

Does Retrograde Crystalloid Cardioplegia Offer Additional Protection Against Ischemia and Oxidative Stress in Coronary Bypass Surgeries?

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Background: Both short and long term results of coronary bypass surgery are partly dependent on adequacy of myocardial protection especially during the cardioplegic arrest portion of the operation. The attraction of using the venous end of the capillary bed for cardioplegia delivery is well founded based on the only too frequent incidence of extensive obstructive pathology in the conventional antegrade delivery route in patients presenting in the present era for CABG. Objective analysis of adequacy of myocardial protection includes changes in serum concentrations of different cardiac enzymes such as creatine kinase and its myocardial brain isoenzyme (CK-MB), Troponin-I (TnI). Other indirect indices of tissue malperfusion and oxidative stress are also valuable including blood lactate level, and two anti oxidant enzymes, Superoxide desmutase (SOD) and glutathione peroxidase (GSH-Px).

Methods: Forty patients scheduled for conventional CABG using cardiopulmonary bypass (CPB) were divided into two equal groups based on the extent of the pathology of there coronary arteries. Group I had a moderate form of coronary artery disease while Group II had severe and extensive pathology. Subsequently , each group was randomly divided into two equal subgroups according to the route of cardioplegia delivery : a- Antegrade cardioplegia and b- combined antegrade-retrograde cardioplegia. Blood samples were taken from each patient for analysis of (Tn-I), CK-MB, lactic acid, (SOD), and (GSH-Px).

Results and Conclusion: As a general outlook, combining retrograde with anterograde cardioplegia was associated with statistically significant lower values of the indices of ischemia and oxidative stress including (Tn-I), CK-MB, lactic acid, (SOD), and (GSH-Px) relative to that of the antegrade cardioplegia only.

Keywords: CABG, retrograde cardioplegia, oxidative stress, ischemia

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Improved results of coronary artery surgeries (CABG) with the traditional use of cardiopulmonary bypass (CBP) entail adequate intraoperative myocardial protection(1). Effective intraoperative myocardial protection requires adequate distribution of cardioplegic solution to all myocardial segments in a safe, simple, and rapid fashion(2). Though

antegrade cardioplegia is an advantageous route, yet, it is associated with a number of actual and theoretical limitations(3,4). Among these drawbacks the non-homogenous distribution of antegrade cardioplegia in severe critical proximal coronary artery stenosis and in evolving myocardial infarction(5), coronary ostial injury during and after aortic valve surgery(6), poor distribution in patients with aortic regurgitation unless the aorta is opened and the coronary ostia are perfused directly(7), the need to interrupt the continuity of mitral valve procedures in order to remove the retractors and avoid aortic distortion during cardioplegic replenishment(8), and it may not be technically possible in patients with type A aortic dissection (9).To obviate these limitations, retrograde coronary sinus perfusion has been proposed as an alternative method of providing myocardial protection that offers an excellent protection of the left ventricle in cases of severe coronary artery stenosis and when internal mammary artery grafts are used (10). However, recent studies have documented that retrograde cardioplegia does not adequately perfuse the right ventricle. The possibility of delayed cardiac arrest due to the low flow rate used for retrograde cardioplegia has also been noted (11).

After testing in our center the efficacy and safety of retrograde cardioplegia delivery in a cohort of patients with extensive coronary artery disease, we thought of designing a prospective randomized clinical study to assess and compare combined alternate use of antegrade-retrograde cardioplegia versus antegrade cardioplegia in providing adequate myocardial preservation during coronary artery bypass graft surgery.

A combination of clinical, hemodynamic, electrocardiographic, and biochemical parameters of ischemia and oxidative stress were used to monitor potential differences between the two methods.

Methodology:

Forty patients (34 males and 6 females) scheduled for conventional CABG surgery using CPB, were operated upon in new Kasr El-Aini teaching hospital, Faculty of Medicine, Cairo University, in the period between December 2002 and November 2004.

Patients were categorized according to the severity of their coronary artery disease pathology into two groups of equal number , group I and group II. Subsequently, patients within a given group were randomly assigned to either receive a conventional antegrade cardioplegia protocol or a combined antegrade / retrograde cardioplegia protocol.

