Allopurinol pretreatment improves postoperative recovery and reduces lipid peroxidation in patients undergoing coronary artery bypass grafting

In this prospective, randomized, double-blind, placebo-controlled study, the clinical, biochemical, and hemodynamic effects of xanthine oxidase inhibition in patients undergoing coronary artery bypass grafting were assessed. Allopurinol pretreatment significantly reduced the use of inotropic support after the operation (5 of 25 patients versus 13 of 25 patients, $p < 0.01$) and increased the rate of peripheral warming (11.4 ± 0.85 hours versus 14.4 ± 1 hours, $p < 0.02$). Twenty patients (9 in the allopurinol group and 11 in the placebo group) underwent invasive hemodynamic monitoring and intraoperative coronary sinus cannulation. The cardiac indexes of both groups were similar before the operation and for the first postoperative hour; thereafter, the cardiac index increased significantly in only the active treatment group ($F = 3.33$ and $df = 5,90$, $p < 0.004$). Products of lipid peroxidation (thiobarbituric acid reactive substances) increased significantly in only the placebo group, with increases being evident both in the systemic circulation (9.5 ± 3.2 nmol/gm albumin, $p < 0.007$, and 24 ± 5 nmol/gm albumin, $p < 0.001$, at 30 seconds and 2 minutes of reperfusion, respectively) and the coronary sinus (19.4 ± 5.8 nmol/gm albumin, $p < 0.004$, and 28 ± 4 nmol/gm albumin, $p < 0.001$, at 2 and 5 minutes of reperfusion, respectively). No significant difference was evident between the groups with respect to cardiac enzyme or vitamin E release. It is proposed that xanthine oxidase inhibition exerts its beneficial effects by reducing the level of free radical activity associated with reperfusion during coronary artery bypass grafting. (J THORAC CARDIOVASC SURG 1994;107:248-56)

J. G. Coghlan, MB, MRCPI,^a W. D. Flitter, PhD,^b S. M. Clutton, BSc,^b
R. Panda, MB, MS, MCh,^a R. Daly, MD,^a G. Wright, MB, LRCP, FFA,^a
C. D. Ilsley, MB, MRCP, FRACP,^a and T. F. Slater, PhD, FIBiol, FRCS,^{b†}
Middlesex and Uxbridge, England

I schemia/reperfusion injury during routine bypass grafting results in a measurable depression in early postoperative cardiac function (myocardial stunning) in up to 50% of patients.^{1,2} Myocardial stunning is widely held to

result from unchecked free radical activity³⁻⁷ and to be amenable to anti-free radical interventions.⁸⁻¹¹ Theoretically, therefore, almost half the patients undergoing bypass operations should benefit from the administration of free radical scavengers. However, studies have failed to demonstrate evidence of myocardial free radical production in patients undergoing bypass procedures^{12,13} and the administration of locally active anti-free radical agents to cardioplegic solutions during bypass has yielded disappointing clinical results.¹⁴⁻¹⁶

Several investigators have found evidence of increased systemic free radical activity during^{12,13,17} and after¹⁸ bypass operations and myocardial antioxidant defenses have been shown to be considerably impaired in this setting.^{14-16,19,20} It has therefore been proposed that circulating radical-generated toxins (e.g., cytotoxic aldehydes²¹) perfusing the myocardium during a period when

From the Department of Cardiology, Harefield Hospital, Harefield, Middlesex,^a and the Department of Biology and Biochemistry, Brunel University, Kingston Lane, Uxbridge, England.

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Address for reprints: J. G. Coghlan, MB, MRCP, Department of Cardiology, Harefield Hospital, Harefield, Middlesex UB9 6JY, England.

†Professor T. F. Slater died in April 1992.

