Adenosine instead of supranormal potassium in cardioplegia: It is safe, efficient, and reduces the incidence of postoperative atrial fibrillation. A randomized clinical trial

Øyvind Jakobsen, MD, PhD, Torvind Næsheim, MD, Kathrine Nergård Aas, MD, Dag Sørli, MD, PhD, and Tor Steensrud, MD, PhD

Objective: We aimed to evaluate the efficacy and safety of a cold crystalloid cardioplegic solution with adenosine (1.2 mmol/L) instead of supranormal potassium.

Methods: Sixty low-risk patients scheduled for elective coronary artery bypass grafting (CABG) were randomized to receive standard cold crystalloid hyperkalemic cardioplegia (hyperkalemic group) or normokalemic cardioplegia in which supranormal potassium was replaced with 1.2 mmol/L adenosine (adenosine group). End points were postoperative release of troponin T and creatine kinase MB, hemodynamics measured by PiCCO arterial thermodilution catheters, perioperative release of markers of endothelial activation and injury, and clinical course.

Results: The adenosine group had a significantly shorter time to arrest than did the hyperkalemic group (mean $\pm$ standard deviation, 11 ± 5 vs 44 ± 18 seconds; $P < .001$). Three hearts in the adenosine group were probably not adequately drained and received additional hyperkalemic cardioplegia to maintain satisfactory cardioplegic arrest. There were no differences between groups with respect to perioperative release of markers of endothelial activation or injury and no differences between groups in postoperative release of troponin T or creatine kinase MB. Postoperative hemodynamics including cardiac index were similar between groups. The incidence of postoperative atrial fibrillation was significantly lower in the adenosine group than in the hyperkalemic group (4 vs 15; $P = .01$).

Conclusions: Adenosine instead of hyperkalemia in cold crystalloid cardioplegia is safe, gives more rapid cardiac arrest, and affords similar cardioprotection and maintenance of hemodynamic parameters, together with a marked reduction in the incidence of postoperative atrial fibrillation. (*J Thorac Cardiovasc Surg* 2013;145:812-8)

We^{1,2} have previously shown in experimental studies that replacement of potassium with adenosine in cold crystalloid cardioplegia resulted in improved postcardioplegic left ventricular systolic function and energetics, attenuated myocardial cell damage, and improved preservation of endothelial function through the endothelium-derived hyperpolarizing factor pathway. It has been shown in a clinical trial that administration of adenosine (0.25 mg/kg) just before administration of standard hyperkalemic cardioplegia during open-chest heart surgery gives faster

cardioplegic arrest, less release of creatine kinase MB isoenzyme (CK-MB) during the operation, and significantly better preservation of cardiac function in the first postoperative phase.³ Administration of adenosine immediately after aortic crossclamp release in valve surgery with standard hyperkalemic cardioplegia has also been shown to be related to reduced troponin I release, reduced inotropic drug use, and shorter intensive care unit (ICU) stay.⁴ Both phase I and phase II studies have been performed with low doses of adenosine (up to 0.1 mmol/L) as an adjunct to hyperkalemic blood cardioplegia showing that adenosine could be safely administered during cardiopulmonary bypass (CPB). However, in these studies there was no proof of improved cardioprotection.^{5,6} Others have shown that higher doses of adenosine (2 mmol/L) as an adjunct to hyperkalemic blood cardioplegia was well tolerated and improved cardioprotection as revealed by less myocardial ischemia and a trend to less use of inotropic drugs.⁷ In pediatric cardiac surgery the combination of lidocaine and adenosine in moderate potassium (10 mmol/L) cardioplegia was superior regarding postoperative pulse pressure and release of troponin I compared with hyperkalemic cardioplegia and with hyperkalemic (20 mmol/L)

From the Department of Cardiothoracic and Vascular Surgery, University Hospital of North Norway and Institute of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway.

This study was supported with a grant from the Regional Health Authorities (Helse Nord). There are no conflicts of interest behind this paper. The study is registered in www.clinicaltrials.gov, with the clinicaltrials.gov ID: NCT01123525.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Oct 25, 2011; revisions received July 8, 2012; accepted for publication July 26, 2012; available ahead of print Sept 10, 2012.

