A New Thermoregulation System for Maintaining Perioperative Normothermia and Attenuating Myocardial Injury in Off-Pump Coronary Artery Bypass Surgery

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(#2002-26052 . . . September 30, 2002)

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ABSTRACT

Background: Most patients undergoing coronary artery bypass surgery demonstrate perioperative mild-to-moderate hypothermia (<36°C). Patients undergoing off-pump coronary artery bypass (OPCAB) grafting may become even more severely hypothermic for want of cardiopulmonary bypass rewarming. One consequence is increased circulating catecholamine levels that induce an elevated systemic vascular resistance (SVR), which causes a subsequent deterioration in cardiac output.

Materials and Methods: We assessed the ability of the Allon thermoregulatory (AT) system to maintain normothermia and its impact on hemodynamics and myocardial function in patients undergoing OPCAB surgery. In this study, the first 60 of 120 suitable patients were assigned to AT (n = 40) or routine thermal care (RTC) (n = 20). Core body temperature, cardiac index (CI), SVR, and cardiac-specific troponin I (cTnI) were analyzed perioperatively for patients in both groups.

Results: Core body temperature was significantly higher in the AT group (from 36.1°C ± 0.5°C at induction of anesthesia to 37°C ± 0.5°C during surgery) than in the RTC group (from 35.8°C ± 0.4°C to 35.2°C ± 0.8°C , respectively; $P < .01$). SVR was significantly lower, and CI was greater (at comparable time points), whereas cTnI levels in the AT group were lower than in the RTC group from the end of surgery until 24 hours postoperatively (7.4 ± 17.7 µg/L versus 31.9 ± 47.4 µg/L; $P = .03$). These findings indicate the possibility for less ischemic damage sustained intraoperatively in the AT group.

Conclusions: Maintenance of perioperative normothermia (36.5°C-37.5°C) during OPCAB procedures can be efficiently achieved with the Allon thermoregulation system. The system was found to be superior to other routinely used methods of temperature maintenance. Benefits may include lowering afterload (as expressed by reduced SVR), an improved CI, and attenuation of myocardial injury (as assessed by cTnI levels).

INTRODUCTION

Patients undergoing coronary artery bypass graft (CABG) surgery are at a greater risk for perioperative cardiovascular morbidity and mortality than are other surgical patients, because their reserves for withstanding the stress of negative inotropic effects and hypoxemia during induction of anesthesia and surgery are diminished [Mangano 1990a, Mangano 1990b, Mangano 1990c, Frank 1993, Frank 1997]. Although problems concerning hypothermia still play a major role in open heart surgery, hypothermia during off-pump coronary artery bypass (OPCAB) grafting surgery is further aggravated by the absence of a cardiopulmonary bypass (CPB) rewarming system [CASS 1983]. Although CPB and its deleterious effects are eliminated in OPCAB surgery, the procedure is still a complicated major operation in which ischemic damage occurs due to heart manipulations and temporary coronary occlusion.

Hypothermia has also been shown to initiate profound elevations in serum norepinephrine concentrations, which thus elevate systemic vascular resistance (ie, cardiac afterload) [Frank 1995]. This response eventually necessitates augmentation of cardiac work by the already ischemic myocardium to provide perfusion to body tissues and thus contributes both to the undesirable effects of coronary occlusion and to reperfusion injury.

Circulating levels of cardiac protein markers have been measured to assess the presence and extent of myocardial injury following CABG surgery [Bonnefoy 1998]. None have been measured to assess myocardial injury during or following OPCAB surgery. Of the various markers that have been

Submitted September 21, 2002; accepted September 30, 2002.

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used, eg, creatine kinase (CK), MB (the isoform of CK [CK-MB]), myosin heavy chain kinase, myoglobin, cardiac troponin T, and cardiac-specific troponin I (cTnI), the last has proven to be the most specific, even though its slow release from myocytes has been thought to make it unsuitable for this purpose [Adams 1994].

