Beneficial Effects of Intravenously Administered N-3 Fatty Acids for the Prevention of Atrial Fibrillation after Coronary Artery Bypass Surgery: A Prospective Randomized Study

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Key words
- cardiovascular surgery
- coronary bypass surgery
- heart disease

Abstract

Background: Atrial fibrillation (AF) is a common complication after coronary artery bypass grafting operation (CABG). Experimental data have shown antiarrhythmic effects of n-3 polyunsaturated fatty acids (PUFA) on myocardial cells. Orally administered PUFA could significantly reduce the rate of postoperative AF. We assessed the efficacy of PUFA for the prevention of AF after CABG. PUFA were given intravenously to prevent variation in bioavailability.

Methods and Results: 52 patients were randomized to the interventional group, 50 served as controls. In the control group free fatty acids (100 mg soya oil/kg body weight/day) were infused via perfusion pump, starting on admission to hospital and ending at discharge from intensive care. In the interventional group PUFA were given at a dosage of 100 mg fish oil/kg body weight/day. Primary end point was the postoperative development of AF, documented by surface ECG. Secondary end point was the length of stay in the ICU. The demographic, clinical and surgical characteristics of the patients in the two groups were similar. Postoperative AF occurred in 15 patients (30.6%) in the control and in 9 (17.3%) in the PUFA group ($p < 0.05$). After CABG, the PUFA patients had to be treated in the ICU for a shorter time than the control patients. No adverse effects were observed.

Conclusions: Perioperative intravenous infusion of PUFA reduces the incidence of AF after CABG and leads to a shorter stay in the ICU and in hospital. Our data suggest that perioperative intravenous infusion of PUFA should be recommended for patients undergoing CABG.

Introduction

Atrial fibrillation (AF) is one of the most common complications after coronary artery bypass grafting (CABG). However atrial fibrillation is not merely a simple rhythm disorder. AF reduces left ventricular function due to the lack of active diastolic left ventricular filling and impaired contractility caused by tachyarrhythmia phases. Additionally, postoperative AF prolongs the patient's stay in the critical care unit, which is associated with clinical complications and increased costs.

Many studies have been undertaken to develop pharmacological or other antiarrhythmic therapies or algorithms for the prevention of postoperative AF. One of the most effective drugs in the prevention of postoperative AF is amiodarone®. However this therapy is associated with a high rate of drug-related complications such as hyperthyroidism, pulmonary fibrosis, and a significant reduction in left ventricular inotropy. Thus, the prophylactic administration of amiodarone® has to be considered as controversial.

Several clinical and experimental studies showed n-3 polyunsaturated fatty acids (PUFA) to be effective for the prevention of atrial fibrillation. PUFA have shown significant antiarrhythmic effects on left atrial tissue in rat experiments. The consumption of fish, resulting in higher plasma PUFA concentrations, has been associated with a lower incidence of AF over a 12-year follow-up. A recent study showed the beneficial effect of preoperative oral PUFA on the postoperative occurrence of atrial fibrillation after coronary arterial bypass surgery. Experimental studies using atrial rat cardiomyocytes showed that PUFA prevent the induction of fibrillation. In a dog model, PUFA suppressed the occurrence of ventricular tachycardia (VT) after infarction.

There are several theories explaining these effects. PUFA provide effective membrane stabilization in the myocardial cell by prolonged inactiva-

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tion of the fast sodium outward channel, resulting in a longer refractory time. Another mechanism is the modulation of calcium release, probably through interaction with the sarcoplasmic reticulum. This is hypothesized to be caused by a direct interaction of PUFA with arachidonic acid metabolism.
These interactions seem to be responsible for the reduction of major cardiac events, including sudden cardiac death, ventricular fibrillation, and AF, after the use of PUFA.

Aim of the study

The aim of this study was to assess the efficacy and safety of intravenously administered n-3 PUFA in preventing the occurrence of atrial fibrillation after CABG.