Address for reprints: Øyvind Jakobsen, MD, PhD, Department of Cardiothoracic and Vascular Surgery, University Hospital of North Norway, 9038 Tromsø, Norway (E-mail: oyvind.jakobsen@unn.no).

0022-5223/\$36.00

Copyright © 2013 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2012.07.058>

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CK-MB	= creatine kinase MB isoenzyme
CPB	= cardiopulmonary bypass
DC shock	= direct-current countershock
ICU	= intensive care unit
t-PA	= tissue-plasminogen activator

adenosine–lidocaine cardioplegia.⁸ An *in vitro* study using the combination of adenosine and lidocaine with varying concentrations of potassium has indicated that normokalemic conditions are favorable regarding postischemic recovery and arrhythmias.⁹ However, to our knowledge no clinical studies have yet investigated the use of adenosine in a cardioplegic solution with normal potassium concentration, and such studies have been requested.¹⁰ The primary objective of this study was therefore to evaluate the efficacy and safety of a cold crystalloid cardioplegic solution with adenosine (1.2 mmol/L) instead of supranormal potassium.

METHODS

Sixty patients scheduled for elective coronary artery bypass grafting (CABG) at the University Hospital of North Norway were in the period between April 2010 and March 2011 randomized to receive either St Thomas' Hospital solution (hyperkalemic group) or a solution in which hyperkalemia was replaced with 1.2 mmol/L adenosine (adenosine group). The solutions were otherwise similar, including procaine hydrochloride and magnesium content. The randomization was performed by using an externally administered randomization program (Microsoft Access; Microsoft Corporation, Redmond, Wash). So that an even distribution of the 2 regimens with time could be ensured, the patients were block randomized with random block size including 4, 6, or 8 patients in each block. Exclusion criteria were preoperative left ventricular ejection fraction below 40%, age above 75 years, pregnancy, and concomitant or emergency procedures. The study was approved by the regional ethics committee and the Norwegian Medicines Agency. All patients provided written informed consent before trial enrollment. The trial is registered in www.clinicaltrials.gov, with the clinicaltrials.gov ID: NCT01123525.

Anesthesia was induced with intravenous fentanyl, midazolam, and thiopental. Vecuronium was used for muscle relaxation. Fentanyl and isoflurane in a mixture of oxygen and air were used for analgesia and anesthesia maintenance before and after CPB. Propofol was used as anesthesia maintenance during CPB. Heparin was given to achieve a target activated clotting time of 480 seconds or more before commencing CPB. The ascending aorta was cannulated and venous drainage was obtained from a cavoatrial cannula. A coronary sinus catheter was inserted retrogradely through a purse-string suture in the right atrium and placed toward the great cardiac vein for blood sampling. Circuits were coated with Bioline polymer (Jostra Medizintechnik, Hirrlingen, Germany) and primed with 1800 mL Ringer acetate. A Quadrox oxygenator (Maquet Cardiopulmonary AG, Hirrlingen, Germany) and a Stöckert S5 roller pump (Stöckert GmbH, Freiburg, Germany) were used. Similar-looking 100-mL vials with concentrated cardioplegic solution were diluted in 900-mL cold Ringer acetate; final concentrations are given in Table 1. Cardioplegic solution was given in a double-blind randomized manner in which only the hospital pharmacy knew which solution was given to each patient. After aortic crossclamping, cardioplegic arrest was initiated with 750 mL of cold (4°C–6°C) crystalloid cardioplegic solution delivered antegradely into the aortic arch. If

cardioplegia was unsatisfactory after 5 minutes, judged by the surgeon, the resulting 250 mL of cardioplegic solution was given. If cardiac arrest was still unsatisfactory, the surgeons were allowed to convert to standard hyperkalemic cardioplegia. Cardioplegic arrest was maintained with 200 mL of cardioplegic solution every 20 minutes. After weaning from CPB, 3 mg/kg of protamine was administered to reverse anticoagulation.

PiCCO technology (Royal Phillips Electronics, Amsterdam, the Netherlands) was used for preoperative and postoperative hemodynamic monitoring and intermittent cardiac output measurements with thermodilution technique using a femoral artery catheter and central venous catheter. Cardiac output measurements were assessed in a steady state situation after anesthesia was induced but before surgery, immediately after sternal closure, at ICU arrival, and then repeatedly during the first 12 hours in the ICU.

