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Role of Endogenous Adenosine in Atrial Fibrillation after Coronary Artery Bypass Graft

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Summary

Background: Atrial fibrillation (AF) is the most common complication following coronary artery bypass graft (CABG). The mechanism of AF after CABG is not well defined; however, it is suggested that endogenous adenosine, released in response to tissue hypoxia, may play a mechanistic role in these arrhythmias.

Hypothesis: The purpose of this study was to examine whether intravenous theophylline, via adenosine A1 receptor antagonism, would correct or modify new-onset early (< 48 h post CABG) atrial fibrillation in patients post CABG, and thereby implicate endogenous adenosine as an inciting agent.

Methods: A prospective double-blind, placebo-controlled study design was applied to 385 consecutive patients with coronary artery disease who had undergone CABG. Any patient who developed AF within 48 h of the operative procedure was randomly assigned to receive 5 mg/kg of intravenous theophylline (Group A) or matched intravenous placebo (Group B). The patients who converted to sinus rhythm within 15 min of drug administration were accepted as showing positive responses.

Results: Thirty patients comprised the study group. In Group A, 8 of the 15 patients (53%) converted from AF to sinus rhythm within 15 min of theophylline administration. One patient who converted to sinus rhythm 20 min after theophylline administration was accepted as showing a negative response. In the placebo-treated group, no patient converted to sinus rhythm within 15 min ($p < 0.007$ compared with Group A).

Conclusions: The mechanism of AF after CABG is not well defined and is probably multifactorial. However, this study demonstrated that antagonism of the adenosine A1 receptor can promptly convert many of these patients back to sinus rhythm, and thereby implicates endogenously released adenosine in a mechanistic role for inciting early (< 48 h) post-CABG AF.

Key words: adenosine, atrial fibrillation, coronary artery disease, coronary bypass surgery, complications, theophylline, cardiac arrhythmia

Introduction

Atrial fibrillation (AF) is the most common complication following coronary artery bypass graft (CABG).[1] Although often transient and benign, AF after CABG prolongs hospital stay and may lead to complications such as hemodynamic instability or thromboembolic events.[2] The mechanism of AF after CABG is not well defined; however, animal studies as well as clinical case studies suggest that endogenous adenosine, released in response to tissue hypoxia, may play a mechanistic role in these arrhythmias.[3,4]

It is postulated that endogenous adenosine, released during the surgical procedure, shortens the atrial action potential duration and effective refractory period. If a premature atrial contraction occurs, AF or atrial flutter may occur.[5] Adenosine A1 receptor antagonism may then convert these atrial arrhythmias to sinus rhythm[5] (Fig. 1). Bertolet *et al*. found that theophylline, when given intravenously in humans, more readily antagonizes the adenosine A1 receptors as opposed to A2 receptors.[6]

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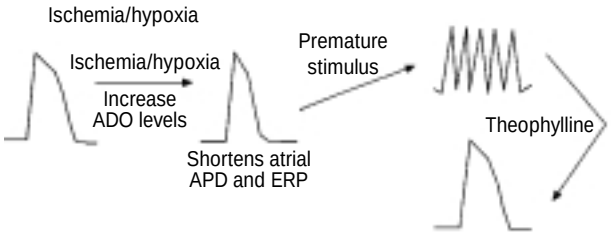

FIG. 1 Endogenous adenosine (ADO), released during a cardiac surgical procedure or in response to ischemia, will shorten the atrial action potential duration and effective refractory period. Atrial fibrillation or atrial flutter may occur if a premature atrial contraction occurs during this refractory period. It is postulated that ADO A1 receptor antagonism may then convert these atrial arrhythmias back to sinus rhythm. APD = action potential duration, ERP = effective refractory period. Figure modified from Ref. No. 5.

The purpose of this study was to examine whether intravenous theophylline, via adenosine A1 receptor antagonism, would correct or modify new-onset early (< 48 h post CABG) AF in patients post CABG, and thereby implicate endogenous adenosine as an inciting agent.

