JAFIB
Original Research
Journal of Atrial Fibrillation
JAFIB Journal of Atrial Fibrillation Volume 1, Number 4 Dec 2008
www. jafib.com

Leukocyte-Aprotinin Atrial Fibrillation Study (LAFFS): Impact of Aprotinin and Leukofiltration on Atrial Fibrillation, Renal Insufficiency and Encephalopathy Post-Cardiopulmonary Bypass

Albert H. O-Yurvati, Steven Rodriguez, Glen Bell,Damon Kennedy, Robert T. Mallet

Departments of Surgery and Integrative Physiology, University of North Texas Health Science Center,3500 Camp Bowie Boulevard,Fort Worth,Texas 76107-2699, USA.

Abstract

Purpose: Atrial fibrillation remains the leading postoperative complication following cardiopulmonary bypass. A randomized trial was undertaken to evaluate the effectiveness of leukocyte filtration and aprotinin, applied separately and in combination, on the incidence of post-operative atrial fibrillation. A secondary component of the study was the impact of these adjunct interventions on post-surgical renal and neurological dysfunction.

Methods: A total of 1,220 patients undergoing primary isolated coronary artery bypass grafting were randomly assigned to one of four treatment groups. The control group (305 patients) received standard cardiopulmonary bypass with moderately hypothermic (34ºC) cardioplegic arrest. In the filtration group (310 patients) leukocyte reducing filters were incorporated into the bypass circuit and deployed strategically. The aprotinin group (285 patients) received full Hammersmith dose aprotinin. The combination therapy group (320 patients) received both aprotinin and leukocyte filtration.

Results: The incidences of atrial fibrillation were 25% in the control group, 16% in the filtration group, 19% in the aprotinin group and 10% in the combination therapy group ($P < 0.001$). Renal dysfunction was detected in 3% of the control group, 2% of the filtration group, 8% of the aprotinin group, and 5% of the combination group ($P < 0.005$). Neurological dysfunction occurred in 2% of the control group, 2% of the filtration group, 1% of the aprotinin group, and 2% of the combination group (P = n.s.).

Conclusions:Combination therapy with aprotinin and leukocyte filtration markedly reduced atrial fibrillation post-cardiopulmonary bypass, and was more effective than the individual treatments. Aprotinin treatment increased the incidence of renal dysfunction, and the addition of leukocyte filtration partially mitigated this detrimental effect of aprotinin. Thus, strategic leukocyte filtration augments aprotinin's anti-arrhythmic effects while suppressing its nephrotoxic sequelae.
Key words: aprotinin, atrial fibrillation, cardiopulmonary bypass, encephalopathy, leukofiltration, renal failure

Corresponding Address :Albert H. O-Yurvati DO, FACOS, FICS, FAHA,Department of Surgery,University of North Texas Health Science Center,3500 Camp Bowie Boulevard,Fort Worth,Texas 76107-2699 USA.

Introduction

Atrial fibrillation ranks among the most frequent and potentially deleterious complications associated with cardiopulmonary bypass. This arrhythmia has been reported in up to 50% of cases, and its incidence remains high despite advances in surgical and anesthetic techniques.[12] The arrhythmia occurs approximately 48-72 hours after surgery and can be manifested by persistent tachycardia, hypotension, and in many cases cardiac failure and cerebrovascular events.[3] Different strategies have been advocated to prevent atrial fibrillation. Pharmacological agents such as anti-arrhythmics have been used in some studies with variable results.[4]Another approach is the use of leukocyte filters,[5] as there seems to be a connection between atrial fibrillation and inflammation.[6,7] Indeed, systemic inflammation can elicit atrial fibrillation by activating the complement system and stimulating release of activated cytokines.[8,9]

To minimize the incidence of atrial fibrillation, we advocate therapy combining a pharmacological strategy, in which the serine protease inhibitor aprotinin is included in the cardioplegia, with a mechanical approach involving the placement at multiple positions within the bypass circuit of filters to selectively remove activated leukocytes.[10,11] In a recent, randomized trial, this type of combination therapy produced a marked, 67% decrease in atrial fibrillation.[12]

In addition to atrial fibrillation, renal and neurological dysfunction rank among the leading comorbidities of cardiopulmonary bypass surgery. Cardiopulmonary bypass causes numerous complex and interactive deleterious effects to the kidney, including inflammatory injury to the organ inflicted by activated neutrophils.[13] Cardiopulmonary bypass also may induce neurological encephalopathy;[14] however, the precise mechanisms of encephalopathy are poorly understood,[15] and its reported incidence is variable, criteria-dependent and subject to clinical judgement.[16]

This study was undertaken to evaluate pharmacological (aprotinin) and mechanical (leukocyte filtration) anti-inflammatory measures, applied singly or in combination during cardiopulmonary bypass, as strategies to minimize the occurrence of atrial fibrillation, renal dysfunction and neurological impairment following coronary artery bypass grafting (CABG) on cardiopulmonary bypass.

