Significance of Paroxysmal Atrial Fibrillation Complicating Acute Myocardial Infarction in the Thrombolytic Era

Michael Eldar, MD; Menachem Canetti, MD; Zeev Rotstein, MD; Valentina Boyko, MSc; Shmuel Gottlieb, MD; Elieser Kaplinsky, MD; Solomon Behar, MD; for the SPRINT and Thrombolytic Survey Groups

Background—Paroxysmal atrial fibrillation (PAF) is considered a frequent complication of acute myocardial infarction (AMI), associated with increased in-hospital and long-term mortality rates. This notion is based on data collected before thrombolysis and additional modern methods of treatment became widely available, and no information is available on the significance of PAF in the general population with AMI in the thrombolytic era. The aim of the present study was to define the incidence, associated clinical parameters, and short- and long-term prognostic significance of PAF in patients with AMI in the thrombolytic era.

Methods and Results—A prospective, nationwide survey was conducted of 2866 consecutive patients admitted with AMI in all 25 coronary care units in Israel during January/February 1992, 1994, and 1996 (thrombolytic era [TE]). The data were compared with a previous Israeli study of 5803 patients with AMI hospitalized in 1981 through 1983 (prethrombolytic era [PTE]). Patients in the TE with PAF were older and had a worse risk profile than those without PAF. PAF in the TE was independently associated with increased 30-day (odds ratio, 1.32; 95% confidence interval, 0.92 to 1.87) and 1-year (relative risk, 1.33; 95% confidence interval, 1.05 to 1.68) mortality rates. The incidence of PAF (8.9% and 9.9%) and the 30-day (25.1% and 27.6%) and 1-year (38.4% and 42.5%) mortality rates of patients with PAF were similar in the TE and PTE, although PAF in the TE occurred in older and sicker patients than those in the PTE. After adjustment for conventional risk factors, PAF was associated with significantly lower 30-day (odds ratio, 0.64; 95% confidence interval, 0.44 to 0.94) and 1-year (relative risk, 0.69; 95% confidence interval, 0.54 to 0.88) mortality rates compared with the PTE.

Conclusions—Patients with AMI who develop PAF in the TE have significantly worse short- and long-term prognoses than patients without PAF, mostly due to their worse risk profile. After adjustment for confounding factors, patients with PAF in the TE have a better overall outcome than counterparts in the PTE, probably reflecting the better management of patients with AMI in the TE. (Circulation. 1998;97:965-970.)

Key Words: myocardial infarction n thrombolysis n fibrillation

Received July 13, 1997; November 13, 1997; accepted November 19, 1997.
From the Neufeld Cardiac Research Institute, Tel-Aviv University, Sheba Medical Center, Tel Hashomer, Israel.
Correspondence to Michael Eldar, MD, Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer 52621, Israel.
E-mail meldar@post.tau.ac.il
© 1998 American Heart Association, Inc.
outcome of the SPRINT randomized patients. Seventy TE patients and 36 PTE patients were excluded because of incomplete files or a history of chronic atrial fibrillation, leaving 2866 and 5803 patients in TE and PTE cohorts, respectively.

AMI was diagnosed by clinical, ECG, and enzymatic findings. One thousand three hundred twenty-eight of TE patients (46.3%), but none of PTE patients, received thrombolytic therapy with either streptokinase or tissue plasminogen activator. PAF was defined according to acceptable criteria and to be included in the study had to be detected during the CCU stay. Demographic, historical, and clinical data during hospitalization were collected on designated forms for all participating patients. For both cohorts, 1-year mortality follow-up was completed for 99% of the patients by periodical examinations, hospital records, examination of the Israeli population registry, and telephone interview of the patients, their families, or their family physician.

Patients in the TE who developed PAF were compared with those who did not. The effects of thrombolytic treatment on the incidence and consequences of PAF were examined as well. Then, TE patients with PAF were compared with their PTE counterparts in the SPRINT registry regarding admission data, hospital course and complications, and 30-day and 1-year mortality rates.