Methods

Study design

The study was designed as a prospective randomized double-blinded trial. The protocol was approved by the ethics committee of our university (file reference 74/04). This study was not supported by a grant, nor was it funded by any pharmaceutical company. Patients were randomized to the control group and to the interventional group. In addition to usual peri- and postoperative therapy, i.v. saturated free fatty acids were given to the control group and PUFA to the interventional group. The infusion pump was started at least 12 hours before CABG surgery and continued until transfer from the ICU to a normal ward.

Patients

The study cohort consisted of 102 patients (70 men, 32 women, mean age 67 ± 9.3 years). The consecutive patients were admitted to the department of cardiovascular surgery from December 2005 to October 2006 for elective CABG surgery. Inclusion criteria were age of more than 18 years, normal sinus rhythm, stable hemodynamic conditions and freedom from angina at rest. Exclusion criteria were concomitant valve surgery, prior history of supraventricular arrhythmias, and current antiarrhythmic therapy other than beta-blockers and calcium channel antagonists. Informed consent had to be given by all patients.

PUFA therapy

52 patients were randomized to the interventional group, 50 served as the control group. In the control group, free fatty acids (100 mg soya oil/kg body weight/day) were infused via a perfusion pump from the time of admission to hospital until transfer to a normal ward. In the interventional group, PUFA were given at a dosage of 100 mg fish oil/kg body weight/day. Free fatty acids and PUFA were purchased from Fresenius (Bad Homburg, Germany). Lipovenös® 10% served as a free fatty acid in the control group. 100 ml Lipovenös® contains 10 g soya oil. The dosage was 1 ml/kg body weight/day; this is equivalent to 100 mg soya oil/kg body weight/day. Omegaven® served as PUFA in the interventional group. 100 ml Omegaven® contains 10 mg fish oil. The dosage was 1 ml/kg body weight/day, which is equivalent to 100 mg fish oil/kg body weight/day.

Data collection

After surgery, all patients were transferred to the intensive care unit (ICU). Continuous rhythm monitoring was performed until transfer to a normal ward. Standard 12-lead ECG was performed daily from admission to hospital until transfer. After admission, all patients were examined by transthoracic echocardiography. This method yielded parameters for left ventricular ejection fraction, left ventricular diastolic diameter, and left atrial diameter.
Cardiopulmonary bypass- and cross-clamping times were documented for each patient. Primary end point of this study was the development of postoperative atrial fibrillation as detected by monitoring or 12-lead ECG during the ICU period. AF was defined as any confirmed episode of AF for longer than 15 minutes. After occurrence of postoperative AF, participation in the study ended for these patients.
The secondary end point was the length of stay in the ICU and in hospital.

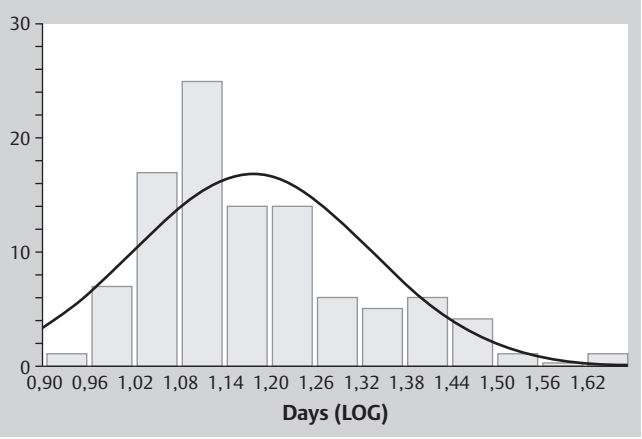

Fig. 1 Total stay in hospital: total length of stay in the hospital shows a log-normal distribution.