Blood samples (CK-MB, troponin T, creatinine, myoglobin, and electrolytes) were obtained the morning before surgery, at ICU arrival, and 4, 8, 12, 18, 24, 36, and 48 hours postoperatively. Perioperative blood samples (white blood cells, interleukin 6, intercellular adhesion molecule, vascular cell adhesion molecule and tissue-plasminogen activator [t-PA] antigen) were simultaneously sampled from the cardioplegia cannula in the aorta and a catheter in the coronary sinus twice; just before crossclamping the aorta and after 5 minutes of reperfusion. Release of troponin T and CK-MB was prespecified as primary end points whereas the other end points were secondary outcome measures.

Statistics

Data are presented as mean $\pm$ standard deviation. Data were analyzed in a statistical software package PASW statistics 18 (SPSS Inc, Chicago, Ill). A 50% difference between groups was considered significant to calculate sample size. On the basis of a previous study,¹¹ together with an experience-based estimate of patients lost to follow-up because of reoperation owing to bleeding, our study with 60 patients would ensure power greater than 80 with a *P* value of .05. Analyses of between-group differences were done by using analysis of variance and analyses of repeated measures by using analyses of variance for repeated measures. Categorical data were analyzed by the χ^2 table and by using Fisher's exact probability test. Operative and postoperative data from the patients receiving both hyperkalemic and adenosine cardioplegia were excluded. Postoperative data from blood samples and PiCCO measurements from the patients reoperated on owing to bleeding were also excluded.

RESULTS

Preoperative

Preoperative data are given in Table 2. There were no differences in gender, age, or weight preoperatively. The hyperkalemic group had a significantly higher level of blood creatinine before surgery. There were no between-group differences in the number of patients treated with beta-blockers or angiotensin converting enzyme I/angiotensin II receptor antagonists.

Perioperative Results

Time on CPB and crossclamp time was similar between groups (Table 2). There was a significantly shorter time to cardioplegic arrest in the adenosine group than in the hyperkalemic group (11 $\pm$ 5 vs 44 $\pm$ 18 seconds). There were no differences between groups with respect to volume of cardioplegic solution given, time on CPB, crossclamp time, or number of distal anastomoses (Table 2). Three patients in the adenosine group were converted to hyperkalemic cardioplegia owing to unsatisfactory arrest as judged by the

TABLE 1. Composition of the cardioplegic solutions in final concentration (mmol/L)

	Hyperkalemic cardioplegia (hyperkalemic group)	Adenosine cardioplegia (adenosine group)
Potassium chloride	20	4
Magnesium chloride	17	17
Procaine hydrochloride	1	1
Calcium chloride	2	2
Sodium acetate	30	30
Sodium chloride	100	100
Adenosine	0	1.2
pH	5-6	5-6

surgeon. Spontaneous rhythm after removal of the aortic crossclamp was achieved in 27 patients in the hyperkalemic group versus 18 in the adenosine group ($P = .05$). Three

TABLE 2. Patient characteristics

Patient characteristics	Hyperkalemic cardioplegia	Adenosine cardioplegia	<i>P</i> value
Preoperative	n = 30	n = 30	
Age	64.0 ± 6.8	63.3 ± 7.1	NS
Female/male	2/28	3/27	NS
Weight	87.3 ± 15.4	86.0 ± 16.4	NS
Creatinine	98.6 ± 44.0	78.5 ± 11.7	.02
Treated with beta-blocker	27	22	NS
Treated with ACE-I/AII antagonist	16	12	NS
Atrial fibrillation	1	3	
Operative	n = 30	n = 27	
Time to arrest (s)	44 ± 18	11 ± 5	<.001
Crossclamp time (min)	43 ± 18	47 ± 17	NS
Time on CPB (min)	75 ± 24	82 ± 27	NS
Distal anastomoses	3.4 ± 1.0	3.4 ± 0.8	NS
Volume of cardioplegia (mL)	1087 ± 260	1181 ± 266	NS
Perioperative myocardial infarction	0	0	NS
Spontaneous rhythm	27	18	.05
Potassium injection/DC shocks	2/1	3/6	NS/0.04
Postoperative	n = 30	n = 27	
Reoperated on owing to bleeding	2	3	NS
	n = 28	n = 24	
Time on ventilator (min)	186 ± 103	169 ± 90	NS
Treatment with inotropics/ pressor	1	1	NS
Nitrogen infusion	1	2	NS
New-onset atrial fibrillation <4 d	15/28	4/21	.01