Statistical Analysis
The SAS software was used for statistical analysis. The comparison of proportions was done using $x^2$ test. Student’s $t$ test was used to compare cohort means for continuous variables. Values of $P \leq .05$ were considered nonsignificant.

Logistic regression analysis of the incidence of PAF, stroke, and the 30-day mortality was performed using LOGISTIC procedure. Multivariate analysis of 1-year mortality was done using the Cox proportional hazard model (PHREG procedure). The parameters in both stepwise analyses included age, sex, past AMI, diabetes mellitus, CHF on admission, history of hypertension, angina pectoris, and anterior AMI location, with the addition of thrombolysis and interventional procedures for analysis in the TE.

Unadjusted survival curves were produced using the Kaplan-Meier method. Adjusted survival curves were constructed using variables entered into the Cox model.

Results

**TE Patients**
PAF occurred in 255 TE patients (8.9%). The incidence of PAF was 6.7% (89 of 1328) among patients treated with thrombolytic therapy and 10.8% (166 of 1538; $P=.001$) among those not receiving this treatment. Those with PAF were significantly older, included more women, and were sicker as demonstrated by a higher incidence of previous AMI, diabetes mellitus, hypertension, and CHF on admission (Table 1). Using a logistic model, age and CHF on admission were found as significant predictors of PAF, whereas thrombolysis was marginally associated with PAF (OR, 0.84; 95% CI, 0.63 to 1.11).

There was a significant decline in the incidence of PAF during the three periods in the TE (1992: 941, 10.2%; 1994: 89 of 999, 8.9%; 1996: 70 of 926, 7.6%; $P$ value for trend = .04). After adjustment for age, CHF on admission, use of thrombolytic treatment, coronary balloon angioplasty, and bypass surgery, the OR for PAF in 1994 was 0.81 (95% CI, 0.59 to 1.11) and the OR in 1996 was 0.81 (95% CI, 0.57 to 1.13) compared with that in 1992.

Stroke occurred more frequently in patients with PAF (10 of 255, 3.9%) than in those without PAF (16 of 2611, 0.6%), $P < .001$. After adjustment for significant predictors, including age, sex, previous AMI, diabetes mellitus, and congestive heart failure on admission, PAF was significantly associated with stroke (OR, 4.60; 95% CI, 1.90 to 10.8). Transthoracic echocardiographic examination, performed in 19 patients with stroke, revealed left ventricular dysfunction (ejection fraction <35%) in 13 patients, left ventricular apical thrombus in 7 patients, and left atrial thrombus in none. Computed tomography of the brain, performed in 11 patients, showed ischemic infarction in 10 patients and hemorrhagic infarction in 1 patient. However, the incidence of stroke was not related to the administration of thrombolytic agents, with an incidence of 3.4% among PAF patients with and 3.9% among those without thrombolysis.

**PAF in TE Versus the PTE**
The incidence of PAF was similar in the TE and PTE (255 of 2866, 8.9%; 577 of 5803, 9.9%, respectively). Compared with patients with PAF in the PTE, those with PAF in the TE were older, were more likely to be female, had more previous AMI and diabetes mellitus, and had a smaller incidence of Q-wave AMI and angina pectoris (Table 2). There was no significant difference in the prevalence of hypertension and current smoking. The prevalence of more severe CHF (Killip classes 3.

---

**Selected Abbreviations and Acronyms**

AMI = acute myocardial infarction
CCU = coronary care unit
CHF = congestive heart failure
CI = confidence interval
OR = odds ratio
PAF = paroxysmal atrial fibrillation
PTE = prethrombolytic era
RR = relative risk
SPRINT = Secondary Prevention of Reischemia Israeli Nifedipine Trial
TE = thrombolytic era

