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Institutional report - Arrhythmia

Prevention of atrial fibrillation after coronary artery bypass grafting via atrial electromechanical interval and use of amiodarone prophylaxis☆

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Abstract

In our previous study, we defined a cut-off point of 120 ms for atrial electromechanical interval (AEMi) to determine the risk of atrial fibrillation (AF) occurrence. Accordingly, the present study sought to investigate whether or not a prophylactic perioperative administration of amiodarone could reduce the incidence of AF in a high-risk group (AEMi >120 ms) undergoing coronary artery bypass grafting (CABG). In this prospective, randomized study, 100 patients with AEMi >120 ms received either amiodarone ($n=50$) or placebo ($n=50$). The endpoints were AF occurrence after CABG and hospital and intensive care unit (ICU) lengths of stay after CABG. The incidence of postoperative AF was significantly higher in the placebo group than that of the amiodarone group (88% of patients in control group vs. 16% of patients in amiodarone group, $P<0.0001$). The prophylactic therapy with amiodarone significantly reduced the ICU length of stay (2.28 ± 1.00 vs. 3.60 ± 0.90 days, $P<0.0001$) and hospital length of stay (5.64 ± 2.35 vs. 7.78 ± 1.46 days, $P<0.0001$). The incidence of postoperative AF among patients with high AEMi was significantly reduced by a prophylactic amiodarone treatment, resulting in shorter ICU and hospital stays.

Keywords: Atrial fibrillation; Coronary artery disease

1. Introduction

Postoperative atrial fibrillation (AF) is associated with an increase in neurological, renal, and infectious complications, as well as an increase in mortality, hospital length of stay, and overall hospital costs [1].

Several antiarrhythmic medications have over the years been used to prevent AF after cardiac surgery [2]. For all the evidence for the efficacy of amiodarone in the prevention of AF and its complications [2, 3], prophylaxis in unselected patients could result in a number of patients who would not develop AF receiving a therapy which is not required and could even beget side effects with unacceptable costs.

In our previous study, we found that atrial electromechanical interval (AEMi) could determine the risk of AF after coronary artery bypass grafting (CABG). The present study was, therefore, designed to investigate whether or not a prophylactic perioperative administration of amiodarone could reduce the incidence of AF in a high-risk group (AEMi >120 ms) undergoing CABG.

2. Method

In this prospective, double-blinded, placebo-controlled, randomized study, 100 patients with AEMi >120 ms received either amiodarone ($n=50$) or placebo ($n=50$). The endpoints were AF occurrence early after CABG and hospital and intensive care unit (ICU) lengths of stay after CABG.

This study initially recruited 1022 consecutive patients who underwent CABG at Day General Hospital (Tehran, Iran) between March 2006 and March 2008. The inclusion criteria were: (1) presence of significant coronary artery disease with an indication for CABG, (2) no need for associated surgery, (3) absence of rhythm other than normal sinus rhythm, (4) absence of AF history, (5) absence of valvular heart disease, and (6) AEMi >120 ms.

Echocardiography was performed for all the patients one week before surgery by one expert echocardiologist blinded to the study details and purpose. In total, 102 patients met the inclusion criteria and were included in the study. One patient died in the hospital, and one patient had to undergo another surgical operation; they were, consequently, excluded from the study. The patients were randomized into two groups of even and odd numbers printed inside envelopes that were placed in their files. The surgery ward nurses subsequently opened the envelopes and adminis-

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tered amiodarone to those with odd numbers and placebo to the ones with even numbers. Informed written consent was obtained from all the patients, and the study protocol was approved by our institutional Ethics Committee on Human Study.