Most studies performed to date have addressed only the assessment of postoperative ischemic injury with the cTnI assay [Bonnefoy 1998]. Our investigation was designed to compare intraoperative myocardial hemodynamics and intraoperative cTnI levels as indices of ischemic insult for 2 groups of patients undergoing OPCAB surgery. One group received traditional warming, and the Allon ThermoWrapping thermoregulation system (MTRE Advanced Technologies Ltd, Or Akiva, Israel) was used with the second group. Assessment of the cardioprotective effect of intraoperative normothermia during CABG surgery was carried out by evaluating hemodynamic factors and specific cardiac proteins.

PATIENTS AND METHODS

This study was a randomized open-label, multicenter study. The institutions participating in the study were the Cleveland Clinic Foundation, Cleveland, Ohio, USA, and the Tel-Aviv Sourasky Medical Center, which is affiliated with the Sackler Faculty of Medicine of Tel-Aviv University, Tel-Aviv, Israel.

Patients

This study was undertaken after obtaining the approvals of the ethical review boards of each institution and the patients' informed consent. No patient was older than 80 years of age, and all patients were scheduled for nonemergent OPCAB surgery. Patients were randomly divided preoperatively into 2 groups according to the type of normothermia maintenance to be used, either the Allon ThermoWrapping thermoregulatory technology (AT) or routine thermal care (RTC).

Surgical Procedures

The OPCABs were performed via midline sternotomy during partial heparinization, the aim being to maintain activated clotting times at around 300 seconds. The left internal mammary artery and, occasionally, the right internal mammary artery were harvested. Mechanical stability of the coronary arteriotomy area was achieved with the Octopus II (Medtronic Inc, Minneapolis, MN, USA). A carbon dioxide blower aided visibility, and hemostasis was obtained by using a soft silicone tourniquet around the coronary arteries. No shunts were used. Elevation of the heart to expose the circumflex and right coronary artery branches was achieved with deep pericardial stay sutures placed above the pulmonary vein. Most internal mammary arteries were incorporated in situ or as composite grafts. When they were not suitable or when more grafting needed to be performed, radial arterial or saphenous vein grafts were added to complete the revascularization. Proximal anastomoses on the aorta were made by partial clamping at the end of the distal anastomoses. Partial reversing with protamine was carried out only when there was evidence of a tendency to bleed.

Anesthesia Induction

Anesthesia was performed in both groups with short-acting hypnotic, opioid, and muscle-relaxing agents. The operating room temperature was kept between 19°C and 21°C. All study patients received standard monitoring equipment (radial artery catheter, 2 surface electrocardiogram leads, pulse oximetry, end-tidal carbon dioxide, and a Swan-Ganz thermodilution pulmonary artery catheter to record continuous cardiac output at each time point (Baxter Vigilance Monitor Model VGS; Baxter Healthcare Corp, Irvine, CA, USA).

Thermoregulation

Warming was initiated before the induction of anesthesia and was continued throughout the operation and for the following 2 hours in the intensive cardiac care unit (ICCU).

In the AT group, the system performed continuous monitoring of the patient's temperature via rectal (core) sensors and a feedback-controlled microprocessor unit that received the data. The system circulated water, and temperature was controlled and maintained within normothermic ranges in a closed loop between the garment and the unit. Thus, water temperature was continuously adjusted automatically through the feedback loop to reach a preset temperature that had been determined by the anesthesiologist and surgeon. This system enabled body temperature control and maintenance throughout the entire procedure. The garment was the actual heat exchanger and was the only component to come in direct contact with the patient's skin surface. It was designed especially to allow optimal exposure as necessary of specific areas of the body during CABG surgery while allowing for optimal heat exchange.

In the RTC group, patient temperature control was maintained by currently available methods that included a combination of water blankets, warm intravenous fluid, humidifiers, convective air warmers, and higher operating room temperatures.

Temperature and Hemodynamic Assessment

Both urinary bladder and skin temperatures were continuously assessed throughout the perioperative period. Hemodynamic variables, including blood pressure, heart rate, pulmonary and wedge pressure, cardiac index (CI, L/min per square meter), and systemic vascular resistance (SVR, dyne/s per cm^{-5}), were assessed at predetermined time points from the induction of anesthesia and insertion of the Swan-Ganz catheter until the end of surgery and arrival at the ICCU.