Methods

A prospective double-blind, placebo-controlled study design was applied to 385 consecutive patients with coronary artery disease who underwent CABG in the period between October 1998 and October 2001 at the University of Osmangazi. Any patient who developed AF within 48 h of the operative procedure was randomly assigned to receive 5 mg/kg of intravenous theophylline (Group A) or matched intravenous placebo (Group B).

A Monolyth® (Sorin Biomedica, Crescentino, Italy) membrane oxygenator, using bicaval venous cannulation, was used in every bypass operation. Cardioplegia was performed using St. Thomas cardioplegia solution #2 (Thomas Medical Products, Inc., Malvern, Penn., USA) in an antegrade fashion at 4˚C. Patients with preoperative rhythm abnormalities, history of AF, pretreatment with class I and II antiarrhythmic agents, emergency operation, associated valvular heart disease, low cardiac output syndrome postoperatively, and perioperative myocardial infarction were not included in the study.

All patients underwent continuous electrocardiographic monitoring through postoperative Day 2. The time of AF onset was identified by visual inspection of the electrocardiogram. Patients who developed transient AF (arrhythmia duration < 30 min) were not included in the study; neither were patients with hemodynamically unstable AF. Prior to the study drug administration, no antiarrhythmic or atrioventricular (AV) node blocking drugs (i.e., amiodarone, beta blockers, calcium blockers) were given. Potassium and magnesium levels were closely observed and administered when needed to maintain normal range serum concentrations.

In treatment Group A, theophylline 5 mg/kg was administered over 5 min intravenously (IV). The patients who converted to sinus rhythm within 15 min of theophylline administration were accepted as showing positive responses. If the rhythm of the patient did not convert to sinus rhythm within 15 min after theophylline administration, appropriate medications were given to decrease the ventricular rate and attempt chemical cardioversion.

In placebo Group B, a physiologic IV solution was given over 5 min. Again, if the patient's AF persisted > 15 min, conventional therapy was delivered.

The study was approved by the ethics committee of the institution, and informed consent was obtained from each patient included in the study.

All values are expressed as mean ± standard error (SE). Differences between the two groups were analyzed using Student's *t*-tests for continuous variables and chi-square analysis for categorical variables. A p value < 0.05 was considered significant.

Results

Atrial fibrillation was detected in 47 of 385 (12%) patients who had undergone CABG. Seventeen of these patients met the prespecified exclusion criteria. Thirty patients (19 men, 11 women, mean age 64.2 ± 3.8 years) comprised the study group. Clinical and operative characteristics of the two treatment groups are shown in Table I. There were no differences in the prescribed medications between the two groups.

TABLE I Characteristics of treatment and placebo groups

	Theophylline group (A) (n = 15)	Placebo group (B) (n = 15)	p Value
Age	65.2 ± 3.7	64.6 ± 3.45	0.41
Gender			
Male	9	10	0.45
Female	6	5	0.4
AF day			
Day 1	5	6	0.56
Day 2	10	9	
Grafted vessels			
2 vessels	5	4	0.23
3 vessels	10	11	0.57
Cross clamp time (min)	67.4 ± 9.7	69.7± 9.8	0.63
Total bypass time (min)	91.7 ± 12.1	92.5 ± 7.0	0.79
Blood gas analysis			
pO_2	87.2 ± 5.7	85.1 ± 6.9	0.23
pCO_2	38.5 ± 2.8	37.2 ± 1.3	0.22
LVEF	52.5 ± 4.5	51.7 ± 2.9	0.25
Left atrial diameter (mm)	34.2 ± 1.8	33.9 ± 1.17	0.78
Central venous pressure (mmHg)	11.9 ± 3.5	12 ± 3.06	0.75
Hypertension	6	7	0.69
Diabetes mellitus	5	4	0.66
Cigarette use	6	5	0.54

Abbreviations: AF = atrial fibrillation, LVEF = left ventricular ejection fraction.

