was more common in older patients and in those with Killip class >1. Also patients with occlusion of the RCA or TIMI flow 0 before primary PCI more commonly had AF after the procedure. Unsuccessful reperfusion was associated with a higher incidence of AF.

Multivariable analyses revealed that statistically significant independent predictors of AF after PCI were age (OR 1.06/years, 95% CI 1.03–1.09), Killip class >1 (OR 2.6, 95% CI 1.2–5.7), and occluded RCA (OR 2.2, 95% CI 1.3–3.9). Failed reperfusion by primary PCI was not independently associated with post-procedure AF (OR 1.88, 95% CI 0.93–3.79).

Mortality

Data on long-term survival were available in 1683 patients (79%) in the total study group, with a mean follow-up

duration of 481 days (SD: 281). In this group, a total of 129 patients (7.7%) died during follow-up. In the 1623 patients with data on atrial fibrillation before PCI, follow-up data were available in 1198 patients; 72 patients (6.0%) died during long-term follow-up (Fig. 1). Among the 1728 patients with data on atrial fibrillation after PCI, follow-up was available of 1270 patients (71%). Of these patients, 71 (5.3%) died during the follow-up period (Fig. 2). Particularly in patients who died before the PCI, or shortly thereafter, no data on rhythm were available.

Both atrial fibrillation before and after primary PCI were associated with increased long-term mortality. Mortality in patients with pre-PCI AF was 21% while in those without AF only 5% ($p<0.01$). In patients with AF after primary PCI, mortality was 23% in contrast to 4.7% in those without AF after primary PCI ($p=0.001$).

After adjusting for differences in age, gender and Killip class on admission by means of multivariable analyses, however, atrial fibrillation after PCI (OR 3.69, 95% CI 1.87–7.29) but not before PCI (OR 1.86, 95% CI 0.89–3.90) remained statistically significantly associated with long-term mortality.

Discussion

The current study underlines the importance of AF in identifying STEMI patients in increased risk, probably requiring more aggressive therapy and closer follow-up.

Prevalence of AF

The overall prevalence of AF among AMI patients has been reported in a range of 5–22%. More recent studies show a slight decrease in incidence of AF in acute myocardial infarction compared with studies of the 1990s. This observed trend might be due to changing definitions of AF, size and characteristics of patient samples studied and

Table 2 Baseline characteristics of 1728 patients with data on atrial fibrillation after primary PCI

Characteristic	AF ($n=52$)	SR ($n=1676$)	p -value
Age, years (mean $\pm$ SD)	67 $\pm$ 9.8	60.2 $\pm$ 11.3	0.001
Men	75	78	0.59
Previous MI	17	9.5	0.06
Previous PCI	5.8	4.1	0.56
Previous CABG	2	2	0.99
History of stroke	2	3	0.66
Diabetes mellitus	6	11	0.25
Hypertension	33	27	0.37
Currently smoker	40	54	0.05
Hypercholesterolaemia	25	21	0.53
Killip class>1	17	6	0.001
Family history	33	42	0.20
Anterior MI	40	49	0.23
Multi-vessel disease	69	52	0.02
Occlusion of LAD	39	46	0.28
Occlusion of RCA	54	34	0.003
TIMI 0 flow before PCI	75	61	0.04
Collaterals	6	9	0.40
Successful reperfusion ^a	79	89	0.03

Data are mean (standard deviation) or% unless otherwise indicated. *MI* myocardial infarction. *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *LAD* left anterior descending, *RCA* right coronary artery. ^a Successful reperfusion denotes TIMI 3 flow and blush grade 2 or 3

Fig. 1 Kaplan-Meier curves of patients with or without atrial fibrillation before primary PCI

Fig. 2 Kaplan-Meier curves of patients with or without atrial fibrillation after primary PCI

differences in therapies that may decrease the risk of AF [1–8, 12]. This trend may be countered by the fact that patients involved in more recent studies (i.e. treated with thrombolysis or primary PCI) were older and in a worse cardiovascular condition than those involved in studies of the pre-thrombolytic era [1]. Advanced age and worse haemodynamic state (worse Killip class) have been uniformly associated with the development of AF in studies involving patients treated conservatively or with thrombolysis or, most recently, with primary, PCI [2–4]. Divergent results are available about the relation between the development of AF and the infarct-related artery (IRA), male or female gender, the presence of hypertension or diabetes [1–8]. In the present study, AF was diagnosed in 3.3% of patients on admission and was associated with advanced age, worse Killip class and inferior infarct location.