Measurement of Cardiac Proteins

Assessment of ischemic myocardial injury was performed with all patients by determining serum levels of total CK, CK-MB, and cTnI. Blood samples were collected at induction of anesthesia, following sternotomy, following completion of the anastomoses, at the end of surgery, and at 6 and 24 hours following the termination of surgery. Serum separation was performed immediately, and samples were kept at –70°C until their delivery to the laboratory. CK-MB mass fraction and cTnI levels were determined within 4 to 6 weeks of the time of extraction.

Clinical Characteristics of the Study Patients*

	Allon Thermoregulation (n = 40)	Routine Thermal Care (n = 20)	*P*
Age, y	67.3 ± 11	66.1 ± 8.6	.76
Male sex	80% (32)	54.5% (12)	.21
Weight, kg	75.5 ± 9.1	68.8 ± 14.9	.12
Height, cm	168.6 ± 6.4	163.3 ± 8.1	.05
Duration of surgery, min	180 ± 77	210 ± 52	.29
Number of grafts	2.05 ± 0.5	2.45 ± 0.5	.04†
Hypercholesterolemia	55% (22)	54.4% (12)	1.0
Hypertension	60% (24)	45.5% (8)	.47
Diabetes	30% (12)	72% (16)	.03†
History of smoking	30% (12)	45% (8)	.4

*Percentage data include patient numbers in parentheses; other data are presented as mean ± SD.

†Significant difference.

Serum CK levels (physiological range, 24-195 IU/L) were measured spectrophotometrically (Cobas Integra; Roche, Indianapolis, IN, USA). Serum cTnI mass (physiological range, <0.5 ng/mL) and CK-MB mass (physiological range, <30 IU/L) were determined by immunoassay with the Abbott Axsym System (Abbott Park, IL, USA).

Statistical Analysis

Differences between groups in temperature, CI, SVR, and cardiac protein level were assessed by analysis of variance. Chi-square analysis and the Fisher exact test were employed for categorical data. All values are given as mean ± SD. A *P* value <.05 was considered significant for all statistical comparisons.

RESULTS

The results presented here were obtained as an interim analysis of the first 60 of the 120 patients who will constitute the final study cohort. The demographic and preoperative clinical data for these 60 participants revealed significant differences between the AT and RTC groups in the numbers of grafts and diabetic patients (Table). The relevant temperature and hemodynamic data (ie, SVR and CI) corresponding to the specific time point measurements are shown in Figures 1, 2, and 3. The patients' core and skin temperatures were higher in the AT group at all time points. SVR measurements were lower in the AT group at all intraoperative and postoperative time points. The CIs were higher, although the main difference was for the period from the end of surgery through the following 3 hours.

Measurement of Cardiac Proteins: Markers of Myocardial Ischemia

Two patients from the AT group and 1 from the RTC group were excluded from the evaluation of cardiac proteins, although the patients were not dropped altogether from the study. One patient of each group underwent surgery during an acute myocardial infarction (MI), which was eventually followed by an unrelated elevation of cardiac enzyme levels during the study period. The third patient had a perioperative