Statistical analysis

The efficacy of intravenously administered PUFA for the prevention of postoperative atrial fibrillation after CABG was investigated. Sample size calculation was based on a 30% occurrence of postoperative AF in the control group and a 20% occurrence in the PUFA group. A sequential method of testing was used. This method tests the result of two different interventions on the probability of two alternative clinical events. For the incidence of atrial fibrillation a probability of 25–30% was assumed, based on the literature. The expected probability of an effective therapy should not be lower than 0.5. The above-described sequential test investigates the possibility of a result after each step. The precondition is the independence of patient characteristics. Preceding statistical analysis, the patients had to be randomized pairwise.
Differences in the length of stay in the ICU and in hospital were analyzed using unifactorial variance analysis. Normal distribution of all investigated factors was proved after transformation by log-normal transformation (**Fig. 1**).

Results

The demographic, clinical and surgical characteristics of the patients in the two groups were similar and showed no significant differences. There was no statistical significant difference between the two groups “atrial fibrillation” and “sinus rhythm” with regard to the parameters “body weight” and “age” (**Table 1**).

Table 1 Demographic data.

	Sex		Body weight (kg)	Age (yrs)	p-value
Control group	male	32 = 64%	88.75 ± 11.05	66.65 ± 10.65	n. s.
	female	18 = 36%	71.06 ± 8.84	70.72 ± 8.18	n. s.
Intervention group	male	38 = 73%	83.47 ± 12.04	61.21 ± 14.12	n. s.
	female	14 = 27%	75.21 ± 16.92	74.42 ± 9.23	n. s.

Table 2 Echocardiography data.

	LA diameter (mm)	Ejection fraction (%)	p value
Control group	40.57 ± 5.09	52.31 ± 15.68	n. s.
Intervention group	40.01 ± 5.14	52.00 ± 15.00	n. s.

Table 3 Postoperative development of atrial fibrillation.

Day postop.	Control group		Intervention group	
1	5 Pat.	4.9%	3 Pat	2.9%
2	11 Pat.	11.58%	7 Pat.	7.37%
3	11 Pat.	11.58%	7 Pat.	7.37%

Parallel to these findings, a comparison of the parameters "left atrial diameter" and "left ventricular ejection fraction" did not show a significant difference between the two groups (**Table 2**). Finally, there was no statistically significant difference between the groups with regard to the parameters "cardiopulmonary bypass" and "cross-clamping". In the group with atrial fibrillation, the cross-clamping times and cardiopulmonary bypass times tended to be longer.

Efficacy of PUFA in preventing postoperative atrial fibrillation: sequential testing method

For the calculation of the acceptance and rejection line, we used the formula depicted in the appendix. The two graphs (**Fig. 2** and **Fig. 3**) show the results of sequential testing of the original data of the study. After the 18th test, the procedure can be stopped with a probability of error of 0.01, because the acceptance line has been crossed (**Fig. 2**). In contrast, there is no effect in the placebo group (**Fig. 3**). And conversely, the protective effect of PUFA on the occurrence of postoperative AF can be proved by this test. Patients treated with PUFA developed AF significantly less often than patients in the control group (**Table 3**).

Compared to patients in sinus rhythm, there was a trend for patients who converted to atrial fibrillation to remain longer in the ICU (**Fig. 4**) and to have a longer total stay in hospital (**Fig. 5**). This was demonstrated by variance analysis.

Discussion

Experimental studies

A large number of experimental studies have shown an effect of polyunsaturated fatty acids (PUFA) on the myocardium, isolated myocardial cells [1] and ion channels [2] in the phospholipid bilayer [3]. These studies focused on the antiarrhythmic and anti-inflammatory [4,5] potential of PUFA. These effects are hypothesized to be the mechanism preventing perioperative atrial fibrillation.

Clinical studies

There are not only positive study results describing the potential of PUFA in preventing atrial fibrillation. A large randomized cohort study could not show this effect [6]. In this study the intake of PUFA was estimated by the intake of fish. Thus, a quantification of PUFA intake is lacking.

Antiarrhythmic effects of PUFA

In a prospective randomized blinded clinical study, the benefit of a PUFA-rich diet in patients after myocardial infarction was examined. The patients in the interventional group showed a significantly lower rate of morbidity, mortality and ventricular arrhythmias [7].