Criteria for extensive coronary artery lesion including in group II included :

- 1-Left main coronary artery involvement.
- 2-Severe occlusion of the left coronary artery > 80% by coronary catheter study.
- 3-Severe occlusion of the right coronary artery > 80% by catheter study.

These patients were randomly and equally distributed to two subgroups :Group IIa and IIb.

The other twenty patients selected with moderately extensive coronary artery disease were similarly distributed to two subgroups : Group Ia and Ib.

Groups Ia, IIa: were scheduled for antegrade cold crystalloid cardioplegia.

Group Ib, IIb: were scheduled for alternate antegrade-retrograde cold crystalloid cardioplegia .

The mode of cardioplegia delivery was the only variable between the two groups, the

composition , timing and frequency of delivery of cardioplegia being identical. All cases in a given group of cardioplegia delivery protocol were operated upon by the same surgeon.

The criteria of exclusion of patients from the study included single vessel coronary artery disease, re operation, combined or emergency procedures.

All patients had a history of chest pain. Routine laboratory investigations were carried out as well as 12 leads electrocardiogram (ECG) one day before surgery. All patients were diagnosed to have coronary artery disease and the extent of the disease was evaluated based on selective coronary angiography.

Biochemical Studies and Sampling Protocol:

Blood samples were taken from a special channel of the C.V.P. catheter.

Serum levels of creatine Kinase, MB isoenzymes (CK-MB), Troponin I, Lactic acid, Superoxide desmutase, and Glutathione peroxidase were taken with the following time schedule:

- Baseline reading: on arrival to the O.R.
- Post-induction: 15 minutes following induction of general anesthesia.
- Post-declamping: 15 minutes following declamping of the aorta.
- Post-recovery: Two hours after arrival to the postoperative ICU.

Anaesthetic Management:

For each patient in the four groups, standard anesthetic protocol was followed in each patient. Anesthesia was induced using thiopentone sodium (3–4 mg/kg), fentanyl (5–7 µg/kg), and vecuronium bromide (0.08–0.1 mg/kg) to facilitate tracheal intubation. The

rest of the monitoring aids were applied: capnography and temperature monitors. Maintenance of anesthesia was carried out using isoflurane 0.8–1% was used as inhalation anaesthetic according to the haemodynamic parameters. Fentanyl was stepped to 8–12 µg/kg before sternotomy and a top-up dose of the muscle relaxant was given whenever needed.

Cannulation for cardioplegia delivery

A Retrograde Cannula was inserted in 20 patients transatrially guided by feeling the tip of the catheter negotiating the entrance of the coronary sinus from the diaphragmatic surface of the right ventricle before going on bypass with the right side adequately filled. This step of the operation was performed successfully after a single attempt in 18 patients and multiple attempts in two cases. In all situations, its insertion was safe with no injury to the coronary sinus. In all cases a 14 fr. retrograde cardioplegia cannula with self-inflatable medium balloon (18 mm) and rigid insertion stylet, CHASE, Medical inc., Richardson, Texas was used. This cannula has a side arm for pressure monitoring in the coronary sinus. An Antegrade Cannula was routinely inserted in the aortic root in all 40 patients. We used a cannula provided with two side ports, one for venting and the other for pressure monitoring (Research Medical, Inc., Midvale, UT, USA).

Conduct of operation and protocol of Cardioplegia delivery:

Patients in the Antegrade cardioplegia only subgroups, groups Ia and IIa, were operated upon using the conventional routine of distal anastomosis performed with the cross clamp on while the proximal anastomosis were performed after aortic declamping using a side biting clamp on the ascending aorta. The pneumatic pump is inflated to 300 mm Hg and a St. Thomas' Hospital solution no. 1 chilled to 4°C was infused in a dose of 15 mL per kg body weight initially and repeated every 15 minutes in a dose of 200 mL.

In group Ib and IIb patients, in whom a combined antegrade / retrograde protocol was used, all distal and proximal anastomosis were performed with one aortic clamp application. Half of the initial dose was given antegradely with a high aortic root pressure and the other half was given retrogradely with coronary sinus pressure ranging between 30 and 50 mm Hg. All subsequent doses were given retrogradely through the coronary sinus as described before Magued et al. The two routes of infusion were never used simultaneously.