**TABLE 1. Characteristics of 2866 TE Patients in a Comparison of Patients With (+) and Without (−) PAF**

<table>
<thead>
<tr>
<th></th>
<th>PAF+ (n=255), No. (%)</th>
<th>PAF− (n=2611), No. (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD y</td>
<td>70±11</td>
<td>62±12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age≤70 y, n (%)</td>
<td>143 (56)</td>
<td>821 (31)</td>
<td>.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>95 (37)</td>
<td>647 (25)</td>
<td>.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>82 (32)</td>
<td>654 (25)</td>
<td>.01</td>
</tr>
<tr>
<td>Past AMI, n (%)</td>
<td>84 (33)</td>
<td>704 (27)</td>
<td>.04</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>117 (46)</td>
<td>1014 (39)</td>
<td>.03</td>
</tr>
<tr>
<td>Anterior AMI, n (%)</td>
<td>120 (47)</td>
<td>1189 (46)</td>
<td>NS</td>
</tr>
<tr>
<td>CHF on admission, n (%)</td>
<td>138 (55)</td>
<td>645 (26)</td>
<td>.001</td>
</tr>
<tr>
<td>Angina pectoris, n (%)</td>
<td>97 (38)</td>
<td>869 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke in CCU, n (%)</td>
<td>10 (3.9)</td>
<td>16 (0.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 d</td>
<td>64 (25.1)</td>
<td>270 (10.4)</td>
<td>.001</td>
</tr>
<tr>
<td>1 y</td>
<td>98 (38.4)</td>
<td>397 (15.4)</td>
<td>.001</td>
</tr>
</tbody>
</table>
Table 2. Comparison of Demographic and Clinical Characteristics Between Patients With PAF in PTE and TE Cohorts

<table>
<thead>
<tr>
<th></th>
<th>PTE (n=577), No. (%)</th>
<th>TE (n=255), No. (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD y</td>
<td>68±9</td>
<td>70±11</td>
<td>.004</td>
</tr>
<tr>
<td>Female</td>
<td>166 (29)</td>
<td>95 (37)</td>
<td>.02</td>
</tr>
<tr>
<td>Past AMI</td>
<td>146 (26)</td>
<td>84 (33)</td>
<td>.04</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>294 (51)</td>
<td>120 (47)</td>
<td>NS</td>
</tr>
<tr>
<td>Q-wave AMI</td>
<td>494 (89)</td>
<td>164 (75)</td>
<td>.001</td>
</tr>
<tr>
<td>CHF on admission</td>
<td>316 (55)</td>
<td>138 (55)</td>
<td>NS</td>
</tr>
<tr>
<td>CHF, Killip class 3 or 4</td>
<td>75 (13)</td>
<td>59 (24)</td>
<td>.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>251 (45)</td>
<td>117 (46)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>112 (19)</td>
<td>82 (32)</td>
<td>.001</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>272 (49)</td>
<td>97 (38)</td>
<td>.004</td>
</tr>
<tr>
<td>Current smoking</td>
<td>132 (23)</td>
<td>58 (23)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3 delineates the hospital course and complications in the two eras. Patients with PAF in the TE and PTE had a similar incidence of complications, including atrioventricular block, ventricular tachycardia and fibrillation, CHF, cardiogenic shock, and cerebrovascular accidents. CHF on admission and during hospitalization taken together occurred similarly in a substantial percentage of patients with PAF in the PTE and TE (57% and 50%, respectively).

Significant differences were noted regarding the mode of therapy between the two eras. Patients in the TE underwent more coronary angiography, angioplasty, and bypass procedures and less hemodynamic monitoring by Swan-Ganz catheter and temporary pacemaker insertion (Table 3). In addition, they received more β-receptor blockers, nitrates, anticoagulants, aspirin, and ACE inhibitors than counterparts in the PTE.

Mortality

In the TE, crude mortality was 11.7% (334 of 2866) at 30 days and 17.3% (495 of 2866) at 1 year. The 30-day and 1-year mortality rates of TE patients with PAF was significantly higher than that of patients without PAF (25.1% versus 10.5%, and 38.4% versus 15.2%, respectively). After adjustment for significant predictors of mortality (age, sex, previous AMI, diabetes mellitus, congestive heart failure on admission) the 30-day OR for mortality among TE patients with PAF was 1.32 (95% CI, 0.92 to 1.87), and the 1-year RR was 1.33 (95% CI, 1.05 to 1.68) compared with counterparts without PAF.