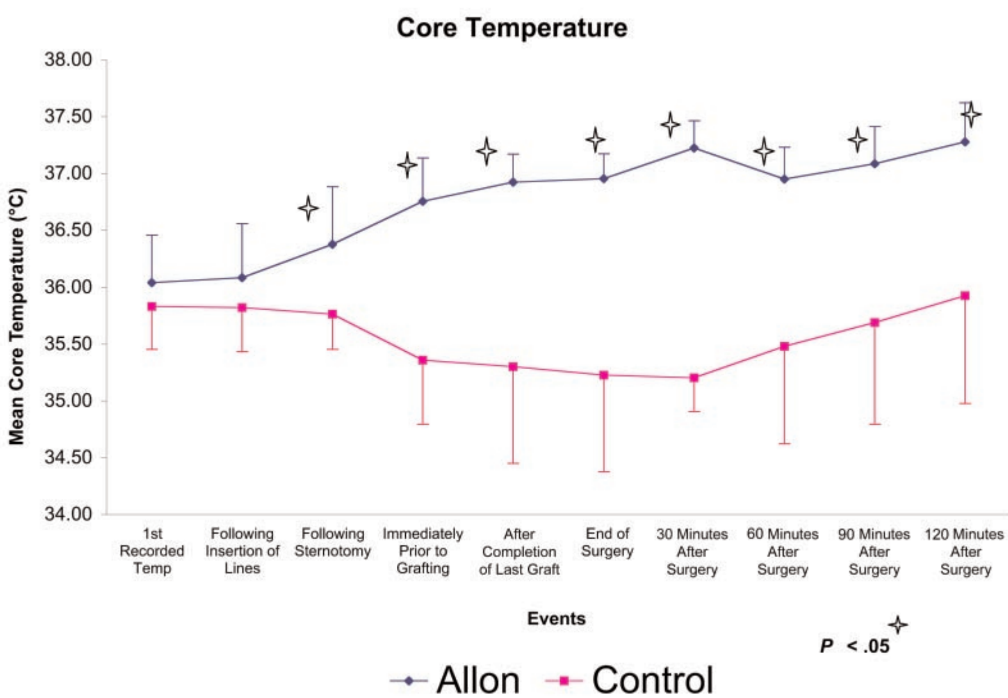

Figure 1. Patient core temperatures during and after off-pump coronary artery grafting surgery. Indicated are mean temperatures ± SD for groups maintained with Allon ThermoWrapping thermoregulatory technology or with routine thermal care (Control).

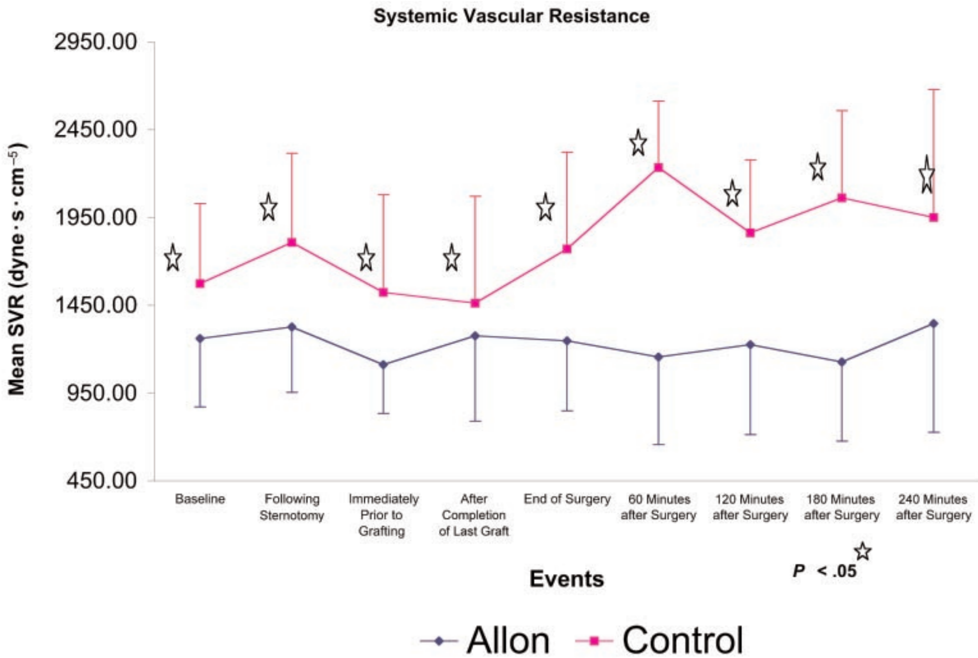

Figure 2. Patient systematic vascular resistance (SVR) during and after off-pump coronary artery grafting surgery. Indicated are mean ± SD for groups maintained with Allon ThermoWrapping thermoregulatory technology or with routine thermal care (Control).

