Does Sodium Nitroprusside Decrease the Incidence of Atrial Fibrillation After Myocardial Revascularization?

A Pilot Study

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Background—Atrial fibrillation (AF) often occurs after coronary artery bypass grafting and can result in increased morbidity and mortality. In the present pilot study, our aim was to investigate whether sodium nitroprusside (SNP), as a nitric oxide donor, can reduce the frequency of post–coronary artery bypass grafting AF.

Methods and Results—To investigate the effectiveness of SNP in the prophylaxis of AF, we conducted a prospective, randomized, placebo-controlled clinical study on 100 consecutive patients in whom we performed elective and initial CABG operations. A control group of 50 patients were treated with placebo (dextrose 5% in water), whereas the SNP group (n=50 patients) was treated with SNP (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during the rewarming period. High-sensitivity C-reactive protein levels were measured before surgery and 5 days postoperatively. All patients were monitored postoperatively with telemetry. Baseline characteristics were similar in both treatment groups. AF occurred in 12% of the SNP group and 27% of the control group. The occurrence of AF was significantly lower in the SNP group ($P=0.005$). The duration of AF in the SNP group was significantly shorter than that in the control group (5.33 ± 1.86 and 7.55 ± 1.94 hours, respectively; $P=0.023$). C-reactive protein levels were higher postoperatively in the control group than in the SNP group ($P<0.05$). Postoperative AF significantly prolonged postoperative hospital stay ($P<0.05$).

Conclusions—The incidence of postoperative AF in the SNP group was reduced significantly. Further studies are needed to better delineate the anti-AF profile of SNP. (***Circulation*. 2008;118:476-481.**)

Key Words: myocardial revascularization ■ atrial fibrillation ■ sodium nitroprusside

Postoperative atrial fibrillation (AF) after open cardiac surgery is rather common. The incidence of AF in patients after coronary artery bypass grafting (CABG) ranges from 20% to 40%.[1,2] Although this complication occurs frequently, the mechanism behind its development has not yet been explained clearly. Numerous studies have identified and enumerated a variety of risk factors for development of AF. These include increased age, male gender, history of AF, discontinuation of preoperative β-blocker therapy, congestive heart failure, electrolyte depletion (low potassium and magnesium), cardiopulmonary bypass, left atrial dysfunction, severity of coronary disease, respiratory disease, and pulmonary disease.[3–8]

Editorial p 467
Clinical Perspective p 481

Many clinical trials have evaluated the effectiveness of a variety of pharmacological and nonpharmacological interventions to decrease the incidence of AF.[9–17] There is evidence that nitric oxide (NO) reduces reperfusion injury.[18] NO is a nonpolar gaseous molecule that is involved in many biological processes. From a clinical prospective, its most important properties are antiapoptotic, antiinflammatory, antistunning, and preconditioning effects.[19]

Sodium nitroprusside (SNP), which acts as an NO donor, is among the most clinically useful vasodilators in cardiac surgery. This is mainly because of its potency, rapid onset, and short duration of action. NO production by SNP requires the presence of vascular tissue.[20]

The aim of the present prospective, blinded, randomized study was to evaluate the usefulness of SNP in preventing AF in patients undergoing first elective CABG. Here, we present the results of a pilot study designed to evaluate the effectiveness of perioperative (during the rewarming period) SNP administration and discuss possible strategies by which SNP treatment can be beneficial to prevent postoperative AF.

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Table 1. Preoperative Characteristics

Characteristic	SNP Group (n=50)	Control Group (n=50)	P
Age, y	60.34±1.53	60.92±1.42	0.782
Male sex, n	30	27	0.547
Current smoker, n	26	28	0.690
Ejection fraction, %	60.34±1.36	61.86±0.88	0.234
Euroscore	4.06±0.38	3.74±0.35	0.543
Angina, n	27	36	0.064
Diabetes, n	21	22	0.841
Hypertension, n	35	29	0.214
Respiratory disease, n	9	13	0.337
Hypercholesterolemia, n	23	19	0.420
Preoperative MI, n	8	10	0.785
Renal disease, n	4	3	0.956
PVD, n	11	19	0.82
Preoperative drugs, n			
β-Blocker	34	29	0.303
Calcium channel blocker	11	15	0.364
ACE inhibitor	11	14	0.493
Nitrate	9	8	0.793
Left atrial dimension, mm	37.72±2.64	38.78±3.35	0.053
Preoperative arrythmia, n	0	0	
Preoperative CRP levels, mg/L	1.49±0.93	1.55±0.42	0.42

MI indicates myocardial infarction; PVD, peripheral vascular disease; and ACE, angiotensin-converting enzyme.