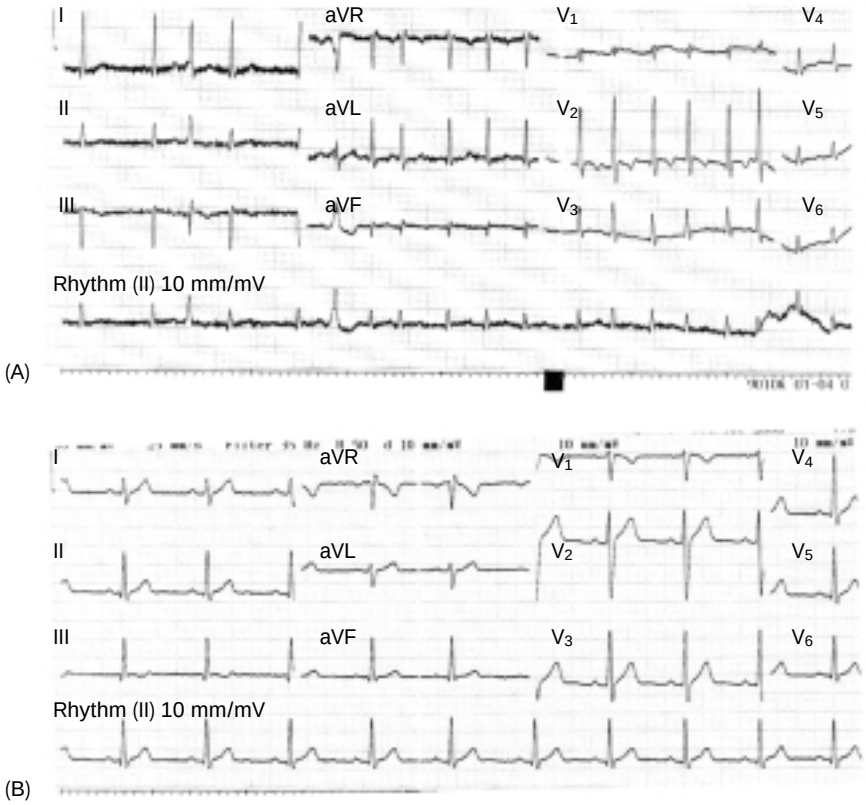

FIG. 2 (A) Electrocardiogram (ECG) showing atrial fibrillation before theophylline administration. (B) ECG showing conversion of atrial fibrillation to sinus rhythm after theophylline administration.

In Group A, the average ventricular rate was 140 beats/min. Eight of the 15 patients (53%) converted from AF to sinus rhythm within 15 min of theophylline administration. The average heart rate after conversion was 85 beats/min. Five of these positive responders converted within 5 min, two at 10 min, and one at the 13th min. One patient who converted to sinus rhythm 20 min after theophylline administration was accepted as showing a negative response. Four of the "converted" patients reverted to AF 5 to 7 h later, likely due to subtherapeutic theophylline levels; however, no additional theophylline was administered. Figure 2 depicts a patient with early AF converted successfully to sinus rhythm. For the nonresponders, the ventricular rate after theophylline increased to 143 beats/min (p = NS compared with baseline).

Table II compares converters to nonconverters. Of note, patients who converted and maintained sinus rhythm following theophylline administration seemed to have a shorter hospital stay and better left ventricular ejection fraction than those who failed theophylline conversion.

In Group B, no patient converted to sinus rhythm within 15 min ($p < 0.007$ compared with Group A).

There was no difference in cardiac troponin-I (TnI) levels between the two groups intraoperatively as well as postoperatively. In Group A, mean TnI levels were 1.2 ± 0.4 ng/ml 20 min after cross-clamping the aorta; 1.4 ± 0.3 ng/ml 20 min after aortic unclamping; 1.1 ± 0.3 ng/ml 24 h postoperatively; and 0.9 ± 0.2 ng/ml on postoperative Day 2. In Group B, the mean TnI levels were 1.1 ± 0.3 ng/ml; 1.3 ± 0.2 ng/ml; 0.8 ± 0.2 ng/ml; and 0.8 ± 0.1 ng/ml, respectively.