MI due to an acute occlusion of the anastomosis to the posterior descending artery, which was visualized on urgent angiography. That patient also had an unrelated elevation of cardiac enzyme levels.

The profiles of the serum levels of the CK-MB mass fraction and cTnI are shown in Figures 4 and 5. The serum CK-MB mass fraction levels were almost comparable for the AT and RTC groups at the time of anesthesia induction (1.99 ± 2.6 IU/L and 6.3 ± 16.06 IU/L, respectively) and throughout the entire operation. From the end of surgery and up to 24 hours postoperatively, the levels demonstrated a steep rise. Both groups behaved almost identically.

During the entire operation, cTnI levels were similar in the AT and RTC groups (0.2 ± 0.5 ng/mL and 5.3 ± 17.3 ng/mL in the AT and RTC groups, respectively, at anesthesia induction, followed by 0.7 ± 2 ng/mL and 3.1 ± 10 ng/mL, respectively, at the onset of surgery; P = .68). A distinctive profile for the cTnI levels then became apparent for each group. In the RTC group cTnI levels were 10.0 ± 7 ng/mL, 35.3 ± 8.5 ng/mL, and 31.9 ± 47.4 ng/mL at the end of

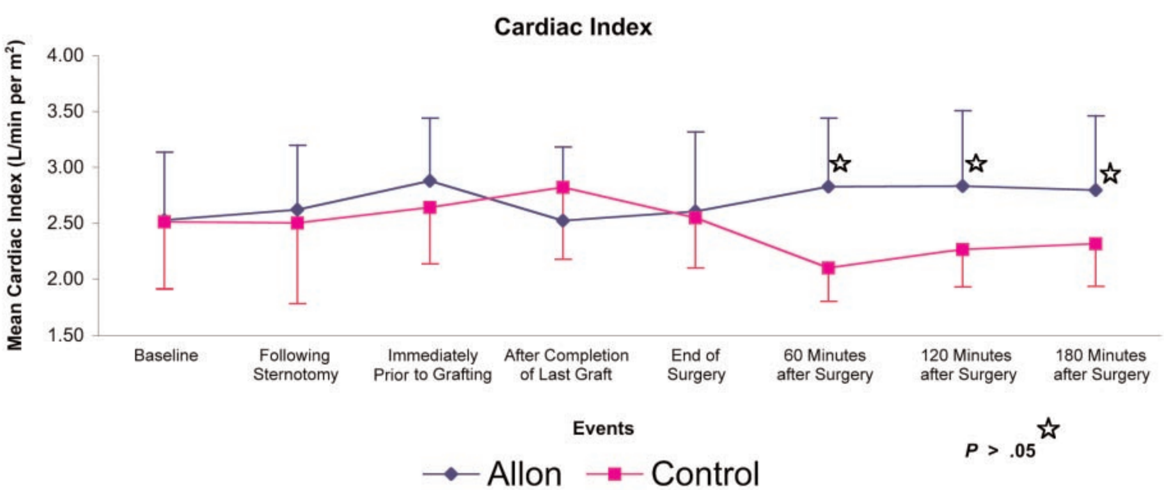

Figure 3. Patient cardiac indices during and after off-pump coronary artery grafting surgery. Indicated are mean ± SD for groups maintained with Allon ThermoWrapping thermoregulatory technology or with routine thermal care (Control).