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Table I. Preoperative characteristics

Characteristic	Allopurinol (n = 25)	Placebo (n = 25)	p Value
Angina*			
I	1	1	
II	5	3	
III	13	13	
IV	6	8	NS
Anginal mediation			
Nitrate	2	3	
β -blocker	11	12	
Calcium antagonist	12	10	NS
No. of diseased vessels			
One vessel	0	3	
Two vessels	1	0	
Three vessels	24	22	NS
Ejection fraction			
<40%	2	0	
<50%	2	5	
+50%	21	20	
Average% $\pm$ SEM	62 $\pm$ 2.5	63 $\pm$ 2.4	NS
Age (yr)			
34-49	4	5	
50-65	15	14	
+65	6	6	
Average $\pm$ SEM	57 $\pm$ 1.8	59 $\pm$ 1.9	NS
Female	3	5	NS
Diabetes	4	3	NS
Previous MI	9	8	NS

Continuous data are expressed as mean $\pm$ standard error of the mean. Categorical data are presented in toto. *Previous MI*, Myocardial infarction more than 6 months before operation; *SEM*, standard error of the mean.

*New York Heart Association classification.

antioxidant defenses are low produces myocardial oxidative stress and stunning.^{12, 17, 18} Although unproved, this theory provides a logical explanation for the limited clinical benefits associated with the use of direct free radical scavenging agents administered only during myocardial ischemia.

Allopurinol prophylaxis in patients undergoing coronary artery bypass graft (CABG) operation has, by contrast, yielded clinical^{22, 23} and biochemical benefits.²⁴ Inhibition of free radical activity has been proposed as the mechanism of action. Allopurinol is a poor direct scavenger of radical species²⁵ but produces almost complete inhibition of the superoxide-generating enzyme xanthine oxidase. Xanthine oxidase is virtually absent from the heart²⁶⁻²⁸; thus suppression of systemic production of radical species must be invoked. If, therefore, allopurinol prophylaxis acts through inhibition of radical activity, it should be possible to demonstrate a reduction in indexes of radical activity in the systemic or coronary circulations, or both, in patients undergoing bypass procedures.

In this study we assess the impact of allopurinol therapy on the clinical and hemodynamic recovery during the

Table II. Surgical details

Procedures	Allopurinol (n = 25)	Placebo (n = 25)	p Value
Total grafts			
1	0	3	
2	1	0	
3	9	5	
4	11	13	
5	3	4	
6	1	0	
Average	3.8	3.6	NS
Mammary grafts			
0	1	3	
1	23	21	
2	1	1	NS
Endarterectomy	1	1	
Aneurysectomy	1	0	
Surgeon			
No. 1	7	7	
No. 2	7	6	
No. 3	9	8	
No. 4	2	4	NS
Total ischemic time (min $\pm$ SEM)	48 $\pm$ 3.4	41 $\pm$ 4.4	NS
Total pump time (min $\pm$ SEM)	113 $\pm$ 5.2	120 $\pm$ 7.7	NS

Continuous data are presented as mean $\pm$ standard error of the mean, and categorical data are presented in toto. Left internal mammary arteries were routinely used. Free right mammary grafts were used in two patients. *SEM*, Standard error of the mean.

first postoperative day. In addition, we examine the effect on an index of free radical activity (lipid peroxidation) in both the systemic and coronary sinus blood during the first minutes of myocardial reperfusion in patients undergoing CABG operation.

Patients and methods

Patient population. We studied patients with stable or unstable angina undergoing their first CABG operation in whom full revascularization was expected and who had not previously experienced an episode of clinical cardiac failure. Ethical approval was provided by the Hillingdon Health Authority ethical committee, with the provision that invasive studies were performed only in patients with low risk operated on by consultant staff. Informed consent was obtained in each case, and invasive monitoring and coronary sinus cannulation were performed when written consent was obtained. Details of the patient population according to their randomization are given in Table I.

Randomization and blinding. Two tablets of allopurinol (300 mg) or an identical placebo were placed in identical containers and assigned numbers 1 through 50 according to a table of random numbers. Each consecutive patient was assigned the next available numbered container and identified thereafter by their hospital and study numbers. The code remained unbroken throughout the study and was broken only after all clinical and hemodynamic data had been collected and all biochemical analyses had been performed.