2.1. ECG assessment

Until the day of discharge, all the patients were monitored with continuous ECG telemetry and had a standard 12-lead ECG recorded every day. AF was defined as AF requiring treatment and lasting >5 min. Brief isolated non-sustained episodes of AF were ignored. In the cardiovascular ICU, automated detection of AF was obtained via the bedside arrhythmia monitor Solar 9500 (GE Medical Systems, Milwaukee, WI). The diagnosis was confirmed by a single experienced investigator. In the step-down units, AF was detected by means of continuous ECG telemetry monitoring (Eagle 4000, GE/Marquette Medical Systems, Milwaukee, WI). The diagnosis of each patient was confirmed by one cardiologist, who led this project. In addition, the cardiologist who made the diagnosis of AF had no information about AEMi and other parameters. Thirty-second ECG signals were acquired and stored on the hardware of the data acquisition system. The ECG waves were then displayed on the computer screen, with the waves enlarged 2–4 times and paper speed increased to 50–100 mm/s.

2.2. Echocardiography

The patients were included into the present study after they had undergone a preoperative transthoracic echocardiography with a tissue Doppler imaging analysis (GE Medical System, Vivid 7, Horton, Norway) during the week leading up to surgery. A single experienced investigator took the recordings. AEMi was measured in milliseconds as time intervals from the onset of P-wave to the beginning of the atrial systole (Am) at the lateral side of the left atrium (left side).

2.3. Operative technique

A median sternotomy was performed in all the patients. Standard cardiopulmonary bypass was established via ascending aortic cannulation and a single two-stage venous cannulation of the right atrium. Myocardial protection was achieved by antegrade intermittent warm blood cardioplegia every 15 min. All the patients received total revascularization.

2.4. Amiodarone prophylaxis

Eligible patients (patients with AEMi >120 ms) were randomly assigned to receive either placebo or amiodarone. Both treatments were identical in shape, size, and color. The day before surgery, 800 mg of oral amiodarone or placebo was administered. Intraoperatively, amiodarone was administered intravenously in a 500-mg bolus for 1 h. Thereafter, the administration of amiodarone was continued as a total maintenance dose of 20 mg/kg weight over 24 h on the first postoperative day, which was followed from day 2 through day 5 with 800 mg oral daily.

2.5. Statistical analysis

The data are presented as mean±S.D., percentage, and total number when necessary. Comparisons were made between the continuous variables using an unpaired *t*-test and between the categorical variables using a χ^2-test. When the data were not normally distributed, the Mann–Whitney test was employed instead of the unpaired *t*-test.

The statistical analyses were performed with the SPSS software package, version 13.0 (Chicago, IL). A $P<0.05$ was considered statistically significant.

3. Results

There was no statistically significant difference between the two groups in terms of gender, age, ejection fraction, atrial volume, A-wave, AEMi, number of coronary artery disease, number of grafts, aortic clamp time, cardiopulmonary bypass time, EuroSCORE, body mass index, prior myocardial infarction, diabetes mellitus, chronic obstructive pulmonary disease, and hypertension (Tables 1 and 2). And nor was there any difference with respect to premedication and the number and kind of coronary grafts (Figs. 1, 3). The control group, however, received beta-

Table 1
Comparisons between the two groups in terms of baseline and surgical characteristics

Variable	Control group	Amiodarone group	PV
Sex (M/F)	35/15	33/17	0.67
Age (years)	64.3±8.7	62.7±7.8	0.34
Ejection fraction	45.8±9.7	43.9±9.3	0.32
AT volume	60.5±13.1	64.8±12.2	0.096
A-wave	47.0±7.5	44.8±5.8	0.11
AEMi	145.4±14.5	143.7±13.3	0.53
VD	2.80±0.54	2.84±0.42	0.68
Number of grafts	3.50±0.95	3.60±0.95	0.60
Aortic clamp time	81.4±10.4	81.6±10.9	0.93
Cardiopulmonary bypass time	97.8±9.1	99.6±15.7	0.47
EuroSCORE	3.62±2.28	3.08±2.24	0.18
Body mass index	26.5±2.1	26.8±2.5	0.46
Prior myocardial infarction (%)	46	44	0.84
Diabetes mellitus (%)	30	32	0.83
COPD (%)	36	38	0.84
Hypertension (%)	46	56	0.32

AT Volume, atrial volume; AEMi, atrial electromechanical interval; VD, number of coronary artery disease; CPB, cardiopulmonary bypass time; COPD, chronic obstructive pulmonary disease.