Two clinical trials showed a beneficial effect of a PUFA-enriched diet on mortality and sudden cardiac death [8,9]. Mozaffarian et al. demonstrated a reduction of atrial fibrillation after oral intake

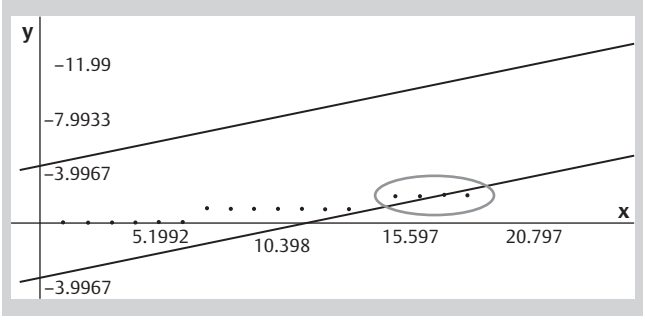

Fig. 2 This graph shows the results of the sequential testing method on the original data of the interventional group. After the 18th test, the procedure can be stopped with a probability of error of 0.01, since the acceptance line has been crossed.

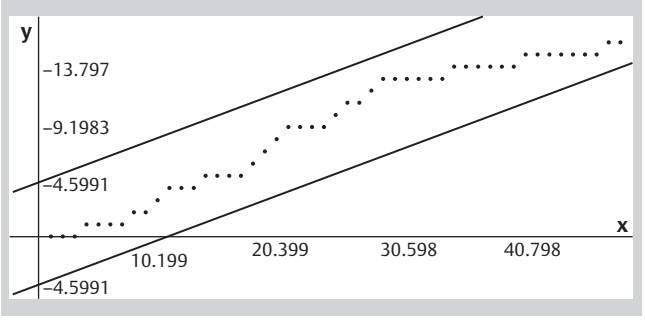

Fig. 3 This graph shows the results of the sequential testing method on the original data of the control group. There is no effect in the placebo group.

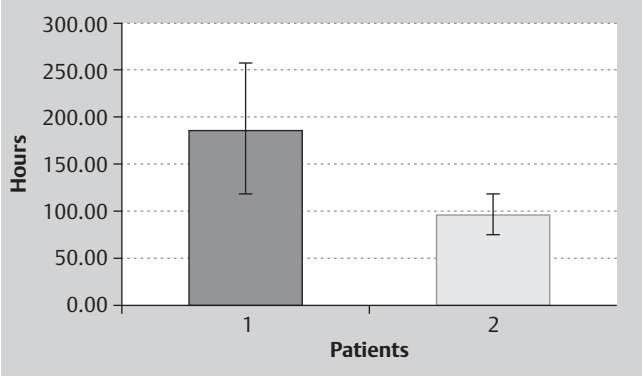

Fig. 4 Total time of stay in the ICU in hours: the gray bar represents the patients with atrial fibrillation; the white bar represents the patients in sinus rhythm.

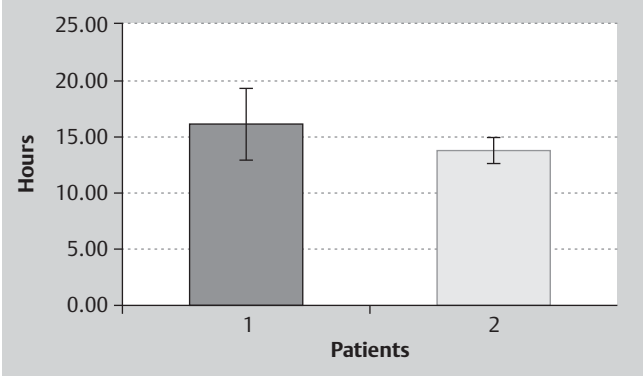

Fig. 5 Total time of stay in the hospital in days: the gray bar represents the patients with atrial fibrillation; the white bar represents those in sinus rhythm.

of omega-3-fatty acids and found similar positive results as we did [10].