Table III. Clinical outcome

Parameter	Allopurinol (n = 25)	Placebo (n = 25)	p Value
Inotrope Rqd	5	13	<0.01
Ep/NEp	2	8	NA
Duration of support >24 hr	1	6	NA
Mean dopamine dose $\pm$ SEM (μ g/kg per minute)			
0-12 hr postoperative	2.1 $\pm$ 0.3	3.1 $\pm$ 0.6	<0.08
12-24 hr postoperative	2.0 $\pm$ 0.4	3.2 $\pm$ 0.7	<0.08
Mean nitrate dose $\pm$ SEM (mg/hr)			
0-12 hr postoperative	5.2 $\pm$ 0.8	5.2 $\pm$ 0.9	NS
12-24 hr postoperative	2.1 $\pm$ 0.7	2.8 $\pm$ 0.7	NS
Warming time (hr)*	11.4 $\pm$ 0.9	14.4 $\pm$ 1	<0.015
Arrhythmia	4	6	NA
Acidemia†	6	6	NS
Oliguria‡	8	7	NS
Ventilation (hr)	11.5(9.5-15.5)	14(11-20)	NS
ITU stay (hr)	21(18.5-41)	25(20.5-54.5)	NS
CNS	1	3	NA
MI	1	2	NA
Death	1	1	NA

Inotrope Rqd, Administration of inotropic agent for hypotension (see Patients and Methods section); *Ep/NEp*, epinephrine or norepinephrine support required; *NA*, not assessed because of insufficient data points; *SEM*, standard error of the mean; *ITU*, intensive therapy unit; *CNS*, postoperative confusional state; *MI*, intraoperative Q wave infarct.

*Hours after the operation for the peripheral temperature to reach 35° C.

†Base excess greater than 5 mmol.

‡Urine output averaging less than 160 ml in any 4-hour period or diuretic given.

Administration of study drug. Each patient received one tablet at 8 PM on the evening before the operation and one tablet with their premedication (1 hour before the operation).

Surgical technique. A standard cardiopulmonary bypass technique was used throughout the study. The same roller pump (Cobe Laboratories, Lakewood, Colo.) and membrane oxygenator (Maxima; Medtronic, Inc., Cardiopulmonary Division, Anaheim, Calif.) were used for all patients. The extracorporeal circuit was primed with Ringer's lactate solution 1.5 L and mannitol 100 ml. In 37 patients, myocardial preservation was effected with moderate hypothermia (30° to 32° C) and intermittent ischemic arrest (including all patients in whom invasive monitoring was performed); in 13 patients, cardioplegic arrest (28° C; 1 L of St. Thomas' Hospital solution II in Ringer's lactate solution), repeated every half hour. The perfusion pressure was maintained between 50 and 70 mm Hg during bypass by varying pump speed (2.2 to 2.4 cardiac index) and, where necessary, by the use of methoxamine (bolus 1 to 5 mg) or nitrate infusion. With intermittent arrest, the heart was defibrillated within 2 minutes of reperfusion in each case. In those patients who underwent cardioplegia, the heart was restarted electrically or spontaneously when core temperature exceeded 33° C. For each patient, the number of grafts placed, the duration of bypass, and the duration of crossclamping was noted.

Patient cannulation. For routine procedures each patient had a 20-gauge radial arterial line, and a 14-gauge venous line placed immediately before anesthesia was induced. Intubation and placement on an internal jugular line was performed after anesthesia. In addition, 20 patients had thermodilution Swan-

Table IV. Influence of cardioplegia on outcome

Parameter	Intermittent crossclamp (n = 37)	Cardioplegia (n = 13)	p Value
Total ischemic time (min)	37.6 $\pm$ 2.47	65.2 $\pm$ 4.9	<0.001
Initial postop temp (° C)	28.3 $\pm$ 0.32	29.1 $\pm$ 0.39	NS
Rewarming time (hr)	13.4 $\pm$ 0.9	11.4 $\pm$ 0.76	NS
Inotrope use	14/37	4/13	NS
Mean dopamine (μ g/kg per minute)*	2.7 $\pm$ 0.4	2.2 $\pm$ 0.6	NS
Mean GTN (mg/hr)*	5.0 $\pm$ 0.6	5.7 $\pm$ 1.5	NS

Continuous data are presented as mean $\pm$ standard error of the mean. *Initial postop temp*, Peripheral temperature on return to intensive care unit; *GTN*, glyceryl trinitrate.

*Dose administered over the first 12 postoperative hours.