Table 2
Comparisons between the two groups in terms of some variables

Variable	Control group	Amiodarone group	PV
AF heart rate	134.9±20.3	105.6±26.4	0.001
Duration of AF	19.8±17.6	15.9±11.3	0.84
Days of AF duration	2.36±0.65	2.25±0.46	0.87
ICU length of stay (days)	3.60±0.90	2.28±1.00	0.000
Hospital length of stay (days)	7.78±1.46	5.64±2.35	0.000
P-wave	86.6±18.0	73.9±36.8	0.031

AF, atrial fibrillation; TDI A-wave, tissue Doppler imaging mitral annular A wave velocity.

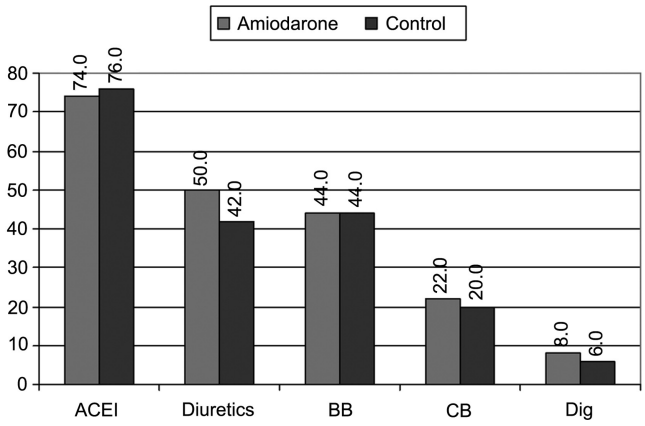

Fig. 1. Comparison between the two groups in terms of medication before surgery. ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CB, calcium blocker; Dig, digoxin.

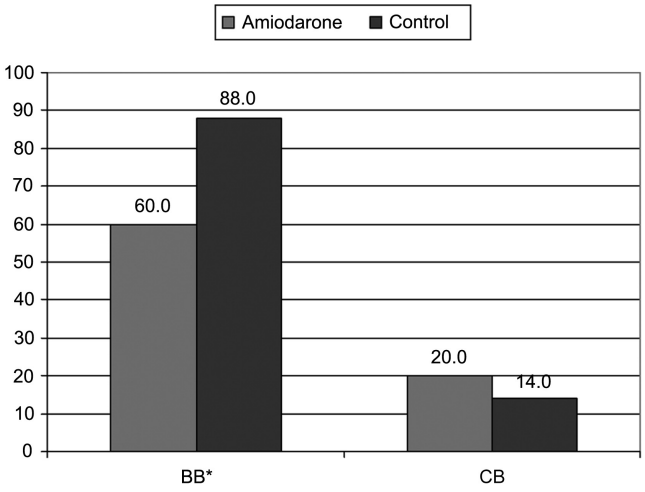

Fig. 2. Comparison between the two groups in terms of medication after surgery. BB, beta-blocker; CB, calcium blocker.

blockers more than did the amiodarone group postoperatively (Fig. 2).

The incidence of postoperative AF was significantly higher in the placebo group than that in the amiodarone group (88% vs. 16% of patients, $P<0.0001$).

The duration of AF was not different between the two groups ($P=0.54$), but the rate of ventricular response was shorter in the amiodarone group ($P=0.001$) (Fig. 4).

Prophylactic therapy with amiodarone significantly reduced the ICU length of stay (2.28 ± 1.00 vs. 3.60 ± 0.90 days, $P<0.0001$) and hospital length of stay (5.64 ± 2.35 vs. 7.78 ± 1.46 days, $P<0.0001$) (Figs. 5, 6).

None of our patients showed bradycardia, hypotension, hepatotoxicity, pulmonary toxicity, QT interval prolongation, and requirement for temporary pacing with amiodarone during patient hospitalization.

4. Discussion

AF after CABG, albeit self-limiting in most cases, is known to be a potential risk of hemodynamic compromise, systemic thromboembolism, and even stroke. Even when uncomplicated, post-CABG AF requires additional medical treatment, a prolonged hospital stay, and concomitant extra costs of operative treatment.