Methods

This study was approved by the Institutional Review Board at the University of North Texas Health Science Center, and included two of the major teaching hospitals associated with the Science The study was constructed as a randomized comparative trial and was designated the Leukocyte-Aprotinin Atrial Fibrillation Study (LAAFS). Only patients undergoing primary CABG were included; all patients undergoing re-do or adjunct procedures, including valve repair/replacement, were excluded. Echocardiograms were performed on all patients to measure pre-operative ejection fraction.

Surgical Preparation and Cardiopulmonary bypass Procedure

All patients were intravenously pre-medicated with 0.7 mg/kg of ranitidine, 2-4 mg/kg of glycopyrrolate, 0.7 mg/kg of diphenhydramine, and 20-40 mg/kg of midazolam. Monitoring catheters were placed in all patients including a radial arterial catheter, a central venous jugular introducer with a continuous cardiac output pulmonary artery catheter (Abbott Laboratories, Abbott Park, IL), and one or two large bore peripheral intravenous cannulae. General anesthesia was induced by 1-2 mg/kg of propofol, 0.7-2.0 mg/kg of sufentanil, and 0.1 mg/kg of vercuronium. After endotracheal intubation, anesthesia was maintained with sevoflurane on supplemental O2. Additional narcotic and relaxants were administered to maintain sedation throughout the surgery.

Patients were systemically heparinized to effect an ACT of > 700 s and were given protamine sulfate to restore clotting after separation from bypass. All patients had direct ascending aorta and right atrial cannulation and were maintained on moderately hypothermic (34 C) cardiopulmonary bypass. Cold blood-crystalloid potassium based cardioplegia (4 vol. blood:1 vol. crystalloid solution) was administered to produce cardiac arrest. Initial induction of cardiac arrest was accomplished by administering 500 ml cardioplegia antegrade via the aortic root, followed by retrograde infusion of an additional

500 ml via the coronary sinus at a pressure of 45 mmHg. Supplemental cardioplegia was administered through the vein grafts at a pressure of 14 mmHg, for 2 min per infusion, after completion of each distal anastomosis.

Treatment groups

From January 2004 - March 2006, a total of 1,220 patients undergoing isolated coronary artery revascularization were enrolled and assigned by a sealed envelope approach to one of the four treatment groups described below. There were no statistically significant differences between the groups regarding demographics, co-morbid conditions, pre-operative laboratory data,durations of cardiopulmonary bypass and cross clamp, or number of grafts completed (Table 1).

Control Group

(n = 305): Standard cardiopulmonary bypass was instituted as described above and cold potassium based cardioplegia was utilized for arrest.

Leukocyte Filtration Group

(n = 310): These patients received standard cardioplegia as in the control group; in addition, leukocyte depleting filters were incorporated into the bypass circuit, including a Pall LGB and a BC1B filter (Pall Biomedical Products, East Hills, NY, USA). The circuit prime and configuration are described in a previous report.[11] These patients were strategically leukodepleted by use of filtration instituted 30 min before crossclamp release, and all arterial, cardioplegia and cell saver blood was leukocyte filtered.

Aprotinin Group

(n = 285): This group received standard cardiopulmonary bypass with cold potassium based cardioplegia, and a standard extracorporeal circuit was employed. In addition, full Hammersmith, regimen A dosing of aprotinin (Bayer Pharmaceuticals,West Haven,CT, USA) was utilized.[12] After a test dose the pump was primed with 200 ml of aprotinin-fortified priming solution, then aprotinin solution was infused at 50 ml/h.

Combination Group

(n = 320): This group received the combination of aprotinin and total leukocyte filtration.

Evaluation of Brain, renal and Electrocardiographic Function

All subjects had pre-operative echocardiography

Table 1 Patient Demographics

	CONTROL	LEUKO-FILTER	APROTININ	COMBINATION	
N	305	285	310	320	ns
Mean age (years)	64	62	64	66	ns
Males	82	80	76	85	ns
Females	18	20	24	15	ns
Mean Wt. (kg)	83	83	81	84	ns
Diabetes	31	35	32	38	ns
COPD	60	58	61	61	ns
Pre-op	1.15	1.16	1.20	1.18	ns
Cr.(md/dl) LVEF (%)	40%	37	39	42	ns
(Mean CPB min)	100	110	104	106	ns
Mean X Clamp (min)	56	59	57	59	ns
Mean #grafts	2.9	3.0	3.0	3.0	ns

ns: No statistically significant differences were detected between the treatment groups.