Ganz catheters (Baxter Healthcare Corp., Edwards Division, Irvine, Calif.) placed through an 8.5F jugular sheath at this time. After routine aortic and right atrial cannulation but immediately before bypass, a 14F retrograde coronary sinus cannula (RC-014-MIBB; Research Medical Inc., Midvale, Utah) was inserted via the lower right atrium.

Sampling and analysis. Paired coronary sinus and arterial blood samples were taken after 5 to 10 minutes of bypass, and 30 seconds, 2, 5, and 10 minutes after the final period of reperfusion (when core temperature had been restored to 37° C). Thiobarbituric acid reactive substances (TBARS) were measured on plasma samples anticoagulated with potassium ethylenediaminetetraacetic acid with the technique described by Yagi.²⁹ Vitamin E was also measured on potassium ethylenediaminetetraacetic acid-anticoagulated plasma with the technique described by Burton, Webb, and Ingold.³⁰ Routine spectrophotometric analysis of serum by Sigma diagnostic kits (Sigma Chemical Co., St. Louis, Mo.) was performed to assess hydroxybutyrate dehydrogenase aspartate transaminase, albumin, and cholesterol.

Perioperative management. Glyceryl trinitrate was administered to all patients after the operation: a dose of 2 to 5 mg/hr was routine; higher doses of glyceryl trinitrate and, where necessary, sodium nitroprusside were given if the systolic blood pressure exceeded 120 mm Hg. Dopamine was administered routinely in a "renal" dose (2 to 5 μ g/kg per minute). Inotropic support was instituted if the systolic blood pressure remained less than 95 mm Hg despite adequate filling (central venous pressure 10 to 12 mm Hg). The inotrope of choice was dopamine, in doses between 5 and 15 μ g/kg per minute; adrenaline or, more rarely, noradrenaline was added if the response was inadequate.

Hemodynamic data. Central venous, mean pulmonary artery, pulmonary artery wedge, and mean arterial pressures, heart rate, and cardiac output (thermodilution) were determined before bypass and 30 minutes, 1, 4, 8, and 24 hours after the end of bypass. Pulmonary artery wedge pressure was kept between 8 and 17 mm Hg, and higher levels were attained by colloid administration where the cardiac index was less than 2.5 or the systolic blood pressure was below 95 mm Hg.

Clinical data. The performance of patients was assessed at intervals of 4 hours from the end of bypass for 24 hours. Further adverse events occurring during their hospitalization were

Fig. 1. Graph of cardiac index against time during the first postoperative day. Values on x axis are hours after bypass. C, Control recordings taken immediately before cannulation for bypass; †, at 4, 8, and 24 hours after bypass, the cardiac index in those patients who received allopurinol exceeded the prebypass cardiac index ($p < 0.001$) and the initial postbypass cardiac index after bypass ($p < 0.02$).

Table V. Early postoperative hemodynamic variables (n = 20, invasive monitoring)

Parameter	Rx	Pre	Hours after bypass				
			0.5	1	4	8	24
Q/m ² (L/min per square meter)	P	1.7 ± 0.07	2.7 ± 0.16*	2.5 ± 0.19	2.6 ± 0.18	2.6 ± 0.16	2.8 ± 0.12*
	A	1.7 ± 0.12	2.3 ± 0.15	2.4 ± 0.12*	3.2 ± 0.25†	3.1 ± 0.21†	3.3 ± 0.20†
LVSWI (gm/m ²)	P	20.8 ± 2.2	22.9 ± 1.5	23.5 ± 2.1	21.9 ± 2.2	20.7 ± 1.8	23.9 ± 1.7
	A	24.6 ± 1.9	21.8 ± 1.7	24.3 ± 2.1	26.4 ± 1.8	25.0 ± 1.7	31.3 ± 3.5
PCWP (mm Hg)	P	7.6 ± .92	10.7 ± 1.3*	10.9 ± 0.91*	10.5 ± 0.77	12.2 ± 0.66*	11.4 ± 0.85*
	A	7.6 ± 0.58	9.7 ± 0.77	11.1 ± 1.1*	10.6 ± 0.99	10.6 ± 0.48*	11.2 ± 1.2
Mean AP (mm Hg)	P	72.4 ± 3.2	72.4 ± 3.9	73.5 ± 4.0	70.4 ± 2.5	68.4 ± 2.3	72.8 ± 1.9
	A	82.7 ± 4.0	76.8 ± 3.5	79.0 ± 2.8	73.0 ± 2.8	70.6 ± 3.4	79.4 ± 5.1
Heart rate (beats/min)	P	72.2 ± 4.4	96.4 ± 7.4*	93.6 ± 8.3*	98.2 ± 5.3*	96.5 ± 5.4*	97.3 ± 4.4†
	A	71.2 ± 3.8	93.6 ± 8.0*	92.4 ± 6.7*	102 ± 5.2†	98.1 ± 4.2†	95.9 ± 5.4†