Methods

Patient Selection

The study was approved by the ethics committee of the institution, and written informed consent was obtained from each patient included in the study. In this prospective, double-blind, placebo-controlled, randomized study, patients received either SNP (n=50) or placebo (dextrose 5% in water; n=50). Patients undergoing CABG in addition to heart valve repair or replacement, resection of ventricular aneurysm, or other surgical procedure were not included. Also excluded were patients who had undergone previous cardiac surgery and patients with bradycardia (heart rate ≤55 bpm while the patient was awake), significant alterations of atrioventricular conduction, sick sinus syndrome, permanent pacemakers, significant electrolyte disorders on admission, known thyroid disease, or abnormal liver function test results. Detailed physical examination, laboratory data with routine thyroid function tests, chest roentgenogram, and transthoracic echocardiography were performed routinely. The preoperative findings for patients in both groups are shown in Table 1.

Anesthetic Management

Before transfer to the operating room, all patients received premedication with diazepam and morphine. General anesthesia was induced with midazolam (0.05 mg/kg) and sufentanil (3 μg/kg), and muscle paralysis was obtained with vecuronium (0.1 mg/kg). Anesthesia was maintained with a continuous infusion of sufentanil (0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and propofol (0.1 to 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$). At the end of the surgical procedure, patients were transferred to the intensive care unit (ICU). Weaning from mechanical ventilation and tracheal extubation were done as soon as possible.

Surgical Techniques

The surgical techniques were standardized in all cases. A median sternotomy was performed. Cardiopulmonary bypass was established by a regular cannulation technique with mild hypothermia (30°C). Myocardial protection was achieved with antegrade cold-blood cardioplegia (blood from the pump reservoir was mixed with crystalloid in a ratio of 4:1, which yielded a 21-mmol/L potassium concentration in the initial doses and 9 mmol/L in subsequent doses) given every 20 minutes, with a terminal dose of warm-blood cardioplegia given antegradely immediately before release of the aortic cross-clamp. The left internal thoracic artery and saphenous veins were used as conduits for bypass grafting. Distal anastomoses were performed during a period of aortic cross-clamping, and proximal anastomoses were performed with partial aortic clamping during rewarming. At the end of the surgical procedure, patients were transferred to the ICU. Patients were discharged from the ICU to the ward as soon as their hemodynamic and respiratory condition was stable. The same medical staff performed all operations and anesthetic management throughout the study period.

Perioperative Measurements

ECGs and hemodynamic variables, including arterial blood pressure, heart rate, and central venous pressure, were monitored continuously throughout the operation and during the period in the ICU. After discharge from the ICU, all patients were monitored with an alarm-triggered telemetry system and double-checked for unnoticed events every morning for at least 5 postoperative days.

A 12-lead ECG was obtained before surgery and on the first 5 postoperative days. Serum magnesium concentration was measured before surgery, immediately after surgery, and every morning for 5 days postoperatively and maintained at a level >1.5 mEq/L. Serum potassium and calcium concentrations were also measured perioperatively and adjusted to maintain potassium levels at >4 mmol/L and calcium levels at >8.5 mg/dL.

Cases were those patients who developed AF within 5 days after CABG surgery. AF was considered significant if it persisted for >15 minutes. All patients who had AF were treated according to protocol with intravenous amiodarone (bolus 5 mg/kg followed by an infusion of 15 mg/kg per 24 hours).

High-sensitivity C-reactive protein (CRP) levels were measured before surgery and daily thereafter for 5 days postoperatively. CRP was determined by a nephelometric method (Dade Behring Marburg GmbH, Marburg, Germany).

SNP Protocol

After release of the aortic cross-clamp (before rewarming had been started), patients received either 5% dextrose in water solution as placebo (control group) or SNP (SNP group). Pump flow during rewarming was kept between 2.4 and 3.0 $L \cdot m^{-2} \cdot min^{-1}$ for all patients. SNP initially was administered as a continuous infusion (0.5 to 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$). This dose was titrated to maintain a mean arterial pressure near 65 mm Hg. No additional volume input was used to achieve this pressure. Mean arterial pressure also was maintained near 65 mm Hg in the control patients. The infusion lasted 60 minutes.