and carotid duplex scanning. Patients exhibiting post-operative encephalopathy,defined as post-operative confusion, agitation or delirium within 24 h after bypass,[17] or frank stroke were evaluated by a neurologist and underwent cerebral CT scanning. Post-operative renal function was categorized by peak post-surgical serum creatinine concentration according to National Kidney Foundation guidelines [normal: creatinine < 1.6 mg/dl; renal dysfunction: creatinine 1.6-2.5 mg/dl; acute renal failure: creatinine > 2.5 mg/dl].[18] All patients exhibiting renal dysfunction or frank renal failure were evaluated by a nephrologist, who determined the need for hemodialysis. All patients had continuous ECG monitoring throughout the hospital stay. Arrhythmias were detected by Hewlett-Packard 78220 arrhythmia monitoring system (Hewlett-Packard, Palo Alto CA, USA) and validated by the cardiology service.>

Statistical Analysis

Values for continuous variables, e.g. ejection fraction or serum creatinine, are expressed as mean ± standard deviation. Between-group comparisons of these variables were accomplished by single-factor analyses of variance (ANOVA), with treatment as the factor. None of these ANOVAs revealed statistically significant differences, so post-hoc tests to identify specific differences were not employed. Incidences of discrete events among the treatment groups were compared by chi-square tests.[19] Yates correction for continuity was applied to chi-square comparisons of two groups.[19] P values < 0.05 were taken to indicate statistically significant treatment effects.

Results

Table 1 summarizes the demographic characteristics of the four treatment groups. Age, gender, and body mass were typical for patients requiring CABG. Occurrences of comorbidities, including diabetes mellitus and hypertension, were also as expected. There were no statistically significant

Figure 1: Impact of aprotinin and leukocyte filtration, applied separately and in combination, on incidence of atrial fibrillation after cardiopulmonary bypass surgery