Thirty-day crude mortality in the PTE patients was 16.8% (975 of 5803), and 1-year mortality was 24.2% (1404 of 5803). Mortality among patients with PAF in the PTE (30 day, 27.6%; 1 year, 42.5%) was similar to that of counterparts in the TE. Because of the differences between the characteristics of patients with PAF in the two periods, a multivariate adjustment was performed. After adjustment, the mortality of patients with PAF was significantly lower in the TE compared with the PTE (30 day: OR, 0.63; 95% CI, 0.44 to 0.94; 1 year: RR, 0.69; 95% CI, 0.54 to 0.88 (Fig 1). Eighty-nine TE patients with PAF (34.9%) received thrombolytic therapy. The 30-day mortality rate was 19.1% (17 of 89) and 28.3% (47 of 166; P=.11), and the 1-year mortality rate was 26.9% (24 of 89) and 44.6 (74 of 166; P=.006) among those receiving and those not receiving thrombolysis, respectively. Both thrombolysis-treated and untreated TE patients had signifi-
significantly reduced by adjusted mortality among patients with PAF in the TE was although crude mortality was similar in the two eras, the incidence of PAF and its short- and long-term mortality rates, whereas its absence in patients with PAF is not associated with improved 30-day and 1-year prognoses. The reason for this finding is not known, and it could be due to different patient populations (see below).

Discussion
This study examined the incidence and clinical significance of PAF in a group of 2866 patients with AMI treated in CCUs during the 1990s, the “thrombolytic era,” of whom 46.3% received thrombolysis. The group was compared with a cohort of 5803 patients with AMI treated in the early 1980s, none of whom had been treated by thrombolytic agents (the “prethrombolytic era”). The main findings of this study are (1) the incidence of PAF during hospitalization in the TE and PTE (35% versus 33% and 51% versus 50%, respectively). Again, after adjustment for major predictors, including age, sex, past AMI, and diabetes mellitus, mortality was lower in the TE than in the PTE (30 day: OR, 0.66; 95% CI, 0.43–1.00; 1 year: RR, 0.75; 95% CI, 0.57 to 0.98). Patients with PAF without CHF had a relatively low 30-day and 1-year mortality rate in the TE and PTE (10% versus 10% and 15% versus 22%, respectively).

Incidence of PAF in the TE
The recent introduction of thrombolysis and additional therapeutic modalities in the acute phase of myocardial infarction, such as β-receptor blockers, ACE inhibitors, and aspirin, as well as interventional procedures, has had considerable effects on the course and prognosis of the disease. Interestingly, only limited information is available on the clinical significance of PAF in patients with AMI in the TE. A recent study on PAF in AMI included 517 patients, only a minority of whom apparently were treated with thrombolysis. However, no specific data on the incidence of PAF in relation to the thrombolysis were provided.

Nielsen et al found a significant reduction in the incidence of PAF among 152 patients with AMI who underwent thrombolysis (from 16% to 3%, P=.009). Our findings in a much larger group of thrombolysis treated patients confirm these observations, although the decline in the incidence of PAF was much smaller, from 10.8% to 6.7%.

The incidence of new in-hospital PAF among the 40 391 GUSTO trial patients, all of whom received thrombolytic therapy, was quite similar to that in our study (3254, 8.0%). We also found a trend toward a decline in the incidence of PAF during the TE. This seems to be, at least partly, due to a decline in the incidence of CHF and the increasing use of thrombolysis, coronary balloon angioplasty, and bypass surgery over this period.

The present study is unique because it is a community-based study that includes all patients treated for AMI in all CCUs in Israel during a 6-month period in the TE, including those who were treated and those who were not treated with thrombolytic agents. Interestingly, the incidence of PAF among all patients with AMI in the TE was only slightly reduced compared with that in the PTE. The risk factors for this finding are not known, and it could be due to different patient populations (see below).

Prognostic Significance of PAF
Patients with PAF in the TE have a dismal short- and long-term prognosis compared with their counterparts without PAF. This partly due to the fact that PAF patients are older and as a group has a higher prevalence of women, diabetes mellitus, hypertension, angina, and previous AMI (Table 1), factors associated with a higher mortality in the post-AMI population. CHF seems to play a pivotal role in the prognosis of these patients, and its absence is associated with a short- and long-term mortality rates similar to those of patients without PAF. Similar findings have been reported by Madias et al. Thrombolytic treatment, as expected, is associated with improved 30-day and 1-year prognoses.