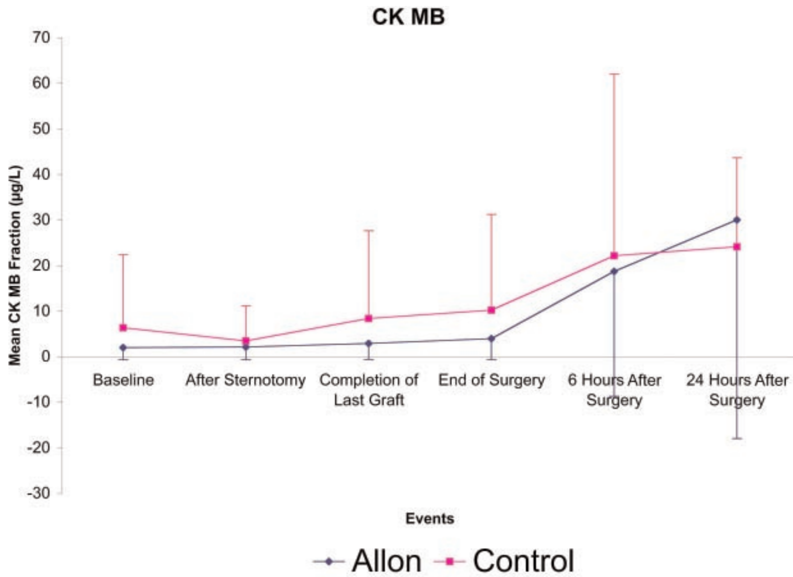

Figure 4. Patient levels of the MB isoform of creatine kinase (CK-MB) during and after off-pump coronary artery grafting surgery. Indicated are mean ± SD for groups maintained with Allon ThermoWrapping thermoregulatory technology or with routine thermal care (Control).

surgery and at 6 and 24 hours postoperatively, respectively, whereas in the AT group cTnI levels were 1.9 ± 2.1 ng/mL, 8.3 ± 15 ng/mL, and 7.4 ± 17 ng/mL at these 3 respective time points ($P = .03$ between the groups at the specified time points).

DISCUSSION

In an attempt to avoid the deleterious effects of CPB, many centers have changed their protocols to allow an increasing number of operations to be performed off-pump. By adopting the ever-developing techniques for off-pump surgery, the hypothetical effects of injury associated with open heart surgery are eliminated. Indeed, there are reports of better results with off-pump surgery for high-risk patients and for those with impaired left ventricular function [Arom 2001], as well as significantly lowered operative mortality [Arom 2000].

It is now well documented that patients who have undergone off-pump CABG surgery have had shorter recovery times than those patients who have undergone on-pump surgery. This result may be due to a better-maintained perfusion pressure under physiological conditions to a level higher than the pressure created by the CPB [Hirose 2001]. Furthermore, in nondialysis, chronic renal-failure patients, renal function remains constant for off-pump patients before, during, and after the operation, in contrast to the on-pump CABG group in which renal function during the operation decreases significantly and exhibits a slow recovery [Gerritsen 2001].

The term “minimally invasive” in cardiac surgery should imply “minimal side effects” for the patients [Ohasuka 2001]. When seen from this point of view, minimal invasiveness can refer not only to the nonuse of extracorporeal circulation but also to the maintenance of improved hemodynamics, better myocardial function, and the reduction of myocardial damage.

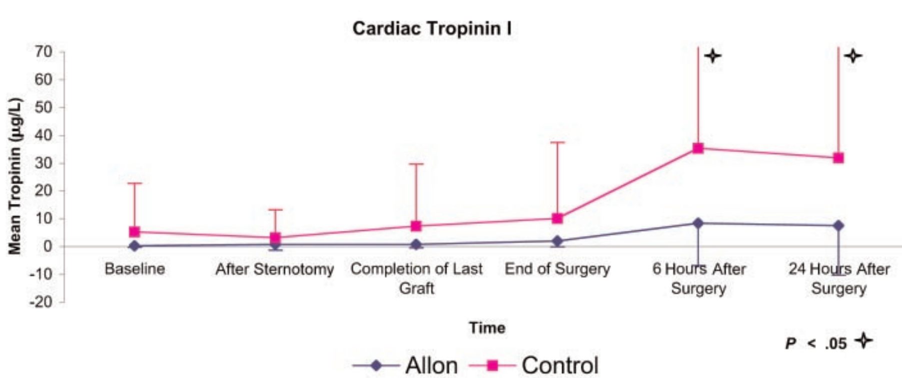

Figure 5. Patient levels of cardiac troponin I during and after off-pump coronary artery grafting surgery. Indicated are mean ± SD for groups maintained with Allon ThermoWrapping thermoregulatory technology or with routine thermal care (Control).