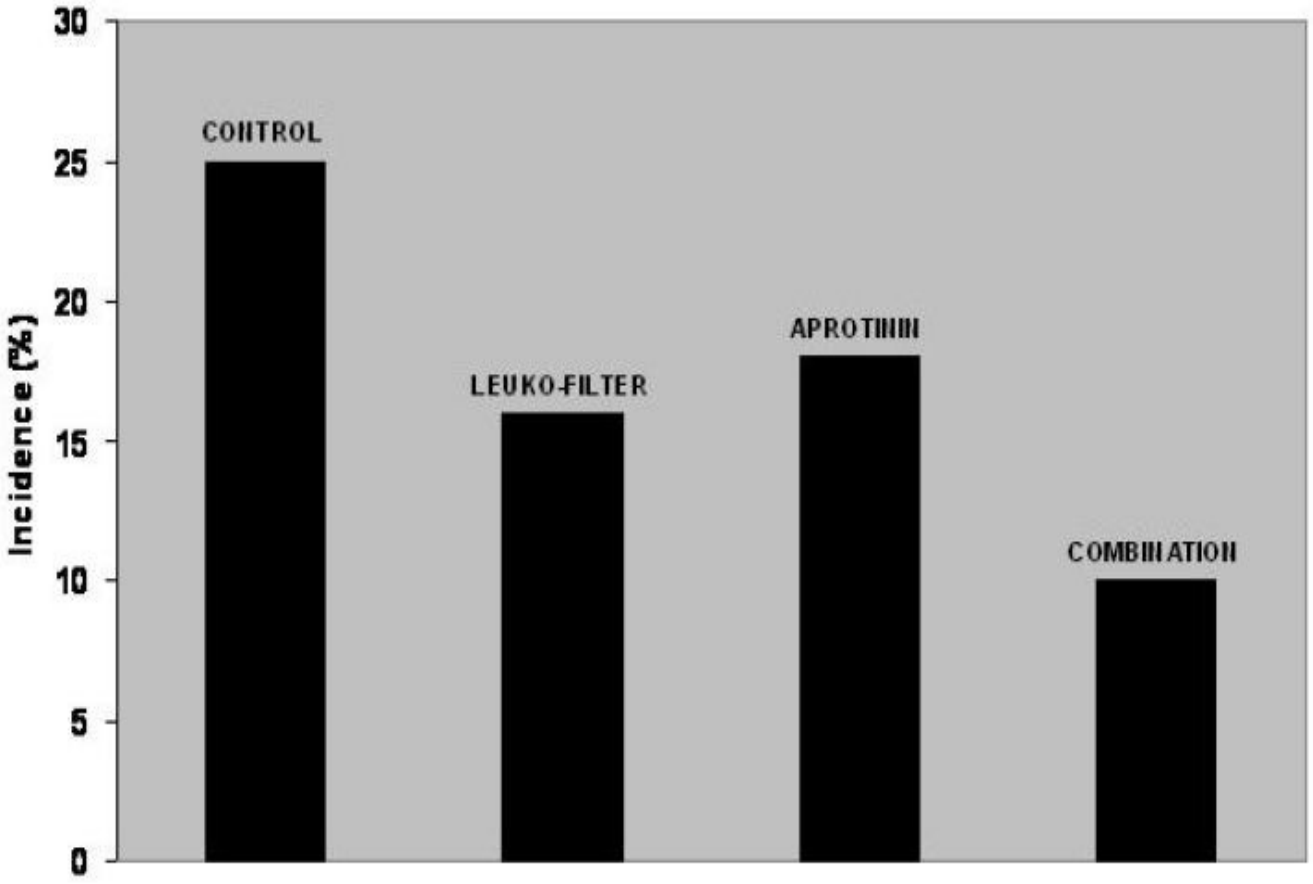
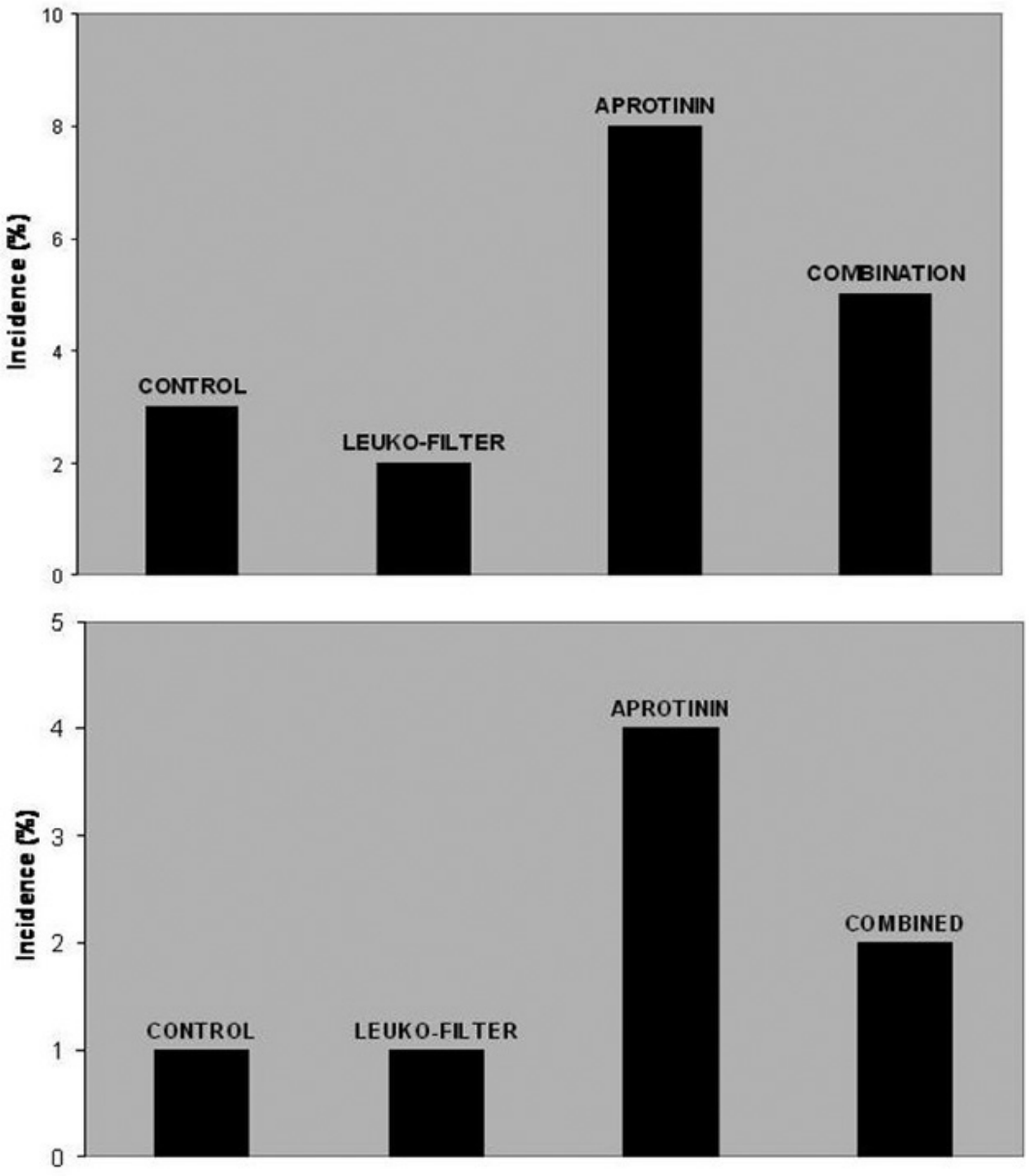


Figure 2: Incidence of post-surgical renal insufficiency (panel A) and acute renal failure requiring hemodialysis (panel B)



differences among the treatment groups for any of these characteristics. Moreover, operative cardiopulmonary bypass and cross clamp times, and number of grafts did not differ among the groups.