Parameters of Intraoperative evaluation:

Apart from the biochemical data already mentioned,

the following data had been estimated:

- Total bypass time (min.).
- Total ischemic time (min.).
- Ease of weaning from CPB.
- Incidence of use of defibrillator.
- Average dose of inotrops (epinephrine µgm/kg/min).
- Incidence of post-bypass ventricular dysrhythmias.
- Incidence of post-bypass persistent myocardial ischemia or infarction.
- Incidence of postoperative mortality.

Statistical analysis:

Statistical analysis was done using SPSS version 7.0 for Windows© and Microsoft® Excel© 2000. All data are presented as means and standard deviations. Inter-group comparisons were made using unpaired t-test. Intra-group comparisons were made using one-way ANOVA. A P value of less than 0.05 was considered statistically significant.

Results:

The four groups of the study were similar in number, age range, average weight, and preoperative morbidity with no statistical significance in these respects (Table: 1).

The preoperative hemodynamics was almost similar in the subgroups of the same main group. However, groups IIa and IIb of severely extensive coronary lesion have got a significantly lower ejection fraction, and a higher incidence of unstable angina compared to groups Ia and Ib (Table: 1). The quantitative analysis of serum Troponin-I (Tp-I) revealed no statistical difference in the basal level between the four groups of the study (Table: 2). In each group of the study, it showed a significant increase in the post-declamping and recovery readings compared to their initial basal readings. However, there was a statistically significant lower value in combined A-C groups compared to the Antegrade cardioplegia groups (Table: 2).

Serum levels of Superoxide Desmutase, Glutathione peroxidase, and lactic acid had a similar pattern of change in this study (Table: 2). Within each group, they exhibited an initial, but statistically significant rise in the post-induction readings, that become more significant in the post-declamping readings, followed by a mild but still significant decrease in the serum levels in the post-recovery readings. However, the combined A-R cardioplegia groups showed a significantly lower value than the Antegrade groups of the same main group.

Because of performing proximal and distal anastomosis with cross clamp on in combined cardioplegia

Table: (1) Demographic, Clinical and Preoperative hemodynamic data of patients of the different groups of the study. Values are expressed as mean (SD) or as percentage of the patients

	Moderately Extensive (Group I)		Severely Extensive (Group II)	
	For AC (a)	For AC+RC (b)	For AC (a)	For AC+RC (b)
Number (n)	10	10	10	10
Age (Years)	56.8 (6.4)	55.2(4.8)	57.5(2.6)	58.2(3.4)
Weight (Kg)	88.4(3.6)	86.2(4.0)	89.0(2.3)	87.6(2.6)
Male: Female ratio	4:1	9:1	4:1	9:1
Preoperative Morbidity:				
Hypertension (%)	60 %	50 %	60 %	60 %
Diabetes (%)	50 %	40 %	40 %	50 %
Hypercholesterolemia (%)	60 %	60 %	70 %	50 %
Ex- Smoking (%):	80 %	80 %	80 %	80 %
History of recent MI (within 6 months) (%)	10 %	10 %	20 %	20 %
Preoperative Hemodynamics EF (%)	40.2 (2.34)	39.2(3.4)	34.3(3.0)	33.7(2.6)
SBP (mmHg)	160.2(8.6)	155.7(9.4)	152.5(7.7)	158(9.0)
DBP (mmHg)	88.2 (4.1)	89.4(6.4)	82.4(7.2)	85.4(5.9)
MBP (mmHg)	113.2(8.4)	111.2(7.6)	104.5(6.6)	108(5.9)
Heart Rate (Beat/min)	83.4(11.2)	82(12.4)	84(11.7)	85(11.5)
ST Segment (mm)	- 1.4 (0.35)	- 1.0 (0.22)	- 1.5 (0.24)	- 1.3 (0.31)
Unstable angina (%)	30 %	30 %	50 %	50 %
Extent of Coronary artery disease (%):				
•Single vessel	0 %	0 %	0 %	0 %
•Two vessels	100 %	100 %	0 %	0 %
•Three vessels	0 %	0 %	30 %	20 %
•More th	0 %	0 %	70 %	80%