Data are mean ± standard error of the mean. Rx, Treatment group; Pre, prebypass (control) value; Q/m², cardiac index; P, placebo group; A, allopurinol group; LVSWI, left ventricular stroke work index; PCWP, pulmonary capillary pressure; Mean AP, mean arterial pressure.

*Significantly change from control value ($p < 0.01$).

†Significantly change from control value ($p < 0.001$).

documented from the case notes. Data obtained during the first 24 hours included the following: blood pressure, urine output, peripheral temperature, inotropic support, vasodilator administration, and acid base balance averaged for each 4-hour period. Adverse events included the following: arrhythmias, hemorrhage, reoperation, neurologic events, and myocardial infarction (evidenced by new Q waves). The duration of ventilation and stay in the intensive therapy unit was also noted.

Statistics. Data are presented as mean ± standard error of the mean (normal data) or median ± interquartile range (non-parametric data). Continuous, normally distributed data were analyzed by *t* testing (for single comparisons) or repeated measures analysis of variance (multiple comparisons) with a grouping factor where appropriate and standard tests for correlation. Continuous nonnormal data were analyzed with the Mann-Whitney U test, and categorical data were analyzed with a χ^2 test. Results were regarded as significant where $p < 0.05$ (sin-

gle-tailed analysis), and the Bonferonni correction was used where three or more data points were tested.

Results

The two patient groups did not differ significantly with respect to preoperative risk status (Table I) or operative conduct (Table II).

Clinical outcome. Two patients died during the study (one from each group): both had a low-output state that developed within hours of the operation for which no cause could be determined on reopening of the chest. Despite inotropic support and intraaortic balloon pumping, their low-output state continued and renal and subsequent hepatic failure developed. The patients

Fig. 2. Scatter graph illustrating the high degree of reproducibility of the TBArS assay. Note the considerable variation in control TBArS levels recorded during this study (44 to 320 nmol/gm albumin). Because two control levels were obtained from each patient (one arterial and one coronary sinus), the degree of intraindividual reproducibility was examined.

Fig. 3. Increase over control TBArS levels recorded in the coronary sinus according to treatment group (allopurinol or placebo) at each sampling time after crossclamp removal (mean $\pm$ standard error of the mean). Significant increases over baseline were recorded only in the placebo group. †, $p < 0.004$; *, $p < 0.001$.

died at 17 and 21 days after the operation. Table III details the clinical outcome after operation for both groups.

All patients received nitrates after the operation. The mean dosage over the first 12 hours (during rewarming) was almost identical: 5.17 ± 0.9 mg/hr in the placebo group and 5.24 ± 0.8 mg/hr in the allopurinol group. Only three patients (two in the allopurinol group) required sodium nitroprusside infusion to maintain systolic blood pressure below 120 mm Hg. The peripheral

temperature on return to the intensive care unit was similar in both groups $28.4 \pm 0.5^\circ\text{C}$ for the placebo group and $28.7 \pm 0.6^\circ\text{C}$ for the allopurinol group; $p = [\text{NS}]$. However, the mean rewarming time for the allopurinol group was less than that of the placebo group (Table III).

Table III shows that the mean dose of dopamine was marginally but not significantly higher in the placebo group. However, fewer patients who received allopurinol required inotropes (Pearson χ^2 test 5.6; $p < 0.01$, Table

III). Although more patients in the placebo group received adrenaline or noradrenaline infusions and required inotropic support for more than 24 hours after the operation, the small number of patients involved render statistical analysis unreliable. Although not significant, fewer patients with active treatment required pacing, had postoperative confusion, and spent less time in the intensive therapy unit.