Atrial fibrillation (Figure 1) occurred in 76 (25%) of the 305 control patients, 49 (16%) of the 310 leukocyte filtered patients, 55 (19%) of the 285 aprotinin patients and 32 (10%) of the 320 combined treatment patients ($P < 0.001$). Leukofiltration ($P < 0.01$) and the leukofiltration:aprotinin combination ($P < 0.001$) lowered incidence of atrial fibrillation vs. control. The combination treatment also decreased atrial fibrillation incidence vs. aprotinin ($P < 0.005$) and leukofiltration ($P < 0.05$) alone.

line-height:200%'>The combination group and, especially, the aprotinin group had higher incidences of renal insufficiency (Figure 2A) and renal failure requiring hemodialysis (Figure 2B). Renal insufficiency occurred in 9 (3%) of control patients, 6 (2%) of leukocyte filtration patients, 22 (8%) of the aprotinin group, and 16 (5%) of the combination group ($P < 0.005$). Acute renal failure requiring hemodialysis (Figure 2B) was observed in 1 control patient, 3 leukocyte filtered patients,

11 aprotinin patients and 6 combined therapy patients ($P < 0.01$). Aprotinin increased incidences of renal insufficiency ($P < 0.02$) and acute renal failure ($P < 0.01$) vs. the respective control rates. These detrimental effects of aprotinin were partially, albeit not significantly ($P \sim 0.10$) mitigated by additional leukocyte filtration.

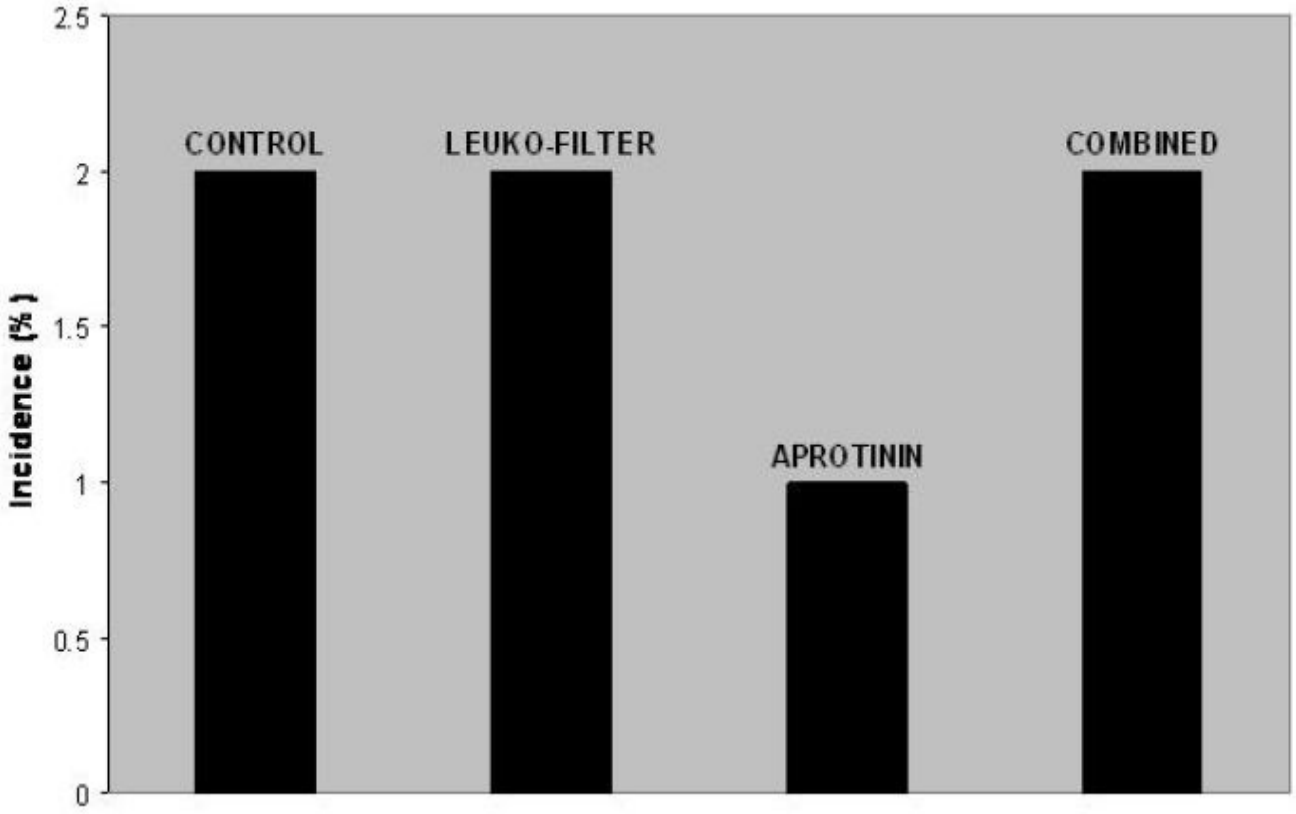
Encephalopathy (Figure 3) was documented in 6 (2%) of the control patients, 6 (2%) of the leukocyte filtered patients, 3 (1%) of the aprotinin patients and 6 (2%) of the combined therapy patients (P = n.s.). Acute cerebral vascular events evidenced by focal neurological signs and CT findings were not detected in the leukocyte filtered and aprotinin groups. Three (1%) of the control patients and one (0.3%) combined treatment patient had neurologically significant findings.