Stroke occurred much more frequently among patients with than in those without PAF. Of note, its incidence was not related to the use of thrombolysis or to atrial thrombus, whereas poor left ventricular function and left ventricular thrombus were relatively frequent in these patients. These findings suggest that stroke in patients with PAF is not directly due to the arrhythmia and most likely reflects the extent of the AMI and its consequences. However, because the number of patients with stroke was relatively small and thrombi were detected by transthoracic and not by transesophageal echocar-
diography (see below), further confirmation of these mechanisms is required.

Interestingly, although most complications of AMI in the TE are associated with a better prognosis than in the PTE, the short- and long-term prognoses of patients with PAF in the TE and PTE remain quite similar. However, the patient population afflicted by PAF is distinctly different, being older and including more women and more past AMI (Table 2). This probably reflects the increasing number of patients surviving their first AMI during the TE. Conceivably, these patients will be older and sicker during a consequent AMI. In fact, after adjustment for conventional confounders, mortality in patients with PAF in the TE was reduced significantly by >30% compared with the PTE (Table 2, Fig 1). A plausible interpretation of these data is that modern thrombolysis and additional therapeutic measures are effective in reducing mortality in the post-AMI period, despite the fact that PAF occurs now in sicker and older patients. The importance of modern therapeutic measures is supported by our data, showing a better 1-year adjusted survival rate for TE patients who were not treated by thrombolysis compared with PTE patients, all of whom did not receive thrombolysis (Fig 2).

Study Limitations

It is generally believed that PAF may cause stroke rather than vice versa. Our data do not allow the time relationship between the two events to be defined, and therefore an association rather than cause and effect is described. Transthoracic echocardiography used in this study may fail to detect a significant percentage of existing left atrial thrombi, particularly those in the appendage. Moreover, the prevalence of left ventricular thrombus in the entire cohort is unknown, and therefore neither the specificity nor its predictive value for stroke can be evaluated. However, the association of poor left ventricular function and thrombi with stroke in patients with PAF remains prominent and seems to best explain the relationship between the two.

Left ventricular ejection fraction is a major predictor of mortality in post-AMI patients. Although not available in these patient cohorts, CHF on admission and during CCU stay was used as a surrogate and was found to be highly associated with PAF and increased mortality.

The causes for the decreased adjusted mortality among patients with PAF in the TE cannot be analyzed in this observational type of study. It may be attributed to improved medical treatment in the acute and early phases of MI. Similarly, a recent report attributed a trend toward better prognosis among patients with heart failure (unrelated to AMI) and PAF in the 1990s to improvements in medical treatment.

Clinical Implications

PAF in the TE identifies a group of older and sicker patients than their counterparts without PAF. These patients probably should be targeted for earlier and more aggressive treatment because their overall prognosis is significantly worse than that of their counterparts without PAF. An echocardiogram to specifically look for left ventricular thrombus in patients with PAF seems mandatory in light of the apparent association between the two found in our study.

In summary, this is the first community-based study that examined the incidence and prognostic implications of PAF in AMI in the TE. We found that thrombolysis did not affect the overall incidence of PAF and the associated short- and long-term mortality rates, which remains as high as those in the PTE. However, this seems to be due to a higher risk profile of the TE patients with PAF. Accordingly, the adjusted contemporary mortality of PAF patients is lower by >30%, probably reflecting more efficient current treatment modalities.

References


Significance of Paroxysmal Atrial Fibrillation Complicating Acute Myocardial Infarction in the Thrombolytic Era
Michael Eldar, Menachem Canetti, Zeev Rotstein, Valentina Boyko, Shmuel Gottlieb, Elieser Kaplinsky and Solomon Behar
for the SPRINT and Thrombolytic Survey Groups

Circulation. 1998;97:965-970
doi: 10.1161/01.CIR.97.10.965

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/10/965

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/