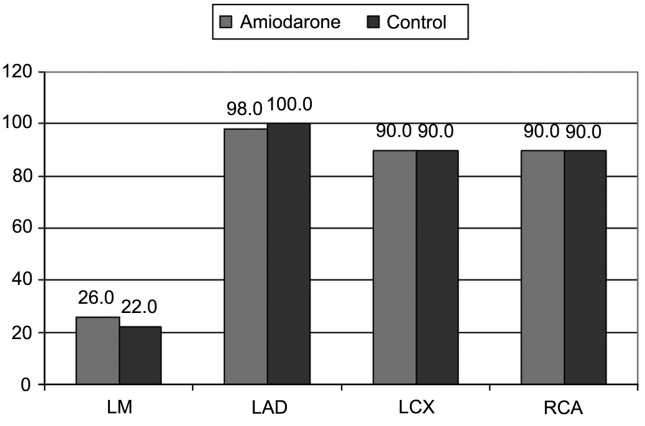

Fig. 3. Comparison between the two groups in terms of the number of coronary arteries operated on. LM, left main disease; LAD, left anterior descending artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

Over the years, different antiarrhythmic drugs have been used to prevent AF after cardiac surgery with success [2]; be that as it may, it should be noted that most of these medications have their own side effects [4].

Amiodarone has often been utilized for the prophylactic treatment of AF. Nonetheless, like other antiarrhythmic

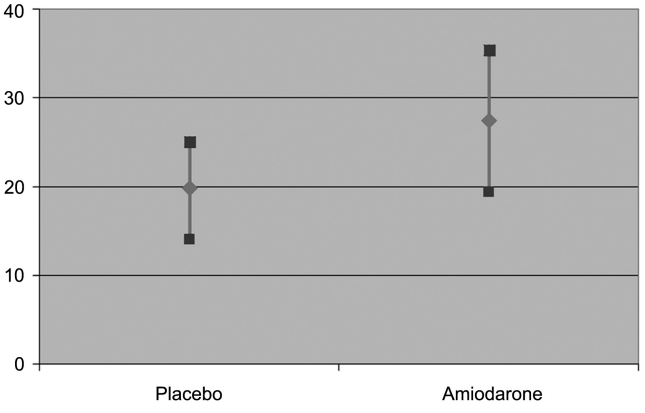

Fig. 4. Comparison between the two groups in terms of AF duration.

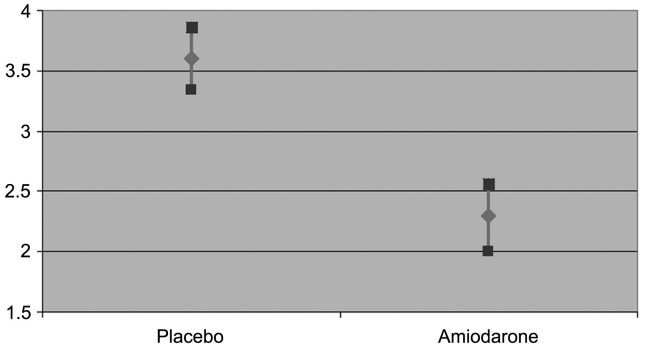

Fig. 5. Comparison between the two groups in terms of ICU duration.

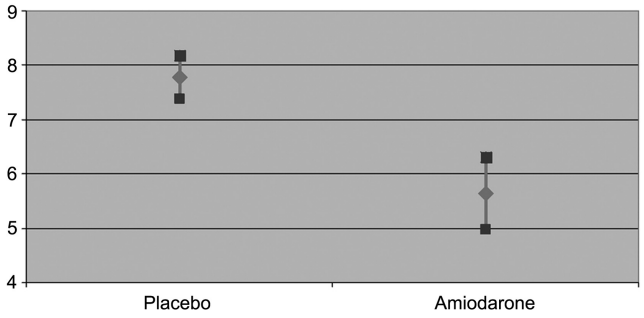

Fig. 6. Comparison between the two groups in terms of hospital duration.

treatments, it may have unfavorable side effects. Several meta-analyses have shown amiodarone to be effective in reducing the incidence of AF and its complications after CABG alone or after combined CABG and valvular surgery [1–3, 5]. In contrast, some researchers have demonstrated the side effects of amiodarone [6, 7], including nausea, bradycardia, hypotension, QT interval prolongation, pulmonary toxicity, hepatotoxicity, postoperative acute respiratory distress syndrome, and requirement for temporary pacing [3, 6]. In light of the said possible side effects, it may be advisable that we reserve amiodarone prophylaxis for the high-risk group and spare patients who are not at risk of AF from an unnecessary medication and its side effects.