Discussion

Atrial fibrillation remains a very common complication post cardiopulmonary bypass with a reported incidence of 25-60%.[1,20] Peak incidence of the arrhythmia occurs between 48-72 post bypass.[21] In a retrospective review of off-pump CABG patients, Edgerton et al.[22] reported an atrial fibrillation incidence between 10.6 and 18.5%, with the lower atrial fibrillation rate occurring in patients who were extubated immediately in the operating room.

Previously we reported incidence of atrial fibrillation in patients undergoing isolated elective CABG.[11] We also observed a tendency of atrial fibrillation to occur within 48-72 hours after surgery. This non-blinded, randomized study enrolled 120 patients (55 control, 65 treatment), with the treatment arm receiving strategic total leukocyte filtration and full Hammersmith dose of aprotinin. The atrial fibrillation rate was lowered from 27% in the control group to 7.6% in the aprotinin group, a reduction of 72%.[11] A follow-up study compared rates of atrial fibrillation in on-pump vs. off-pump procedures.[12] In that study the incidence of atrial fibrillation in the on-pump leukocyte filtered-aprotinin group was 7.8% compared to 23.3% in the non-treatment group. In the off-pump cohort of 90 patients, atrial fibrillation rate was 17.8%.[12]

Figure 3: Incidence of encephalopathy post-cardiopulmonary bypass



The current LAFFS trial also demonstrated a reduction in atrial fibrillation by the combination of aprotinin and leukocyte filtration. Atrial fibrillation occurred in 10% of the combination treatment group, as compared to 25% in the control group. The combined application of aprotinin and leukocyte filtration appears to produce a synergistic anti-inflammatory effect in the clinical setting, by impacting both complimentary and distinct pathways of the inflammatory cascade.[23] Indeed, Lamm et al [24] reported a strong correlation between elevated post-operative white blood cell counts and atrial fibrillation. In their study of 253 patients, consisting of both primary CABG and valve cases, the atrial fibrillation rate was 39.1%.[24] Collectively, these results are concordant with the concept that reduction in activated neutrophils either by mechanical (filtration) or pharmacologic (aprotinin) means, could directly impact the development of atrial fibrillation post cardiopulmonary bypass.

In the present study, the aprotinin group experienced increased incidence of renal insufficiency and acute renal failure requiring hemodialysis. Interestingly, the leukocyte-filtered group was observed to have a slightly reduced incidence (2%) of renal insufficiency and acute renal failure vs. respective control values, although these trends did not reach statistical significance. Mangano et al.,[25] utilizing a propensity-adjusted, multivariate logistic regression analysis of an observational study of 4,474 patients, found a 5.5% vs. 1.8% ($P < 0.001$) incidence of renal dysfunction in aprotinin-treated vs. untreated patients, an apparent tripling of the risk of renal failure requiring dialysis.[20] In contrast, the Bayer pharmaceutical aprotinin package insert from a pooled data base of 2,003 aprotinin and 1,084 control patients reported a 1% incidence of acute renal failure in the aprotinin treatment arm and 0.6% in the placebo arm.[26] A meta-analysis by Sedrakyan et al.[27] showed that the risk ratio of developing renal failure from aprotinin was 1.01 (95% CI 0.55-1.83) vs. placebo. Sedrakyan et al.'s analysis examined studies drawn from MEDLINE, EMBASE and PHARMLINE from 1988-2001, and included data from 35 CABG trials.[27]

Cardiopulmonary bypass has also been associated with a spectrum of neurological impairments[14,15] from transient encephalopathy to frank stroke (CVA).[28] In a retrospective analysis of 1,524 patients undergoing CABG, Frumento et al.[29] reported a reduced incidence of cerebral events in aprotinin-treated patients. The study consisted of control, half-dose and full dose aprotinin groups. The overall incidence of CVA was 16% in the control versus 0% in the full dose aprotinin group; interestingly, the half-dose cohort had a CVA incidence of 22%.[29] There were no acute strokes in either the filtration or aprotinin group, and the incidence of encephalopathy did not differ significantly among the groups.