Influence of cardioplegia. Table IV shows that the patients who underwent cardioplegia had significantly longer total ischemic times but were otherwise similar to the remainder of the group. Eight of the patients who underwent cardioplegia were randomized to the active treatment group versus five to the placebo group ($p = \text{NS}$). Excluding the patients protected with cardioplegia, the cumulative duration of crossclamping was slightly longer in the those patients who received allopurinol (40.7 ± 3.2 minutes versus 33.5 ± 3.5 minutes; $p = \text{NS}$). In the 37 patients protected with intermittent crossclamping, the mean time to rewarm was less in the allopurinol group (11.53 ± 1.2 hours versus 15 ± 1.3 hours; $t = 2.01$, $p < 0.03$) and inotrope usage was less frequent (4 of 17 patients versus 10 of 20 patients; Pearson χ^2 test 2.74, $p < 0.05$). None of the patients undergoing invasive hemodynamic assessment underwent cardioplegia.

Hemodynamic outcome. Indexes of cardiac function recorded after induction of anesthesia depended largely on the adequacy of anesthesia. Thus, low cardiac indexes before the operation were found in all patients, and no significant differences were found between the treatment groups. After the operation, the cardiac index was initially slightly higher in the placebo group but failed to increase significantly over the next 24 hours. By contrast, the cardiac index rose sharply between 30 minutes and 4 hours after the operation in the active treatment group ($F = 6.35$, $df = 8$; $p < 0.02$) and remained greater than 3 L/m^3 thereafter. Repeated measures analysis of variance confirmed that the increase in cardiac output in the active treatment group significantly exceeded that recorded in the placebo group ($F = 3.3$, $df = 5,90$; $p < 0.004$). The difference between the absolute cardiac indexes for the two groups approached significance at three individual time points: 4 hours ($p < 0.04$), 8 hours ($p < 0.04$), and 24 hours after bypass ($p = 0.015$, Fig. 1). The cardiac indexes of the treatment group significantly exceeded those of the placebo group from 4 hours after bypass ($F = 8.07$, $df = 1,18$; $p < 0.006$). No significant differences in preload, afterload, or heart rate between the groups was found at any time before or after the operation (Table V). Left ventricular stroke work index in the active treatment group significantly exceeded that of the

placebo group from 4 hours after the operation ($F = 5.48$, $df = 1,18$; $p < 0.016$).

Lipid peroxidation. The circulating levels of TBARS at baseline varied considerably among patients, ranging from 44 nmol/gm albumin to 320 nmol/gm albumin. The reproducibility of the test was excellent, and the comparison of the two baseline samples obtained from each patient (one arterial, one coronary sinus) gives an r value of 0.98 (Fig. 2).

Fig. 3 shows the change with time for TBARS in the coronary sinus for each group. In the placebo group, the coronary sinus TBARS concentration increased from a control value of 95 ± 24 nmol/gm albumin to 114 ± 26 nmol/gm albumin at 2 minutes ($+19 \pm 5.8$ nmol/gm albumin; $F = 11$, $p < 0.004$) and to 122 ± 26 nmol/gm albumin at 5 minutes reperfusion ($+28 \pm 4$ nmol/gm albumin; $F = 48$; $p < 0.001$). An increase over the control level of 98 ± 24 nmol/gm albumin in circulating TBARS was also found in the arterial circulation both at 30 seconds (108 ± 25 nmol/gm albumin representing a change of $+9.5 \pm 3.2$ nmol/gm albumin; $F = 8.73$; $p < 0.007$) and 2 minutes (122 ± 28 nmol/gm albumin, an increase of 24 ± 5 nmol/gm albumin; $F = 23.5$; $p < 0.001$) after crossclamp removal (Table VI). For the active treatment group, a much smaller (nonsignificant) increase in TBARS was observed again in both the coronary sinus and arterial blood. No significant arteriocoronary sinus difference was observed at any time in either group.