Another advantage of the administration of prophylactic amiodarone to exclusively high-risk patients is a significant drop in hospital costs. Perhaps it goes without saying that prophylactic amiodarone is not cost-effective if given to all patients [8]. There are many studies in the existing medical literature that chime in with this observation in that they have shown that cost saving is most when the prophylaxis has been given to high-risk patients [9]. The fact that the prophylaxis of the whole patient population undergoing CABG is not reasonable renders the identification of at-risk patients of post-CABG AF very helpful.

Several factors such as age, male gender, past history of AF, chronic obstructive pulmonary disease, valve surgery, and withdrawal of beta-blockers and ACE inhibitors have been shown to be the predictors of AF [10]. The echocardiographic findings of an increased left atrium dimension [11] and increased P-wave duration on signal-averaged ECG [12] are believed to be able to identify patients at risk of AF. Unfortunately, none of these factors is powerful enough to predict postoperative AF after CABG to any clinically meaningful extent [13].

In a previous study, we found that in the 4-chamber view of transthoracic echocardiography, the time intervals from the onset of P-wave to the beginning of the backward motion of the mitral valve were prolonged in patients at risk of AF [14]. We, therefore, postulated that AEMi, as a measure of atrial impairment, could be helpful in detecting patients facing the risk of post-CABG AF. We defined a cut-off point for AEMi and chose 120 ms for categorization, which yielded 100% sensitivity and 94.8% specificity [14]. We used the same cut-off point in the present study. This high sensitivity essentially includes all patients at risk of AF. We treated this high-risk group with perioperative amiodarone and assessed its effect in reducing the incidence of AF and lengths of stay in hospital and ICU. The important question was: 'How should amiodarone be administered?' The problem with oral regimens is that amiodarone requires seven to twenty-one days of therapy to reach effective blood levels to be able to control arrhythmias [7], which, due to the emergency nature of CABG surgeries, is not possible in most cases. On the other hand, IV-only regimens can cause bradycardia [15] and impair patient mobilization after surgery. We used a combination of IV loading and oral continuation so as to achieve effective blood levels and avoid side effects. Our regimen was commenced prior to surgery, IV dosing was given only intraoperatively and on the first postoperative day, and the daily regimen did not exceed 1 g, which does not increase side effects and can be a safe, practical, and cost-effective regimen if given to patients at high risk of AF in the wake of CABG.

Our results showed that the incidence of postoperative AF was significantly higher in the placebo group than that in the amiodarone group.

Although the duration of AF was not different between the two groups, the rate of ventricular response was shorter in the amiodarone group, the patients of which were less symptomatic. It could also be regarded as another benefit of amiodarone prophylaxis inasmuch as we need less medicine in order to reduce ventricular response in patients suffering an AF occurrence.

In line with the results of previous studies, prophylactic therapy with amiodarone significantly reduced the ICU and hospital lengths of stay in our study.

5. Summary

Amiodarone prophylaxis appears to be effective in the prevention of new-onset postoperative AF. It also reduces the ventricular response after CABG.

Despite these benefits, amiodarone has some serious side effects that limit its application, hence the necessity to administer amiodarone only to patients at high risk of post-CABG AF.

We conclude that a prophylactic amiodarone treatment among patients at high risk of AF occurrence after CABG (based on AEMi measurements) can significantly reduce the incidence of postoperative AF and result in shorter ICU and hospital stays.