Post-PCI AF was diagnosed in 3% of our patients and was associated with advanced age, worse Killip class and the occlusion of RCA. Post-PCI AF, however, was assessed on ECGs obtained 3 h after the procedure, thus representing early AF occurrence. No additional data are available about AF occurrence during the preceding and the following period of hospitalisation. This offers an explanation for the lower post-PCI AF rate as compared with the findings of Kinjo et al. [4]. In that study the rate of post-PCI AF was 7.7% representing AF occurrence rate during the entire hospitalisation. Similar in-hospital occurrence rates were reported by Pizzetti et al. (6%), Wong et al. (6.5%) and Crenshaw et al. (7.9%) among patients treated with thrombolysis [2, 6, 8]. Associated risk factors have been divergent among these studies regarding infarct-related artery, hypertension and diabetes, but worse Killip class and advanced age have been uniformly associated with the development of AF. The AF mechanism in acute coronary artery disease is multifactorial. Experimental studies in dogs revealed that atrial

ischaemia promotes AF triggers and creates a substrate for AF maintenance by sustained reentry [13, 14].

Predictive value of AF

The prognostic value of AF in long-term and in-hospital mortality has been extensively studied previously in the thrombolytic and pre-thrombolytic era, and a recent meta-analysis revealed that AF in myocardial infarction was associated with at least a 40% increase in mortality compared with patients with sinus rhythm [15]. However, there is great variation among the different studies [9].

In the pre-thrombolytic era, the prognostic importance of AF in patients suffering an AMI is not completely clear, but probably AF was an independent risk factor for long-term mortality [3, 5, 7, 9].

In patients receiving thrombolysis the impact of AF on mortality seems to be reduced, also with controversial results [1]. In GUSTO-I late onset AF (onset during hospitalisation) was independently associated with increased 30-day mortality and in-hospital stroke but neither pre-admission nor late-onset AF had significant influence on 1-year mortality [2]. However, in GISSI-3 (319 pre-admission AF and 1069 late onset AF patients) AF was an independent predictor of both in-hospital and 4-year mortality [6]. In GUSTO-III both early (within 48 h after onset of AMI symptoms) and late (after 48 h) onset AF were independently associated with increased 30-day and 1-year mortality [8]. Asanin et al. found that late AF was an independent predictor for long-term (seven-year) mortality but not for in-hospital mortality [16]. Unfortunately, the definition of early and late onset AF varied between the different studies. In the GUSTO trials, late AF was defined as development of AF 48 h after onset of symptoms whereas Asanin et al. classified late AF as AF more than 24 h after symptom onset. Also the term ‘new AF’ may cause confusion. Some studies used ‘new AF’ to describe patients with AF on admission [8, 17] whereas other studies used this term exclusively to describe new-onset AF developed during admission. [4, 6, 15]

The prognostic value of AF in patients receiving primary PCI treatment for STEMI has been studied less extensively so far. Kinjo et al. proved the incremental value of late onset AF (AF during hospitalisation), but not baseline AF, in predicting long-term mortality in patients undergoing primary PCI for STEMI [4]. In-hospital mortality, however, was not independently predicted by either baseline or late-onset AF. In the APEX-AMI trial, new onset AF was independently associated with 90-day mortality [18].

Our data confirmed the findings of Kinjo et al. The strength of the present study is, however, that all patients were included who were hospitalised with acute STEMI

minimising selection bias. In our study, ECGs were obtained 3 h after PCI, and so AF with later onset or earlier termination was not taken into consideration. Therefore, our results suggest that early post-PCI AF may reflect less complete reperfusion or a more compromised cardiac status, even though these potential confounders were included in our multivariate analyses. The possible causative role of AF also has to be taken into consideration, given its well-known detrimental effect on myocardial metabolism, blood supply and remodelling in such a highly vulnerable period.

The divergent way ‘early’ and ‘late’ onset AF and ‘long-term follow-up’ are defined in the above-mentioned studies makes the interpretation of the data harder and partially explains the controversial results. The establishment of a uniform classification may aid further evaluations and lead to a consensus regarding the incremental predictive value of AF in patients with acute STEMI.

Study limitations

Evaluation of pre-PCI AF’s prognostic value is always hindered by the absence of data on AF history, making it impossible to really distinguish between acute onset and persistent AF (i.e. not related to the acute ischaemic event). It is possible that pre-PCI AF could also have represented significant prognostic value if only patients with new onset AF had been taken into consideration.

Post-PCI AF was assessed routinely on ECGs obtained 3 h post-procedure. Therefore are conclusions about the prognostic value of post-PCI AF only applicable for patients with early AF occurrence, and not for the entire hospitalisation period? The results, however, are in agreement with the findings of Kinjo et al. (4) where any AF period during hospitalisation was taken into consideration. We had no data on medication during the follow-up period, such as aspirin, clopidogrel or coumarins.

Conclusion

In patients treated with primary PCI for STEMI, atrial fibrillation after but not before the PCI has independent prognostic implications. It is unclear what the mechanism is of the worse prognosis, decreased LV function, less complete reperfusion or other medication during the follow-up period.

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Appendix

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