Several population studies have shown a significantly positive correlation between fish consumption, plasma levels of PUFA, and the rate of serious coronary-related events [11–14]. There is only one study on the primary prevention of coronary heart disease using PUFA. This randomized, double-blinded clinical trial showed a significant reduction of myocardial infarction and unstable angina rates but no effect on the rate of SCD [15].

Some clinical trials report a beneficial effect of PUFA on chronic or acute inflammation [16–18]. A clinical study on inflammatory processes in atherosclerotic carotid plaques showed an enrichment of PUFA in the plaque core. In these patients, biomarkers of inflammation and expression of metalloproteinases were significantly reduced by PUFA [19]. The observed effects are very similar to those of statins. Thus, statins are also hypothesized to have a suppressive effect on ventricular and atrial arrhythmias [20].

Clinical recommendations concerning PUFA

Scientific statements published by the American Heart Association [21,22] recommend the prescription of 2–4 g polyunsaturated fatty acids (EPA und DHA) to lower elevated plasma triglyceride levels to a range under 200 mg/dl. There are several studies which have shown a beneficial effect of PUFA on elevated LDL-plasma levels [8,15,23].

Studies in postoperative AF

Calo et al. [24] published a prospective randomized clinical trial to investigate the effect of oral PUFA on the reduction of perioperative atrial fibrillation in patients undergoing CABG. The clinical end point was the postoperative occurrence of atrial fibrillation. The secondary end point was the total length of stay in the hospital after CABG. Statistical evaluation was performed by intention-to-treat analysis. The demographic data were similar in the control and the intervention group. There was a significant reduction of perioperative atrial fibrillation in the intervention group. The number needed to treat was 5.5 in this study. There was no difference between the groups with regard to morbidity and mortality. This study showed that oral PUFA reduce the length of stay in the hospital to a range similar to that of patients without atrial fibrillation.

The results of Calo's study are essentially congruent with those found in our analysis. However, there is an important difference between these two studies. In the study of Calo, PUFA were administered orally. There were no tests on the bioavailability or plasma levels. To exclude the problem of fluctuating plasma levels of PUFA, we decided to administer PUFA intravenously. The PUFA dosage was adapted to the patient's body weight as described above.

Discussion of statistical methods

Our study was planned as an intention-to-treat analysis. For simple statistical tests, the inclusion of more than 400 patients would have been necessary. The statistical calculations were more difficult due to the lower number of patients enrolled. Many concomitant parameters were documented but were unusable for the calculation of clinical predictors. The statistical methods of our data analysis have been validated. Thus, our results are directly comparable to those derived from other trials. Additionally, to a great extent, our results are congruent with the findings of substantially comparable clinical trials.

Conclusions

The results yielded from our study data have a high clinical relevance. Perioperative atrial fibrillation not only causes life-threatening complications but is also responsible for excessive costs in the clinical treatment of CABG patients. Due to the proven beneficial effect on perioperative atrial fibrillation, PUFA are recommended for the perioperative therapy of patients undergoing CABG. Our results suggest that further investigations should follow, which would include more patients. Thus, subgroup analysis would be available, aiding calculations of clinical predictors. Intravenous administration is advisable, to prevent the problem of fluctuating bioavailability.

Statement of responsibility

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

Appendix

The coefficients for the acceptance and rejection lines (a_1, a_2 and b) are calculated using the following equations:

$$b = \frac{\lg\frac{1-p(0)}{1-p(1)}}{\lg\left(\frac{1-p(0)}{1-p(1)}\right)\cdot\lg\left(\frac{p(1)}{p(0)}\right)} \quad (1)$$

$$a_1 = \frac{\lg\left(\frac{1-\beta}{\alpha}\right)}{\lg\left(\frac{1-p(0)}{1-p(1)}\right)+\lg\left(\frac{p(1)}{p(0)}\right)} \quad (2)$$

$$a_2 = \frac{\lg\left(\frac{\beta}{1-\alpha}\right)}{\lg\left(\frac{1-p(0)}{1-p(1)}\right)+\lg\left(\frac{p(1)}{p(0)}\right)} \quad (3)$$

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Conflict of Interest

None

Statement of responsibility

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

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