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Conference discussion

Dr. J. Maessen (*Maastricht, Netherlands*): This is really a nice example of tailoring treatment to increase the efficacy by risk analysis based on new physiological concept, the AEMi, described in your paper in Circulation a couple of years ago.

My questions. First, about economics. Of course, you bring down the post-op AF incidence from 88 to 16%, but only in the group of 100 selected patients. To obtain this group, you had to do 1,000, or a little bit more echocardiographies.

In those 1,000 patients you probably had 300 cases of post-op AF. Now you reduce it to 72 patients. Do you think we are willing to do 1,000 echos to achieve that? That's my first question.

The second question is about the length of stay. You got a reduction, in length of stay, but again, in a small group of patients. If it's that important, why not be a little bit more liberal to discharge patients with post-op AF, for instance, asymptomatic or with a mild AF? I think that in that way you create a more profound reduction in lengths of stay. I would like to know your opinion about that.

Dr. Roshanali: Could I answer your questions one by one? I may forget and leave out something.

Dr. Maessen: Sure.

Dr. Roshanali: Thank you.

Dr. Maessen: You're welcome.

Dr. Roshanali: For the first question, we routinely perform echocardiography for all patients undergoing CABG. AEMi is not time-consuming at all; on the contrary, it only takes echocardiologists less than a minute. In addition, it's not very hard to measure the AEMi in all patients.

Dr. Maessen: So all your CABG patients get echocardiography?

Dr. Roshanali: A routine echocardiography in our center. We perform transthoracic echocardiography in all patients.

Dr. Maessen: Okay.

Dr. Roshanali: I think we should perform echocardiography in all patients not just because of this but to rule out other possibilities; for example, a clot, MR, or other things.

And for the second question?

Dr. Maessen: Yes. Are you willing to send the patient with mild post-op AF and asymptomatic, back to his referring hospital or even send him home?

Dr. Roshanali: We would rather manage patients in the hospital until they become asymptomatic and are ready to be discharged. Did I answer your question?

Dr. Maessen: Yes.

And my final question, of course, the incidence of post-op AF is determined by pre-op parameters, determinants, but of course, also by intraoperative determinants. Wouldn't it be better based on the results of this study to do an echo at the end of surgery and then discriminate between patients with a longer AEMi interval or shorter?

Dr. Roshanali: You mean we should measure the AEMi intraoperatively?

Dr. Maessen: Yes.

Dr. Roshanali: Then we would have to do an intraoperative echocardiography in all CABG patients. It would not be cost-effective, I think.

Dr. Maessen: Maybe you are right.

Dr. I. Tzanavaros (*Cottbus, Germany*): It's a bit surprising for me to see in the control group the postoperative AF was 88%.

Dr. Roshanali: Yes, because these are high-risk patients.

Dr. Tzanavaros: That's very high. And why there was a difference considering the beta-blocker therapy?

Dr. Roshanali: From a total of 1,000 patients, we selected these 100 patients. These are high-risk patients. As you see in our table, they are slightly older with higher atrial volumes on all indexes that were high risk for AF prediction. All these 100 patients had a high risk of postoperative AF.

Dr. Tzanavaros: And maybe I missed it, but when did you discontinue amiodarone and what happened afterwards?

Dr. Roshanali: We discontinued amiodarone suddenly at day 6.

Dr. Tzanavaros: And what happened after?

Dr. Roshanali: When? Five days postoperatively?

Dr. Tzanavaros: And after there was no difference.

Dr. Roshanali: Nothing, no, no. No difference.

Dr. G. Bolotin *(Haifa, Israel)*: Can you please tell us what was the rate of atrial fibrillation in the other 900 patients that were operated in the same period?

Dr. Roshanali: $<$120. We only choose 120 or more.

Dr. Bolotin: Yes.

Dr. Roshanali: All the 900 patients had an AEMi of $<$120 ms.

Dr. Bolotin: Yes, it is important to know what was the rate of postoperative atrial fibrillation in the case of low risk?

Dr. Roshanali: Oh, no, we don't do it because it is not cost-effective and because we would have to monitor the patients with telemonitoring or something like that. It is not routine; not just in our center but I think in all other centers.