Operative data from 27 patients in the adenosine group are given inasmuch as 3 patients received both adenosine and hyperkalemic cardioplegia. Postoperative data from the patients reoperated on owing to bleeding are excluded. Data are given in mean ± standard deviation. NS, Not significant; ACE-I/AII, angiotensin converting enzyme I-angiotensin II; CPB, cardiopulmonary bypass; DC shock, direct-current countershock.

hearts in the adenosine group and 2 in the hyperkalemic group converted to sinus rhythm after potassium injection, whereas 6 patients in the adenosine group versus 1 in the hyperkalemic group needed additional direct-current countershocks (DC shocks) to convert to sinus rhythm (Table 2). The results from the perioperative blood samples from the aorta and the coronary sinus are displayed in Table 3. There was a significant increase in white blood cells and t-PA antigen both in arterial blood and in the coronary sinus in both groups, and a significant increase of vascular cell adhesion molecule in the coronary sinus in the adenosine group. No differences between groups were however revealed.

Postoperative Results

Three patients in the adenosine group and 2 patients in the hyperkalemic group needed temporary cardiac pacing owing to bradycardia for the first postoperative hours, 18 hours at most. Three patients in the adenosine group and 2 patients in the hyperkalemic group were reoperated on owing to bleeding. One patient in the hyperkalemic group received treatment with norepinephrine for the first 21 hours postoperatively, and 1 patient in the adenosine group received treatment with dobutamine between 8 and 18 hours postoperatively. Four of 21 patients in the adenosine group had postoperative new-onset atrial fibrillation (3 patients with preoperative atrial fibrillation, 2 patients reoperated on owing to bleeding, and the 3 patients converted to hyperkalemic cardioplegia excluded), and 15 of 28 patients in the hyperkalemic group had postoperative new-onset atrial fibrillation (2 patients reoperated on owing to bleeding excluded, 1 of them with preoperative atrial fibrillation). There were no differences between groups with respect to postoperative release of troponin T or CK-MB (Figure 1) or myoglobin (data not shown). There were no differences between groups in postoperative creatinine, but the hyperkalemic group had a significantly higher value of cystatin C 12 and 24 hours postoperatively (in milligrams per liter: hyperkalemia, 0.79 ± 0.30 and 0.87 ± 0.33 vs adenosine, 0.64 ± 0.13 and 0.70 ± 0.13 ; $P = .04$ and $.02$ respectively) and also higher value of potassium 24 hours postoperatively (4.4 ± 0.4 vs 4.1 ± 0.3 ; $P = .04$).

There were no differences between groups before or after surgery in cardiac index or systemic vascular resistance and no differences in postoperative heart rate or mean arterial pressure (Figure 2). Also, there were no differences between groups in central venous pressure or global end-diastolic volume index (data not shown).

DISCUSSION

Adenosine instead of hyperkalemia in the cardioplegic solution provided adequate, and even more rapid, cardiac arrest in 27 of 30 patients. In the 3 patients who were converted to hyperkalemic cardioplegia, different reasons

TABLE 3. Results from the perioperative arterial and coronary sinus blood samples, taken immediately before crossclamping the aorta and after 5 minutes of reperfusion

	Group	Before crossclamp		After 5 minutes of reperfusion	
		Arterial	Coronary sinus	Arterial	Coronary sinus
WBC (10 ⁹ /L)	K	4.53 ± 1.48	4.40 ± 1.68	9.18 ± 3.04*	8.36 ± 2.80*
	A	3.98 ± 1.60	3.82 ± 1.64	8.34 ± 3.03*	7.38 ± 2.61*
t-PA antigen (ng/mL)	K	7.36 ± 3.94	8.50 ± 3.32	10.86 ± 4.94*	13.17 ± 5.81*
	A	5.99 ± 1.96	7.28 ± 3.35	10.60 ± 5.04*	12.05 ± 5.93*
ICAM (pg/mL)	K	200 ± 97	183 ± 120	181 ± 94	179 ± 79
	A	136 ± 65	117 ± 59	135 ± 87	123 ± 45
VCAM (pg/mL)	K	659 ± 528	675 ± 426	857 ± 490	772 ± 346
	A	623 ± 346	581 ± 275	787 ± 338	741 ± 267*
P-selectin (pg/mL)	K	33.9 ± 11.0	31.7 ± 12.1	31.1 ± 10.2	33.2 ± 8.3
	A	28.9 ± 8.9	26.6 ± 7.8	28.4 ± 10.1	28.1 ± 7.2
E-selectin (pg/mL)	K	28.6 ± 13.0	28.0 ± 14.3	25.4 ± 10.1	26.1 ± 9.9
	A	22.7 ± 10.6	21.5 ± 10.9	22.3 ± 13.9	20.3 ± 11.0