Statistical Analysis

Statistical analyses were performed with the SPSS for Windows 11.0 software system (SPSS Inc, Chicago, Ill). Variables were expressed as mean±SD. Univariate analyses between groups were compared by *t* test, χ^2 test, and Fisher's exact test where appropriate. Univariate ANOVA and ANOVA with repeated measurements were used for the comparison of groups with regard to CRP values. Binary logistic regression analysis with the backward Wald method was performed to determine the independent predictors of AF. Independent variables for the multivariate model were selected from those identified in a review of the literature. These variables were age and sex. Also included were variables that had an association of $P<0.2$ with AF in the univariate model. A difference on a 2-tailed test was considered statistically significant for $P<0.05$.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Table 2. Operative and Postoperative Characteristics

Characteristic	SNP (n=50)	Control Group (n=50)	*P*
Operation time, min	164.16±3.96	164,4,08	0.972
Bypass time, min	71.10±3.90	65,44±1.83	0.193
Cross-clamp time, min	42.03±3.22	38.10±10.10	0.269
LIMA used, n	50	50	1.00
Grafts per patients	2.62±0.11	2.46±0.12	0.354
Intraoperative defibrillation	9	24	0.001
Perioperative infarction	0	0	
Operative mortality	0	0	
Postoperative AF, n	6	18	0.005
Inotropic agent use, n	5	7	0.185
Hospital stay, d	7.34±0.717	9.10±1.22	0.000
MBP during rewarming, mm Hg	70.6±5.2	70.1±5.6	0.658
Mean CVP after bypass, mm Hg	2.4±1.4	2.5±1.5	0.768
Heart rate after bypass until onset of AF, bpm	73.6±5.8	73.8±4.6	0.267

LIMA indicates left internal mammary artery; MBP, mean blood pressure; and CVP, central venous pressure.

Table 3. Comparison of All Patients With and Without AF

	With AF (n=24)	Without AF (n=76)	*P*
Male sex, %	41.7	61.8	0.1
Age, y	64.08±10.98	59.53±10.05	0.062
Preoperative drugs, %			
β-Blockers	62.5	63.2	1.000
Calcium antagonists	20.8	27.6	0.601
Preoperative LVEF, %	60.41±7.24	60.0±8.61	0.831
Preoperative MI, %	83.3	73.7	0.419
Diabetes mellitus, %	45.8	42.1	0.815
Hypertension, %	66.7	63.2	0.812
Angina, %	70.8	60.5	0.469
Renal disease, %	25.0	15.8	0.363
Peripheral vascular disease, %	41.7	26.3	0.202
Smoker, %	41.7	42.1	0.168
No. of distal anastomosis	2.54±0.88	2.53±0.85	0.991
LIMA used, %	100	100	
Intraoperative defibrillation, %	45.8	28.9	0.141
Operation time, min	160.41±22.39	165.47±29.98	0.449
Cross-clamp time, min	36.75±11.82	41.10±19.97	0.294
Bypass time, min	63.87±13.76	69.65±23.50	0.256
Inotrope used, %	4.2	14.5	0.284

Abbreviations as in Tables 1 and 2.

Results

Preoperative Characteristics

This randomized, prospective clinical trial was performed in 100 patients. Fifty patients received SNP, and 50 received placebo. Statistically significant differences were not found for the variables of age, EuroSCORE (EUROpean System for Cardiac Operative Risk Evaluation), left ventricular ejection fraction, diabetes mellitus, hypertension, respiratory disease, preoperative myocardial infarction, or left atrial dimensions. In addition, there was no significant difference between groups in preoperative use of β-blockers, nitrates, calcium channel blockers, or angiotensin-converting enzyme inhibitors. Preoperative characteristics of the patients are summarized in Table 1.

Operative Characteristics

Among the operative characteristics (Table 2), the difference between bypass times and cross-clamp times were not significant. In all patients, the left internal mammary artery was used with an in situ technique. After release of the aortic clamp, defibrillation of the heart was necessary in 9 patients in the SNP group and 24 in the control group ($P=0.001$).

Postoperative Characteristics

The physicians and nurses in the ICU were blinded to the group status of patients in the SNP and control groups. There were no perioperative myocardial infarctions or in-hospital deaths in either group.

More patients in the SNP group were free of inotrope use than in the control group, and the period of inotropic medication use was also shorter in the SNP group, but these differences did not reach statistical significance. Intra-aortic balloon pumps were not required in any of the patients. Patients were weaned from mechanical ventilation when they were hemodynamically stable, responded to verbal stimulation, and were completely rewarmed and when blood loss did not exceed 100 mL/h. Cardiovascular and respiratory values and temperatures were recorded every 15 minutes before extubation and then hourly until discharge from the ICU. Patients were discharged from the ICU on the first morning that they were hemodynamically stable, had normal blood gases during spontaneous breathing, and had satisfactory renal function. The length of stay in the ICU was similar in both groups ($P=0.654$). The mean hospital stay was significantly lower in the SNP arm than in the control arm of the study (Table 2).