TABLE II Comparison of Group A "Converters" and Group A "Nonconverters"

	Converters (n = 8)	Nonconverters (n = 7)	p Value
Age	65.2 ± 3.7	65.2 ± 3.7	NS
Male (%)	62.5	57.1	NS
Postop day AF developed			
Day 1	2	3	NS
Day 2	6	4	NS
LVEF	69.1 ± 3.5	54.3 ± 4.6	0.05
HR following theophylline	85.4 ± 2.5	143.1 ± 3.5	0.05
Hypertension (%)	50	28.6	NS
Diabetic (%)	25	42.9	NS
Hospital length of stay	5.4 ± 2.5	9.6 ± 2.2	0.05
Mortality	—	—	NS

Abbreviations: HR = heart rate, NS = not significant. Other abbreviations as in Table I.

Discussion

One of the most frequent complications after CABG is AF, occurring in up to 40% of patients.[7] These arrhythmias are often transient and do not influence long-term graft patency;[8] however, post-CABG AF has been associated with increased morbidity and commonly prolongs the hospital stay.[9] Perhaps because of improved surgical and anesthetic techniques, the incidence of postoperative AF has dramatically decreased over the past 20 years.[9] Atrial fibrillation occurred in 12.2% of the patients in this study.

The mechanism of AF after CABG is not well defined and is probably multifactorial. Most episodes occur within the first four postoperative days.[9] The use of cardiopulmonary bypass, the type of cardioplegia, presence of myocardial ischemia, and number of grafts placed are all possible factors responsible for the occurrence of postoperative AF.[10] It has been proposed that endogenous adenosine, released due to tissue hypoxia, may cause early (< 48 h) postoperative AF.[5] Cox observed that atrial ischemia following cardiac surgery could induce early AF.[7] Moreover, exogenously administered adenosine has been shown to induce AF in both animal and humans.[11, 12] Accordingly, patients were only included in this study if they developed early postoperative (< 48 h) AF.

Animal studies affirm that endogenous adenosine released in response to tissue hypoxia may play a mechanistic role in arrhythmias associated with myocardial ischemia or hypoxia. The action of adenosine on the fibrillatory threshold, effective refractory period, electric diastolic threshold, and mechanical activity of the atrial and ventricular myocardium was studied in vivo and in vitro.[13] These same investigators observed that atrial hypoxia would shorten the atrial action potential, which could be antagonized or reversed with aminophylline.[14] Lerman *et al.* showed that the administration of dipyridamole, an adenosine uptake blocker, could induce atrial flutter and revert back into sinus rhythm after IV aminophylline.[15] Bertolet *et al.* showed in two patients with new-onset AF following acute myocardial infarction that sinus rhythm could be restored by the administration of theophylline.[5] These studies provide strong support for the hypothesis that endogenous adenosine, released in response to tissue hypoxia, may produce rhythm disturbances such as AF and atrial flutter (Fig. 1), and that adenosine A1 receptor antagonism may reverse this dysrhythmia.

The dose of theophylline (5 mg/kg IV) used in this study is well supported by laboratory[6] and clinical case studies;[5, 16] however, smaller doses may also be effective. Higher doses of theophylline may increase the ventricular response and should be avoided.

Conclusion

This is the first study to demonstrate that endogenously released adenosine plays a mechanistic role in early (< 48 h) post-CABG atrial fibrillation. Furthermore, this study demonstrates that antagonism of the adenosine A1 receptor can promptly convert many patients back to sinus rhythm. Even though a limited number of cases are presented, this study lays the foundation for more research into the role of endogenous adenosine in post-CABG atrial fibrillation.

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