The net increase in products of peroxidation in the coronary sinus blood (expressed as area under the curve increase in TBARS concentration) was significantly less in those patients who received allopurinol (93.5 ± 40.2 nmol min/gm albumin) than in the placebo group (219.4 ± 40.2 nmol min/gm albumin, $t = -2.2$, $df = 18$; $p < 0.02$). A trend toward a greater net increase in circulating (arterial) products of peroxidation was also evident in the placebo group (179.5 ± 67.6 nmol min/gm albumin versus 83 ± 59 nmol min/gm albumin in the active group; $t = -1.1$, $df = 18$; $p < 0.15$).

Net TBARS release (area under the curve) was independent of control vitamin E levels, cardiac enzyme release (multivariate regression analysis), and duration of aortic crossclamping (Spearman's test) in both the placebo group alone and the whole group combined.

Vitamin E. A net myocardial loss of vitamin E was found 30 seconds after reperfusion in the placebo group ($-0.96 \pm 0.3 \mu\text{mol}/\text{mmol}$ cholesterol; $F = 9.9$, $df = 10$; $p < 0.01$). Table VI shows this net loss of vitamin E to come partly from a slight reduction of arterial vitamin E levels and partly from a slight increase in coronary sinus vitamin E levels. No significant differences were present

Table VI. Biochemical parameters (n = 20, invasive monitoring)

Parameter	Coronary sinus					Arterial				
	C	30	120	300	600	C	30	120	800	600
TBARS (nmol/gm albumin)										
Allopurinol	110	112	121	126	111	112	120	125	120	118
SEM	28	27	27	27	26	32	30	31	27	32
Placebo	95	98	114	122	118	98	108	122	120	108
SEM	24	21	26	26	34	24	25	28	34	30
Vitamin E (μ mol/mmol cholesterol)										
Allopurinol	5.2	5.2	5.2	5.0	5.3	5.1	5.1	4.9	4.9	5.2
SEM	0.4	0.4	0.4	0.3	0.2	0.3	0.3	0.4	0.2	0.4
Placebo	5.5	5.7	5.3	5.2	5.0	5.8	4.7	5.1	5.3	4.9
SEM	0.5	0.5	0.4	0.4	0.4	0.5	0.5	0.4	0.4	0.5
AST (U/L)										
Allopurinol	12	25	27	28	29	12	25	26	28	28
SEM	2	3	4	4	4	2	4	4	4	4
Placebo	9	22	22	23	25	9	22	23	24	26
SEM	1	2	3	3	4	1	3	3	3	4
HBD (U/L)										
Allopurinol	86	196	210	207	192	90	218	208	199	184
SEM	9	31	33	29	21	10	37	32	27	17
Placebo	93	206	206	209	230	101	209	203	228	236
SEM	11	22	25	24	36	13	23	24	33	35

A-CS, Arterio-coronary sinus difference; C, control sample obtained before aortic crossclamping; 30-600, seconds after final crossclamp; SEM, standard error of the mean; AST, aspartate transaminase; HBD, hydroxybutyrate dehydrogenase.

between the two treatment groups. Vitamin E loss by the myocardium (area under the curve) was independent of net cardiac enzyme release (multivariate regression analysis) and aortic crossclamp duration (Spearman's test) in the placebo group and in both treatment groups when combined.

Cardiac enzymes. Both aspartate transaminase and hydroxy butyrate dehydrogenase levels were significantly elevated with respect to the control level at each time point during reperfusion (Table VI). No further increase was documented during the first 10 minutes of reperfusion. The net release of cardiac enzymes is almost identical for both groups. Cardiac enzyme release did not correlate with vitamin E loss or duration of aortic crossclamping for the group as a whole or for either of the treatment groups when considered separately.

Discussion

The main findings of this study are that allopurinol pretreatment produces an improvement in early postoperative cardiac function and a reduction in perioperative lipid peroxidation. Only a small, nonsignificant reduction in the net myocardial loss of vitamin E occurred, and no reduction in early myocardial enzyme loss was found.