Minimal invasiveness should also refer to the avoidance of prolonged intubation, lengthy intensive care unit and hospital stays and, consequently, all their associated risks and costs [Ohasuka 2001, Venek 2001]. In OPCAB surgery, there is no further need for cooling the patients, even to the mild level of hypothermia that is desirable when CPB is conducted. However, while we eliminate the need for cooling, we also eliminate the ability to rewarm the patient through the CPB procedure. Therefore, the patient loses heat during all phases of surgery.

As in every major operation, normothermia should be maintained during OPCAB surgery. In the present study, we have demonstrated that the maintenance of normothermia throughout OPCAB surgery can be achieved more successfully with the application of the Allon system than with other traditional methods. We also have demonstrated that by maintaining normothermia we can attenuate ischemic injury to the myocardium, as was demonstrated by the improved hemodynamic variables and the reduced levels of serum cTnI, a sensitive marker of intraoperative myocardial ischemic insult.

Cardiac troponin I and CK-MB mass are specific markers of myocardial injury and have been used previously to detect myocardial damage in the postoperative period following CABG surgery [Bonnefoy 1998]. Troponin I is part of the troponin-tropomyosin complex in striated muscle. Its isoform, cTnI, is specific to cardiac tissue and is therefore considered a more useful marker than the conventional CK and CK-MB markers, which are also found in regenerating skeletal muscles [Adams 1993, Adams 1994].

It is noteworthy that postoperative augmentation of cTnI levels has been reported for all patients undergoing CABG surgery, although little data on cTnI levels following OPCAB surgery have been reported [Braun 2000]. This increase is attributed to myocardial ischemia during the initial phases of the operation and throughout the CPB period when the myocardium has not yet been vascularized. Additional mechanisms that can contribute to the further augmentation of myocardial damage in CABG surgery include manipulation of the myocardium, dissection of the myocardium for intramyocardial artery exposure, local occlusion of the coronary artery while performing the anastomoses during OPCAB surgery, and reperfusion injury [Bonnefoy 1998]. The degree to which cTnI levels rise during cardiac surgery has been ascribed to the type and extent of surgery, the method of myocardial protection and the length of coronary occlusion [Braun 2000, Nesher 2001], the preoperative cardiac status of the patient [Bleier 1998], the anesthetic protocol applied [Braun 2000], and the extent of reperfusion injury [Eigel 2001].

We observed significant differences between the 2 groups of patients who underwent the same OPCAB surgery, had the same anesthetic protocol, were similar in their preoperative cardiac status, had similar surgical times and numbers of anastomoses, and apparently differed only in the method used for intraoperative thermoregulation. We contend that the differences in cTnI profiles and cardiac indices observed for the 2 groups stem from the differences in the patients' body temperatures during the entire perioperative period. It is currently believed that mild-to-moderate hypothermia plays a protective role in preventing myocardial damage by reducing oxygen consumption, mainly in open heart surgery [Hayashida 1994]. The protective role of hypothermia may not bestow any benefit for OPCAB surgery but, rather, may be even more hazardous by causing dangerous life-threatening arrhythmias.

Although most previously published data have reported elevations in cTnI levels during the postoperative period, almost all of these reports, including our previews report [Nesher 2001], refer to open heart surgery. We found only 2 reports, besides our latest, on the changes in serum cTnI profiles occurring throughout open heart operations [Bleier 1998, Eigel 2001], but none of these changes were measured in OPCAB procedures. The present study has confirmed these findings and further contributes to our knowledge by documenting the effect of normothermia versus hypothermia on the attenuation of intraoperative myocardial ischemic damage, as expressed in the levels of a cardiac-specific protein.

The dramatic augmentation in cTnI levels reflecting myocardial injury that occurs from the end of surgery to at least the following 24 hours is intriguing. Patients undergoing an OPCAB procedure are at risk for myocardial injury because of the decreased tolerance of the hypoperfused heart to stress and an increased afterload [Hall 1997, Birdi 1999]. In addition, coronary occlusion may be caused during the operation (if no shunt is used) by virtue of a tourniquet surrounding the target vessel, which may aggravate the ischemic damage.