Data are given in mean ± standard deviation. Patients receiving both hyperkalemic and adenosine cardioplegia are excluded. No between-group differences were revealed. A, Adenosine group (n = 27); K, hyperkalemic group (n = 30); WBC, white blood cells; t-PA, tissue-plasminogen activator; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule. *Significant compared with baseline values (within group).

were given. In the first patient, cardiac arrest was achieved with adenosine cardioplegia within 2 seconds after administration. However, after 4 to 5 minutes of arrest the heart resumed contractions, and according to the protocol more adenosine cardioplegia was given and cardiac arrest was again achieved. The heart again reanimated after 5 additional minutes, and therefore hyperkalemic cardioplegia was given. In this patient the surgeon noticed retrograde bleeding from the coronary arteries, so washout of the cardioplegic solution, together with more rapid rewarming, is suspected, likely owing to unsatisfactory emptying of the pulmonary vascular bed before clamping and/or poor venous drainage. In the second patient, cardioplegia was achieved after 13 seconds, but after administration of 500 mL of cardioplegic solution, ventricular fibrillation was observed and was still present after 1000 mL of

cardioplegic solution. According to the protocol, hyperkalemic cardioplegic solution should then have been given if the arrest was unsatisfactory 5 minutes after administration of the cardioplegia. However, it was converted to hyperkalemic cardioplegia immediately, so the protocol was not strictly followed. In the third patient, ventricular fibrillation was observed 10 seconds after administration of adenosine cardioplegia and was still present after 750 mL. Another 250 mL was therefore given and the cardioplegia was satisfactory. After 10 minutes of cardioplegia, the heart started to fibrillate again, and then hyperkalemic cardioplegic solution was given. This patient was known to have aortic insufficiency. We therefore conclude that the use of adenosine instead of hyperkalemia in the cardioplegic solution gives a more rapid cardiac arrest, but the maintenance of cardiac arrest seems more susceptible to

FIGURE 1. Release of troponin T and creatine kinase MB (CKMB) preoperatively (pre) and 0 to 48 hours postoperatively in patients receiving hyperkalemic cardioplegia (closed circles, n = 28) or cardioplegia with 1.2 mmol/L of adenosine instead of supranormal potassium (open circles, n = 24). Data are given as mean and error bars denote standard deviation. Patients reoperated on owing to bleeding and patients receiving both adenosine and hyperkalemic cardioplegia are excluded.

FIGURE 2. Cardiac index and systemic vascular resistance index measured immediately before surgery (*preop*), after sternal closure (*postop*), immediately after arrival at the intensive care unit (*arrival ICU*), and 4, 8, and 12 hours after arrival at the ICU. Heart rate and mean arterial pressure were measured immediately after arrival at the ICU and 4, 8 and 12 hours after arrival at the ICU. All parameters were measured with PiCCO arterial thermodilution catheters in patients receiving either hyperkalemic cardioplegia (*closed circles*, $n = 28$) or adenosine cardioplegia (*open circles*, $n = 24$). Data are given as mean and *error bars* denote standard deviation. Patients reoperated on owing to bleeding and patients receiving both adenosine and hyperkalemic cardioplegia were excluded.

washout of the cardioplegic solution from the coronary arteries and mixing with normothermic blood.

We could not detect any differences in postoperative release of CK-MB or troponin T, and the postoperative hemodynamic measurements including cardiac index were similar between groups. This study included patients having elective CABG with ejection fraction above 40%, no recent myocardial infarction, and age below 75 years. This means low-risk patients with short aortic crossclamp time. Inasmuch as the ischemic period is short and these hearts supposedly tolerate the ischemic period well, a difference in cardioprotection with the end points we used could hardly be expected. This is also reflected in the results with no postoperative mortality, low postoperative morbidity, together with high postoperative cardiac outputs. However, to our knowledge this is the first study to investigate the efficacy and safety of adenosine instead of hyperkalemia in cardioplegia, and we therefore found it important to do the first clinical study in a low-risk population.