Allopurinol pretreatment of patients undergoing bypass procedures has previously been reported to reduce postoperative mortality,²² inotrope usage,^{22, 23} and the frequency of arrhythmias.²³ In two other trials, structur-

al³¹ and biochemical²⁴ evidence for reduced perioperative myocyte damage was found in patients receiving prophylactic allopurinol. The findings presented here—a significant reduction in inotrope usage and a greater improvement of hemodynamic performance over the first postoperative day—are consistent with the results of previous studies. The low dose of allopurinol used in this study and in two of the previously mentioned studies^{22, 31} almost certainly excludes direct free radical scavenging as the mechanism of benefit.²⁵

Preferential use of vasodilators in the active treatment group is one potential mechanism that might explain the greater cardiac output and more rapid rewarming observed in the allopurinol group. Table III shows that nitrate administration was almost identical in the two groups over the first 24 hours after operation. Furthermore, the left ventricular stroke work indexes were higher in the allopurinol group, and the cardiac indexes remained higher in the allopurinol group after full rewarming had been achieved in both groups. From these data, it is clear that improved hemodynamic performance gave rise to the more rapid increase in peripheral temperature and not the reverse.

In the study presented here, significant lipid peroxidation during myocardial reperfusion was found only in the placebo group. Pretreatment with allopurinol attenuated the increase in TBARS levels in arterial and coronary sinus blood. As in our previous study¹³ and in the study of Dav-

A-CS					
C	30	120	300	600	
2	8	5	-6	7	
6	5	4	4	9	
4	10	8	-2	-10	
2	5	4	10	6	
-0.1	-0.1	-0.4	-0.1	-0.1	
0.2	0.2	0.2	0.2	0.2	
0.2	-0.9	-0.2	-0.1	-0.1	
0.2	0.3	0.2	0.2	0.4	
0.4	-0.8	-0.4	-0.4	-0.6	
0.8	1.3	0.5	0.4	0.6	
-0.1	0	0.6	0.7	0.5	
0.5	0.6	0.4	0.6	2	
4	22	-2	-7	-8	
7	15	4	4	6	
9	3	-2	19	6	
4	3	4	12	29	

ies and associates,¹² systemic radical activity appears to dominate because TBARS levels rose more rapidly (30 seconds and 2 minutes, Table VI) in the arterial circulation and no net arteriocardiac sinus difference was found in either group at any time point. The net release of products of peroxidation was, however, significantly attenuated in the coronary sinus blood ($p < 0.02$) but not in the systemic circulation ($p < 0.15$) by the use of allopurinol.

A possible explanation for the data presented is that the effects of extracorporeal circulation and consequent hypoperfusion of organs such as the liver and the lung is the stimulus for lipid peroxidation. The enzyme xanthine dehydrogenase is degraded to xanthine oxidase in these hypoperfused organs and is the main source of free radical generation (thus explaining the reduction with allopurinol). During the minutes to hours after bypass, the heart is perfused with toxic radical by-products from the liver and lung, but levels of these toxins have been substantially reduced in the allopurinol group. It is known from several authors that the heart is especially vulnerable to oxidative attack in the phase early after bypass.^{14-16, 19, 20}

The early myocardial loss of vitamin E noted in our previous study¹³ has been confirmed in this study. Baseline vitamin E levels were not predictive of the highest rates of lipid peroxidation in this study, even when one considers the placebo group alone. Furthermore, aortic crossclamping times were not predictive of myocardial vitamin E loss. These latter findings are in contrast to our

previous results.¹³ One important difference between these two studies is that, in the previous study, all operations were performed by the same surgeon. For practical reasons, four different surgeons were involved in the present study. Variations in practice, handling of the heart, and, possibly most importantly, venting of the heart (routinely performed by two of the surgeons) may be obscuring such relationships.

It is evident that the group studied is far from homogeneous. Patients underwent operations performed by four different surgeons with the use of two methods of myocardial protection; patients also differed with respect to degree of myocardial impairment, number of diseased vessels, and the duration of ischemic insult. With respect to each of these potential sources of bias, data have been provided to show that their distribution between the treatment groups was entirely random and did not influence the outcome significantly.

In conclusion, low-dose allopurinol pretreatment significantly improves the recovery of myocardial function in the first postoperative day while reducing peroperative lipid peroxidation. It is proposed that the mechanism of action of allopurinol in this setting is inhibition of xanthine oxidase activity. The weight of available evidence suggests that lipid peroxidation during bypass arises predominantly from noncardiac sources.

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