Postoperative AF

During the study period, 18 patients in the control group (36%) developed postoperative AF, whereas 6 (12%) of the SNP patients developed AF ($P=0.005$). AF occurred a mean of 2.66±0.52 days after surgery in the SNP group and 2.55±0.51 days after surgery in the control group ($P=0.650$). There was a significant difference between groups in the duration of AF (5.33±1.86 versus 7.55±1.94 hours, $P=0.023$). Electrical cardioversion was not performed on any patient in either group. There were no statistically significant differences in any variable between patients who experienced postoperative AF and those who did not (Table 3).

Baseline CRP levels were similar in the SNP and control groups. During the study, the average level of postoperative CRP in both groups increased, with a peak concentration on the second day (Table 4). Patients who received SNP had lower levels of CRP throughout the entire postoperative period than patients in the control group ($P<0.05$). Elevated

Table 4. Course of CRP Levels in Control and SNP Groups

	Control Group			SNP Group			
Time Point	No AF (n=32)	AF (n=18)	*P* Within Group	No AF (n=44)	AF (n=6)	*P* Within Group	*P* Between Groups
Preoperative	1.6±0.5	1.4±0.3	NS	1.5±0.4	1.4±0.1	NS	0.42
Postoperative day 1	46.8±12.5	52.1±8.4	NS	34.1±9.4	35.0±5.1	NS	<0.05
Postoperative day 2	59.1±8.6	58.3±13.2	NS	43.6±9.9	44.5±2.0	NS	<0.05
Postoperative day 3	45.46±9.0	47.3±5.3	NS	32.7±7.9	38.3±15.0	NS	<0.05
Postoperative day 4	32.5±8.0	34.4±5.8	NS	22.9±6.5	23.0±8.0	NS	<0.05
Postoperative day 5	14.3±4.8	15.9±3.2	NS	9.1±3.5	8.9±3.2	NS	<0.05

Values are CRP levels expressed as mean±SD (mg/L).

CRP levels decreased and did not return to normal levels by day 5 in either group. When preoperative and operative variables were included in the multivariate analysis, SNP (OR 4.282, 95% CI 1.495 to 12.267, $P=0.007$) and age (OR 1.049, 95% CI 0.998 to 1.102, $P=0.062$) were the only independent predictors of postoperative AF.

Discussion

Despite the major advances in cardiac surgery generally and CABG in particular, the frequency of post-CABG AF remains high. Supraventricular tachyarrhythmia, particularly AF, is the most common dysrhythmia developed after CABG.[1,2] Even though postoperative AF is often a short-lived, self-limiting complication, it is associated with significant morbidity.

Several factors may contribute to the development of AF after cardiac surgery through alterations in atrial refractoriness and/or local reentry: operative trauma, rise in atrial pressure due to postoperative ventricular stunning, increase of atrial electrical susceptibility from rapid return of temperature after cardioplegic arrest, atrial distention by fluid overload, chemical stimulation during infusion of inotropic drugs, reflex sympathetic activation, and pericardial or respiratory complications.[5–7] Altered load is often accompanied by changes in myocardial segment length that, acutely, can result in decreased resting potential and the occurrence of afterdepolarizations that cause extrasystoles that originate in the region of greatest stretch.[8] We were unable to properly evaluate factors such as hemodynamic variables because data on these variables were not universally collected (pulmonary artery catheters were not used routinely; Table 2). Recent clinical studies have also suggested the possible role of inflammatory mechanisms in the pathogenesis of AF after cardiac surgery.[9]

The efficacy of pharmacological prophylaxis in reducing the incidence of AF has been investigated in several studies. Several studies have demonstrated the efficacy of amiodarone in decreasing the incidence of postoperative AF.[10–13] There have been different studies for prevention of post-CABG AF with digoxin, β-blockers, magnesium, or a combination of these drugs.[14–16] Aerra et al[17] confirmed that the combination of sotalol and magnesium can significantly reduce the incidence of postoperative AF. Recent data have suggested a possible protective role of statins[18] and steroid drugs.[19] The usefulness of nonpharmacological strategies, such as continuous overdrive atrial pacing through temporary epicardial electrodes, is currently under investigation.[20]

Beneficial effects of SNP in cardiac surgery have been reported in many studies. Massoudy et al[21] reported that administration of SNP (as an NO donor) for just the first 20 minutes of reperfusion to patients undergoing CABG led to a reduction of the acute inflammatory response, especially a reduction in levels of interleukin-6 and interleukin-8. Kaya et al[22] showed that SNP could inhibit the deleterious effects of cardiopulmonary bypass on the kidney. Cakir et al[23] described an antiinflammatory action of SNP in lung tissue during total cardiopulmonary bypass.