There was a higher postoperative value of cystatin C in the hyperkalemic group, but since we did not measure preoperative cystatin C and the preoperative value of creatinine also was higher in the hyperkalemic group, we cannot conclude with any differences in renal protection between the 2 cardioplegic solutions. Also, there was no difference between groups in postoperative creatinine when compared with baseline values. The role of posts ischemic perivascular inflammation in posts ischemic cardiac injury is generally accepted as important, and the interaction between white blood cells and the endothelium is a key step in this inflammatory process. We² have previously shown in a large animal model that adenosine instead of supranormal potassium in the cardioplegic solution improves postcardioplegic endothelium-derived hyperpolarization factor-dependent vasodilation. We therefore wanted to measure markers of endothelial activation and injury, results given in Table 3. We found higher values of white blood cells and t-PA antigen in both groups after

5 minutes of reperfusion, but these results did not add any sensitivity to our end point measurements.

Six patients in the adenosine group, versus 1 in the hyperkalemic group, needed DC shocks because of ventricular fibrillation refractory to extra potassium injections in the reperfusion period. Two of the patients needed 2 DC shocks, and 1 needed 3 DC shocks to gain sinus rhythm. This did not lead to any problems with weaning from CPB in any of the patients or any increase in the release of troponin T or CK-MB in the adenosine group. However, ventricular fibrillation during the reperfusion and rewarming period may contribute to myocardial damage owing to increased myocardial oxygen consumption and decreased subendocardial blood flow. Adenosine is a potent vasodilator, and we² have previously shown in the preclinical study that endothelium-derived hyperpolarization factor-dependent vasodilation was better preserved in the adenosine group than in the hyperkalemic group. Reperfusion arrhythmias are suggested to be due to abrupt washout of toxic metabolites, and decreased arrhythmias are reported with reduced rates of reperfusion.¹² A theoretical explanation might therefore be that the hearts in the adenosine group have a more dilated coronary vascular bed; hence these hearts are more susceptible to rapid crossclamp release and need a gentler reperfusion.

New-onset atrial fibrillation remains the most common complication after cardiac surgery; its peak incidence is between the second and third postoperative days. In larger patient series it is reported to occur in 25% to 40% of patients after CABG and in up to 62% after combined CABG and valve surgery.¹³ New-onset atrial fibrillation is widely known to increase morbidity after cardiac surgery,^{14,15} and a recent meta-analysis has shown that new-onset atrial fibrillation after CABG appears to increase short- and long-term mortality.¹⁵ Atrial fibrillation after cardiac surgery is also an independent risk factor of delayed stroke,¹⁶ lengthening hospitalization and increasing the overall expenses of cardiac surgery. If changing the cardioplegic solution could reduce the incidence of atrial fibrillation after cardiac surgery, it would be a major improvement in the handling of patients undergoing cardiac surgery. New-onset atrial fibrillation occurred in only 4 (19%) of 21 patients in our adenosine group versus 15 (54%) of 28 in our hyperkalemic group ($P = .01$). The pathophysiology of atrial fibrillation after heart surgery is not known, but its etiology is thought to be multifactorial. Abnormal electrophysiologic state of the atria, unequal shortening of the atrial myocytes refractory period, ischemia of the atrial tissue, increased sympathetic activation, and exaggerated inflammatory response have been suggested to play triggering roles.¹⁷ With largely unknown pathophysiology, any suggested mechanisms behind the lowered incidence of atrial fibrillation must be speculative. Our results demonstrate no difference in global ischemia or inflammatory

response, but the atria have not been studied exclusively. The cardioplegic solution with adenosine instead of hyperkalemia does, however, give a nondepolarizing arrest with several theoretical advantages concerning the electrophysiology, as a more balanced transmembrane ion gradient and a reduction in ionic imbalance. Adenosine has little or no effect on the duration of ventricular action potential^{18,19} but shortens the action potential in atrial myocardium and attenuates the increase in action potential duration often seen after stimulation with catecholamines.¹⁸ Afterdepolarizations and triggered arrhythmic activity induced by catecholamines are also attenuated or abolished by adenosine,²⁰ and the anti- β -adrenergic effect, which is shown to be prolonged after administration of adenosine,²¹ may possibly reduce the rate of postoperative atrial fibrillation.