The difference in cTnI values observed between our 2 study groups immediately after termination of the operation most probably reflects damage that had already been sustained by the myocardium prior to the completion of revascularization (ie, that time during which the chest was opened, the heart was prepared and stabilized, and the conduits were harvested).

The most plausible mechanism for the diminished myocardial injury in our normothermic group is probably the significant reduction in afterload, as evidenced by the group's lower SVR value, which is the result of the peripheral, direct influence of the thermowrapping thermoregulatory technology. Notably, there were no differences in the amounts of vasodilatory and vasoactive drugs administered to the 2 groups; hence, it is reasonable that the reduction in afterload is due solely to the effect of normothermia attenuating the release of norepinephrine.

Numerous studies have shown that restoration of blood supply to ischemic tissue is not free of complications. Albeit some degree of reperfusion injury (as reflected by the release of cardiac proteins) was observed in both our groups, the revascularized hearts of patients in the normothermic group were received by a much "friendlier" environment, ie, one with a reduced SVR (afterload). As a result, myocardial injury at this phase was less pronounced in normothermic patients (as assessed by cTnI). Therefore, the difference between the groups in the recovery stages is most probably attributable to the differences in temperatures that were present during the hypothermic phase of the operation.

Intraoperative assessment of myocardial damage is important in any type of surgery, but it is especially vital during procedures involving the heart. Postoperative evaluation is not sufficient, because it may underestimate the amount of damage the tissue has experienced [Eigel 2001]. Just as enzymatic assessment of cardiac marker proteins has been proposed as a method of risk stratification in patients with acute coronary syndromes [Antman 1996], information on the status of enzyme activity should be made available and applied intraoperatively, as well as postoperatively, in the determination of patient prognosis [Eigel 2001]. The current study once again has confirmed the lack of specificity of intraoperatively measured CK-MB mass fraction compared with measurements of cTnI, the only marker that has enabled delineation between our 2 study groups. This finding is supported by the fact that CK-MB is expressed in injured striated muscle and is not specific to the myocardium, as is cTnI [Adams 1993, Mangano 1994].

The serum cTnI cutoff value has been suggested as a marker for postoperative MI. Levels of cTnI >11.6 ng/mL at 24 hours following unclamping of the aorta were previously determined to be highly sensitive and specific for a diagnosis of MI [Sadony 1998]. More recently, Carrier and colleagues proposed that serum cTnI levels >3.9 ng/mL at 24 hours following CABG surgery should be accepted as an indicator of postoperative MI [Carrier 2000]. In the present investigation, 2 patients from the AT group and 1 patient from the RTC group demonstrated a perioperative MI (assessed by the conventionally accepted criteria, ie, newly appearing Q waves presented in the electrocardiogram and CK-MB mass level >50 IU/L) or unexplained hemodynamic instability (evidenced by a newly recognized reduction of wall motion demonstrated by echocardiography). These patients were withdrawn from the cardiac enzymes assessment, but they were not excluded from the analyses of the other study parameters. However, a nonperioperative MI in a patient does not necessarily mean that no injury has been sustained by the myocardium, especially in light of the observations in this study of elevations in the serum concentrations of cardiac proteins. Specifically, cTnI levels were elevated beyond the aforementioned cutoff values for MI at more than 1 intraoperative time point, and this observation, as Eigel and colleagues have suggested, may play a role in late prognosis [Eigel 2001].

On the basis of our current findings, we propose using this new thermoregulation strategy for adequate maintenance of normothermia in OPCAB surgery and conducting intraoperative cTnI measurements as a method for more precisely assessing perioperative myocardial injury. These measures may also provide a method for assessing the efficacy of currently applied cardioprotective strategies as well as future pharmacologic and mechanical approaches. Our findings have clearly indicated the beneficial role that maintaining normothermia during the entire surgery has on the myocardium. Such an approach may prove fateful for patients with even lower functional reserves.

Acknowledgment

Esther Eshkol is thanked for editorial assistance.

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