Limitations

A limitation to the LAFFS study may be a bias in patient selection as only isolated primary CABG subjects were enrolled, as well as a lack of risk-stratification. Nevertheless, the reduction in atrial fibrillation with leukocyte filtration and or aprotinin is striking. In comparison Gunaydin et al. also found a reduction in post-operative atrial fibrillation in patients who had leukocyte filtration.[30] In their study patients were assigned to three distinct groups based on Euroscore risk stratification: low risk Euroscore 0-2, medium risk Euroscore 3-5, high risk Euroscore 6+. These groups were further subdivided to conventional, non-filtered extracorporeal circuit (control), phosphorylcholine inert surface coated circuit, or leukocyte filtered. Leukocyte filtration lowered incidence of atrial fibrillation in the medium and high Euroscore groups. The non-coated, non-filter group medium to high risk Euroscore had a 13% incidence of atrial fibrillation versus the leukodepleted medium to high risk Euroscore group, which had a 3% incidence of atrial fibrillation ($p<0.05$).[30]

A second limitation of this trial is that other pre-existing factors that could possibly affect the incidence of post-operative atrial fibrillation, including hypertension, valve disease, hyperlipidemia, pre-operative atrial fibrillation, medications or nutraceuticals, were not recorded. However, the size and randomized design of the trial make it likely that these factors were evenly distributed among the four groups and therefore were not independent contributors to the different outcomes. In addition, post-operative factors, in-

cluding post-pericardiotomy syndrome and the use of anti-inflammatory agents, were not documented.

Summary

Leukocyte filtration and aprotinin were both effective in reducing the incidence of atrial fibrillation after cardiopulmonary bypass surgery for coronary revascularization. The synergistic combination of both treatment modalities was the most effective. However, aprotinin treatment was associated with increased post-surgical incidence of renal insufficiency and acute renal failure. The addition of leukocyte filtration lessened the incidence of renal dysfunction in aprotinin-treated patients. There are two important components to leukocyte filtration: leukocyte filters must be deployed strategically (30 minutes prior to cross-clamp release), and total leukocyte filtration must also be employed. Further research is necessary to define the mechanisms and pathophysiology involved in the generation of atrial fibrillation post-cardiopulmonary bypass, and to develop newer molecular strategies to address this major complication of cardiopulmonary bypass surgery. With the recent withdrawal of aprotinin from the U.S. market, implementation and refinement of strategic leukocyte filtration, including the use of novel absorptive materials and carbon-based nanotechnology, seem warranted.

Acknowledgements

Funding for this work was provided by research grant no. 02-18-522 from the Osteopathic Heritage Foundation.

References

1.Kleine P, Dzemali O, Moritz A. Internal cardioversion for treatment of postoperative atrial fibrillation. Surg Technol Int 2003; 11:197-201

2.Rodrigo R, Cereceda M, Castillo R, Asenjo R, Zamorano J, Araya J, Castillo-Koch R, Espinoza J, Larrain E.Prevention of atrial fibrillation following cardiac surgery: basis for a novel therapeutic strategy based on non-hypoxic myocardial preconditioning. Pharmacol Therapeut 2008; 118:104-127.PubMed

3.Ommen SR,Odell JA, Stanton MS.Atrial arrhythmias after cardiothoracic surgery. N Engl J Med 1997; 336:1429-1434.CrossRef PubMed

4.Bradley D, Creswell LL, Hogue CW Jr., Epstein AE, Prystowsky EN, Daoud EG. Pharmacologic prophylaxis: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest 2005; 128 (suppl):39S-47S.CrossRef PubMed

5.Sutton SW, Patel AN, Chase VA, Schmidt LA, Hunley EK, Yancey LW, Hebeler RF, Cheung EH, Henry AC 3rd, Meyers TP, Wood RE. Clinical benefits of continuous leukocyte filtration during cardiopulmonary bypass in patients undergoing valvular repair or replacement. Perfusion 2005; 20:21-29.CrossRef PubMed

6.ML, Mathew JP, Rinder HM, Zelterman D, Smith BR, Rinder CS; Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Atrial fibrillation after cardiac surgery/cardiopulmonary bypass is associated with monocyte activation. Anesth Analg 2005; 101:17-23.PubMed

7.Canbaz S, Erbas H, Huseyin S, Duran E. The role of inflammation in atrial fibrillation following open heart surgery. J Int Med Res 2008; 36:1070-1076