There were different surgeons operating on the study patients, with some variations in both experience and surgical techniques, which leads to some variation in crossclamp time and time on CPB. The patients also had different degrees of coronary disease and hence perhaps also different degrees of coronary distribution of the cardioplegic solutions. Both these factors result in an increased variance in the degree of both global and local ischemia. A more strict selection of patients with more homogenous coronary disease, together with fewer surgeons, could have lowered the variance and hence strengthened the study. Another limitation with our study is that inasmuch as the incidence of postoperative atrial fibrillation was not a primary end point, the patients were only monitored with continuous electrocardiography during the stay at the ICU, and thereafter once daily or when the patients had symptoms indicating atrial fibrillation. We can therefore not exclude that some patients had short episodes with asymptomatic atrial fibrillation that we have not registered. A future larger scale study to confirm our results should therefore include continuous postoperative electrocardiographic monitoring, and the patient population should be more homogeneous. The ideal population might be patients going through isolated aortic valve replacement and also with preoperative impaired ventricular function. These patients are more in need for an improved cardioplegic solution, and an improvement will be better detectable. Such a patient group will also be more homogeneous with respect to crossclamp time, time on CPB, and coronary distribution of the cardioplegic solution, which again will lower the variance in both global and local ischemia. This population does also have a higher incidence of postoperative atrial fibrillation, and a reduction of this will therefore be even more convincing.

Blood cardioplegia is generally accepted as superior to crystalloid cardioplegia, although the superiority is scant,²² still debated,²³ and a large-scale randomized study with CABG patients failed to prove superiority.²⁴ Adenosine instead of hyperkalemia in blood cardioplegia leads to some extra challenges owing to its rapid metabolism in blood,

but this might just be a question of dose and temperature. Concentrations of adenosine greater than 0.2 mmol/L inhibit adenosine deaminase, concentrations greater than 10 μ mol/L inhibit adenosine kinase in intact human erythrocytes, and hypothermia also inhibits adenosine metabolism.²⁵ Sufficient doses of adenosine instead of hyperkalemia in hypothermic blood cardioplegia could therefore both give acceptable cardioplegia and activate the cardioprotective mechanisms. The question of optimal dose is an unresolved issue. A method with a different line for delivery of adenosine can also be used to avoid the challenge with breakdown of adenosine. The future larger-scale study, as suggested earlier, should perhaps be performed with blood cardioplegia inasmuch as this is generally more accepted as today's gold standard cardioplegic regimen.

CONCLUSIONS

Adenosine instead of supranormal potassium in cold crystalloid cardioplegia is safe and efficient provided adequate drainage. In low-risk patients it results in similar cardioprotection with respect to release of cardiac enzymes and similar preservation of hemodynamics and cardiac index. When hyperkalemia is replaced with adenosine, the cardioplegic arrest was significantly more rapid and the incidence of postoperative atrial fibrillation was significantly reduced. Further studies in high-risk patients and more long-lasting procedures are warranted.