SD: Standard Deviation of the mean
RC: Retrograde Cardioplegia
EF: Ejection Fraction
DBP: Diastolic Blood Pressure

AC: Ante grade Cardioplegia
MI: Myocardial Infarction
SBP: Systolic Blood Pressure
MBP: Mean Blood Pressure

groups, both cross clamp and bypass durations time were significantly longer than in the antegrade only groups. However, combined groups showed a statistically significant decrease in inotropic dose, incidence of post-bypass dysrhythmias and post bypass ischemia

This was also reflected on the ease of separation from cardio pulmonary bypass machine observed in the combined cardioplegia group and was even more pronounced in the severely affected coronary lesions subgroup (Table: 3).

Table: (2a) Levels of estimated parameters of patients in group I a .

Group 1 a	Troponin-I (mµgm/L)	Creatinine Kinase-MB (U/L)	Superoxide Desmutase (U/gmHb)	Glutathione Peroxidase (U/L)	Lactic acid (mg/dL)	ST segment (mm)
Baseline	1.0(0.25)	15.5(3.2)	334.2 (147.5)	44.1(2.1)	13.4(3.0)	- 1.4 (0.35)
Post-induction	0.9(0.33)	17.2(2.6)	675.6(240.4) *	87.9 (3.7) *	23.8(3.1) *	- 1.1 (0.20) *
Post-declamping	2.2(0.11) * ♦ ‡	23.7(5.8) * ♦ ‡	1914.2(401.1) * ♦	152.4(3.7) * ♦ ‡	36.4(2.2) * ♦ ‡	- 1.87(0.44) * ♦
Post-recovery	2.3(0.2) * ♦ ‡	26.6(6.6) * ♦ ‡	1672.4(325)* ♦	141.0(2.6) * ♦	34.4(2.0) * ♦ ‡	- 0.6 (0.021) * ♦

A-R: Alternate antegrade-retrograde cardioplegia; *: Statistically significant (P<0.05) compared to baseline values of the same group; ♦: Statistically significant to post-induction values in the same group; ‡: Statistically significant on comparing group: I a to II a or I b to II b.

Table: (2b) Levels of estimated parameters of patients in group I b .

Group 1 b	Troponin-I (mµgm/L)	Creatinine Kinase-MB (U/L)	Superoxide Desmutase (U/gmHb)	Glutathione Peroxidase (U/L)	Lactic acid (mg/dL)	ST segment (mm)
Baseline	0.83(0.1)	14.8(4.1)	339.7(138.6)	42.1(1.8)	12.7(2.2)	- 1.0 (0.22)
Post-induction	0.84(0.3)	16.3(4.3)	683.4(268.1) *	88.6(4.4) *	22.4(2.4) *	- 0.71 (0.54) *
Post-declamping	0.95(0.7) ‡	18.2(3.8) ‡	1622.4(294.6) * ♦ ‡	132.4(2.1) * ♦ ‡	31.5(1.8) * ♦ ‡	- 0.6 (0.53) * ♦ ‡
Post-recovery	1.1(0.3) * ‡	18.4(4.5) ‡	1453.4(303.1) * ♦ ‡	122.2(2.3) * ♦ ‡	29.9(1.2) * ♦ ‡	- 0.2 (0.047) * ♦ ‡

A-R: Alternate antegrade-retrograde cardioplegia; *: Statistically significant (P<0.05) compared to baseline values of the same group; ♦: Statistically significant to post-induction values in the same group; ‡: Statistically significant on comparing group: I a to II a or I b to II b.

Table: (2c) Levels of estimated parameters of patients in group II a .