8.Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM, Wildevuur CR, Eijsman L, Trouwborst A, Hack CE. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 1997; 96:3542-3548

9.Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, Bauer JA, Tchou PJ, Niebauer MJ, Natale A, Van Wagoner DR. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001; 104:2886-2891.CrossRef PubMed

10.Matheis G, Simon A, Scholz M. Strategic leukocyte filtration: clinical and experimental experience. In: Matheis G, Moritz A, Scholz M (eds): Leukocyte depletion in cardiac surgery and cardiology. Karger, 2002, pp. 101-108

11.Olivencia-Yurvati AH, Wallace WE, Wallace N, Dimitrijevich D, Knust J, Haas L, Raven PB. Intraoperative treatment strategy to reduce the incidence of postcardiopulmonary bypass atrial fibrillation. Perfusion 2002; 17:35-39.CrossRef PubMed

12.Olivencia-Yurvati AH, Wallace N, Ford S, Mallet RT. Leukocyte filtration and aprotinin: synergistic anti-inflammatory protection. Perfusion 2004; 19:S13-S19.PubMed

13.Utley J. Renal effects of cardiopulmonary bypass. In: Utley JR (ed.) Pathophysiology and techniques of cardiopulmonary bypass. Baltimore: Williams and Wilkins, 1982, pp. 40-54

14.Selnes OA, McKhann GM, Borowicz LM Jr., Grega MA. Cognitive and neurobehavioral dysfunction after cardiac bypass procedures. Neurol Clin 2006; 24:133-145.CrossRef PubMed

15.Selnes OA, McKhann GM. Neurocognitive complications after coronary artery bypass surgery. Ann Neurol 2005; 57:615-621.CrossRef PubMed

16.Furlan AJ, Breuer AC. Central nervous system complications of open heart surgery. Stroke 1984; 15:912-915

17.McKhann GM, Grega MA, Borowicz LM Jr., Bechamps M, Selnes OA, Baumgartner WA, Royall RM. Encephalopathy and stroke after coronary artery bypass grafting: incidence, consequences, and prediction. Arch Neurol 2002; 59:1422-1428.CrossRef PubMed

18.Chirumamilla AP, Wilson MF, Wilding GE, Chandrasekhar R, Ashraf H. Outcome of renal insufficiency patients undergoing coronary artery bypass graft surgery. Cardiology 2008; 111:23-29.CrossRef PubMed

19.Zar JH. Biostatistical Analysis (3[rd] Ed.).River, NJ: Prentice Hall, 1996

20.Olshansky B. Management of atrial fibrillation after coronary artery bypass graft. Am J Cardiol 1996; 78(suppl 8a):27-34. CrossRef PubMed

21.Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, Collins JJ Jr., Cohn LH, Burstin HR. Predictors of atrial fibrillation after coronary artery surgery: current trends and impact on hospital resources. Circulation 1996; 94:390-7
22.Edgerton JR, Herbert MA, Prince SL, Horswell JL, Michelson L, Magee MJ, Dewey TM, Edgerton ZJ, Mack MJ. Reduced atrial fibrillation in patients immediately extubated after off-pump coronary artery bypass grafting. Ann Thorac Surg 2006; 81:2121-7.CrossRef PubMed
23.Rubens FD, Mesana T. The inflammatory response to cardiopulmonary bypass: a therapeutic overview. Perfusion 2004; 19 (suppl 1):S5-S12.PubMed
24.Lamm G, Auer J, Weber T, Berent R, Ng C, Eber B. Postoperative white blood cell count predicts atrial fibrillation after cardiac surgery. J Cardiothorac Vasc Anesth 2006; 20:51-56.CrossRef PubMed
25.Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. New Engl J Med 2006; 354:353-365. CrossRef PubMed
26.Trasylol package insert. Bayer Pharmaceutical Corp.West Haven,CT,USA
27.Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. J Thorac Cardiovasc Surg 2004; 128:442-448.CrossRef PubMed
28.Barbut D, Grassineau D, Lis E, Heier L, Hartman GS, Isom OW. Posterior distribution of infarcts in strokes related to cardiac operations. Ann Thorac Surg 1998; 65:1656-1659.CrossRef PubMed
29.Frumento RJ, O'Malley C MN, Bennett-Guerrero E. Stroke after cardiac surgery: a retrospective analysis of the effect of aprotinin dosing regimens. Ann Thorac Surg 2003; 75:479-483.CrossRef PubMed
30.Gunaydin S, McCusker K, Vijay V, Sari T, Sargon MF, Onur MA, Kocakulak M, Gurpinar A, Tezcaner T, Zorlutuna Y. Clinical significance of strategic leukocyte filtration in different cohorts undergoing cardiac surgery. Filtration 2005; 1:95-106.