References

- Jakobsen O, Muller S, Aarsaether E, Steensrud T, Sorlie DG. Adenosine instead of supranormal potassium in cardioplegic solution improves cardioprotection. *Eur J Cardiothorac Surg*. 2007;32:493-500.
- Jakobsen O, Stenberg TA, Losvik O, Ekse S, Sorlie DG, Ytrebo LM. Adenosine instead of supranormal potassium in cardioplegic solution preserves endothelium-derived hyperpolarization factor-dependent vasodilation. *Eur J Cardiothorac Surg*. 2008;33:18-24.
- Chauhan S, Wasir HS, Bhan A, Rao BH, Saxena N, Venugopal P. Adenosine for cardioplegic induction: a comparison with St Thomas solution. *J Cardiothorac Vasc Anesth*. 2000;14:21-4.
- Jin ZX, Zhou JJ, Xin M, Peng DR, Wang XM, Bi SH, et al. Postconditioning the human heart with adenosine in heart valve replacement surgery. *Ann Thorac Surg*. 2007;83:2066-72.
- Cohen G, Feder-Elituv R, Iazetta J, Bunting P, Mallidi H, Bozinovski J, et al. Phase 2 studies of adenosine cardioplegia. *Circulation*. 1998;98(19 Suppl):II225-33.
- Fremes SE, Levy SL, Christakis GT, Walker SE, Iazetta J, Mallidi HR, et al. Phase 1 human trial of adenosine-potassium cardioplegia. *Circulation*. 1996;94(9 Suppl):II370-5.
- Mentzer RM Jr, Birjiniuk V, Khuri S, Lowe JE, Rahko PS, Weisel RD, et al. Adenosine myocardial protection: preliminary results of a phase II clinical trial. *Ann Surg*. 1999;229:643-9.
- Jin ZX, Zhang SL, Wang XM, Bi SH, Xin M, Zhou JJ, et al. The myocardial protective effects of a moderate-potassium adenosine-lidocaine cardioplegia in pediatric cardiac surgery. *J Thorac Cardiovasc Surg*. 2008;136:1450-5.
- Sloots KL, Dobson GP. Normokalemic adenosine-lidocaine cardioplegia: importance of maintaining a polarized myocardium for optimal arrest and reanimation. *J Thorac Cardiovasc Surg*. 2010;139:1576-86.
- Hammon JW. Why change? *J Thorac Cardiovasc Surg*. 2010;140:1218-9.
- Steensrud T, Muller S, Endresen PC, Sorlie DG. Clinical testing of nicorandil supplemented normokalemic cardioplegic solution. *Interact Cardiovasc Thorac Surg*. 2006;5:521-5.
- Manning AS, Hearse DJ. Reperfusion-induced arrhythmias: mechanisms and prevention. *J Mol Cell Cardiol*. 1984;16:497-518.
- Cox JL. A perspective of postoperative atrial fibrillation in cardiac operations. *Ann Thorac Surg*. 1993;56:405-9.
- Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol*. 2004;43:742-8.
- Kaw R, Hernandez AV, Masood I, Gillinov AM, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2011;141:1305-12.
- Hedberg M, Boivie P, Engstrom KG. Early and delayed stroke after coronary surgery—an analysis of risk factors and the impact on short- and long-term survival. *Eur J Cardiothorac Surg*. 2011;40:379-87.
- Koniari I, Apostolakis E, Rogkakou C, Baikoussis NG, Dougenis D. Pharmacologic prophylaxis for atrial fibrillation following cardiac surgery: a systematic review. *J Cardiothorac Surg*. 2010;5:121.
- Belardinelli L, Shryock JC, Song Y, Wang D, Srinivas M. Ionic basis of the electrophysiological actions of adenosine on cardiomyocytes. *FASEB J*. 1995;9:359-65.
- Jakobsen O, Steensrud T, Ytrehus K, Sorlie DG. Adenosine protects against hypoxic injury at hypothermia in guinea pig papillary muscles. *Scand Cardiovasc J*. 2010;44:183-90.
- Song Y, Thedford S, Lerman BB, Belardinelli L. Adenosine-sensitive afterdepolarizations and triggered activity in guinea pig ventricular myocytes. *Circ Res*. 1992;70:743-53.
- Arvola L, Hassaf D, Melnikov AL, Helgesen KG, Ytrehus K. Adenosine induces prolonged anti-beta-adrenergic effects in guinea-pig papillary muscle. *Acta Physiol Scand*. 2002;175:11-7.
- Jacob S, Kallikourdis A, Sellke F, Dunning J. Is blood cardioplegia superior to crystalloid cardioplegia? *Interact Cardiovasc Thorac Surg*. 2008;7:491-8.
- Fallouh HB, Chambers DJ. Is blood versus crystalloid cardioplegia relevant? Significantly improved protection may require new cardioplegic concepts! *Interact Cardiovasc Thorac Surg*. 2008;7:1162-3.
- Ovrum E, Tangen G, Tollofsrud S, Oystese R, Ringdal MA, Istad R. Cold blood cardioplegia versus cold crystalloid cardioplegia: a prospective randomized study of 1440 patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2004;128:860-5.
- Klabunde RE. Dipyridamole inhibition of adenosine metabolism in human blood. *Eur J Pharmacol*. 1983;93:21-6.