The clinical observations of the present study suggest that SNP influences post-CABG AF. The protocol tested in the present study, in which patients without a history of atrial arrhythmias were given SNP (as an NO donor), has demonstrated a clinical benefit, with a reduction of postoperative AF and a significant reduction in length of hospital stay. Additionally, AF duration was significantly lower in the SNP group, thus decreasing the length of hospitalization, which has important clinical and economic implications.

The mechanism involved in the SNP effect of suppression of postoperative AF is not clear; however, several underlying mechanisms might explain this. On the basis of the finding that NO function is disrupted because of ischemia-reperfusion injury in cardiac surgery, recent studies have focused on the effect of replacement therapy on NO in cardiac surgery. The addition of L-arginine, the precursor of NO, or NO donors such as nitrovasodilators has been demonstrated to aid in the recovery of NO function.[24] NO-induced inhibition of the L-type calcium current (I_{CaL}) by cGMP mechanisms leads to less activation of the calcium-induced calcium release process, thereby reducing atrial contractility and, consequently, energy consumption. NO-induced reduction of I_{CaL} may also act to protect cardiomyocytes from atrial tachycardia/fibrillation-induced calcium overload, which is emerging as a key player in the electrical remodeling process.[25]

The potential role of inflammation in the pathogenesis of post-CABG AF has been proposed with some supporting data.[26] Bruins et al[27] were the first to propose the inflammation-AF hypothesis, after their observations of an increased frequency of AF after coronary artery bypass surgery. They noted that the peak incidence of AF occurred on the second and third postoperative days, which coincided

with the peak elevation of CRP levels.[27] In our present clinical observations, serum CRP concentration increased markedly in the postoperative period in both groups; however, CRP concentrations were reduced significantly in the SNP group during the postoperative period (Table 4). This appears to support the idea that a higher concentration of CRP is an important factor in the development of postoperative AF; however, the present study did not show any statistically significant within-group association of CRP level in the AF-positive and -negative groups, nor was the study sufficiently powered to evaluate the role of other predictors of AF.

The development of a number of NO donors has enabled the investigation and application of biologically active NO in experimental research and therapeutic trials.[28] The optimal timing of NO donor intervention is still unclear in the literature. Inhibition of the production of endogenous NO was found to be greatest starting with postischemic reperfusion. With supplementation of the NO donor, we reduced the harmful effects of ischemia-reperfusion injury (as a predisposing factor of AF).[29] In the present study, this was evidenced by the lesser use of inotropes and reduced necessity for defibrillation after cardiac arrest in the SNP group.

In conclusion, the present study shows that treatment with SNP, initiated before rewarming, significantly decreases the incidence and duration of postoperative AF after CABG. SNP was well tolerated and did not increase the incidence of perioperative complications.

Study Limitations

This was a pilot study, and thus, the limited number of patients is the first limitation of the present study. Small samples cannot be used to derive a satisfactory statistical analysis of different perioperative variables that would possibly influence atrial arrhythmogenesis. Another limitation is that the recording period lasted only 5 days postoperatively. The incidence of AF might be higher and the sensitivity and specificity for analysis of data more appropriate if the recording time were longer.

Disclosures

None.

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CLINICAL PERSPECTIVE

Postoperative atrial fibrillation (AF) is a frequent complication after coronary artery bypass grafting and is associated with increased morbidity and hospital stay. In this pilot study, we investigated whether sodium nitroprusside (SNP), a nitric oxide donor administered during surgery, can reduce the frequency of AF. We prospectively randomized 100 consecutive patients undergoing elective coronary artery bypass graft operations to a control group (dextrose 5% in water) and an SNP group (treated with SNP 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the rewarming period). During the hospitalization, AF episodes were significantly reduced in the SNP group, and the duration of AF in the SNP group was significantly shorter than that in the control group. C-reactive protein levels were higher postoperatively in the control group than in the SNP group. Postoperative AF patients had a prolonged postoperative hospital stay. The present study shows that intraoperative treatment with SNP decreases postoperative AF. Whether this is mediated through an antiinflammatory mechanism of NO is unclear. These findings will require confirmation in a larger study.

Does Sodium Nitroprusside Decrease the Incidence of Atrial Fibrillation After Myocardial Revascularization?: A Pilot Study

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