Group II a	Troponin-I (mµgm/L)	Creatinine Kinase-MB (U/L)	Superoxide Desmutase (U/gmHb)	Glutathione Peroxidase (U/L)	Lactic acid (mg/dL)	ST segment (mm)
Baseline	1.03(0.22)	16.4(2.1)	377.1(162.2)	45.2(1.5)	14.7(3.1)	- 1.5 (0.24)
Post-induction	1.1(0.38)	16.6(4.5)	725.4(298.2) *	92.5 (5.2) *	26.7(2.5) *	- 0.88 (0.66) *
Post-declamping	3.1(0.23) * ♦ ‡	31.2(4.1) * ♦ ‡	1956.4(401.4) * ♦	163.0(4.9) * ♦ ‡	40.2(3.1) * ♦ ‡	- 1.0 (0.2) * ♦
Post-recovery	3.0(0.17) * ♦ ‡	33.5(5.2)* ♦ ‡	1755.2(287.1) * ♦	(146.6(3.4)* ♦	37.2(1.5) * ♦ ‡	- 0.51(0.3) * ♦

A-R: Alternate antegrade-retrograde cardioplegia; *: Statistically significant (P<0.05) compared to baseline values of the same group; ♦: Statistically significant to post-induction values in the same group; ‡: Statistically significant on comparing group: I a to II a or I b to II b.

Table: (2d) Levels of estimated parameters of patients in group II b .

Group II b	Troponin-I (µg/m/L)	Creatinine Kinase-MB (U/L)	Superoxide Desmutase (U/gmHb)	Glutathione Peroxidase (U/L)	Lactic acid (mg/dL)	ST segment (mm)
Baseline	1.0(0.41)	15.8(3.8)	365.8(157.2)	47.3(1.8)	14.1(3.4)	- 1.3 (0.31)
Post-induction	0.9(0.52)	16.3(5.1)	732.3(304.5) *	95.3(4.7) *	27.3(2.0) *	- 0.85 (0.42) *
Post-declamping	1.1(0.33) ♦	21.3(4.2) * ♦ ‡	1789.2(202.4) * ♦ ‡	144.2(3.5) * ♦ ‡	35.9(1.6) * ♦ ‡	- 0.71(0.21) * ♦
Post-recovery	1.4(0.32) * ♦ ‡	23.0(3.7) * ♦ ‡	1502.3(280.5) * ♦ ‡	133.2(3.0) * † ♦ ‡	33.2(1.0) * ♦ ‡	- 0.22 (0.1) * ♦

A-R: Alternate antegrade-retrograde cardioplegia; *: Statistically significant ($P<0.05$) compared to baseline values of the same group; ♦: Statistically significant to post-induction values in the same group; ‡: Statistically significant on comparing group: I a to II a or I b to II b.

Table: (3) Patient Parameters of different groups.

Values are expressed as mean \pm SD or as percentage of the patients.

	Moderately Extensive (Group I)		Severely Extensive (Group II)	
	For AC (a)	For AC+RC (b)	For AC (a)	For AC+RC (b)
Mean cardioplegia volume (mL)	1150 \pm 211	1317 \pm 250 ♣	1321 \pm 220	1520 \pm 280 ♣
Mean number of grafts	2.3 \pm 0.7	2.5 \pm 0.8	3.7 \pm 1.1	3.8 \pm 0.9
Total ischemic time (min.)	49.4(7.8)	63.9(11.7) *	58.4(9.4)	65.2(10.7) *
Recovery pattern from CPB:				
- Spont. Defib.	60%	90% ♣	40%	70% ♣
- Sinus Rhythm	90%	100%	70%	90% ♣
- pacemaker use	10%	0%	20%	10%
- inotropics use	40%	20% ♣	100%	80% ♣
- Ease of weaning from CBP	80%	90%	50%	70% ♣
Average dose of Epinephrine as an inotrope (gm/min)	5.5(3.3)	2.1(2.0) *	6.4(3.2)	2.3(2.7) *
Frequent use of DC shock (%)	40%	10% *	40%	10% *

SD: Standard Deviation of the mean

RC: Retrograde Cardioplegia

CPB: Cardiopulmonary Bypass

AC: Antegrade Cardioplegia

MI: Myocardial Infarction

♣: Death within a week postoperatively

*: Statistically significant ($P<0.05$) compared to the AC group of the same category.

Discussion:

The optimal route of delivery of cardioplegia is still in debate in patients with ischemic heart disease. Cardiothoracic surgeons and anesthesiologists exhibited great concern about the comparison between different routes and composition of the cardioplegic solutions in coronary patients in particular since myocardial protection is the cobblestone of improvement of the early and delayed surgical outcome of such surgical procedures (12).

Since the introduction of the retrograde route for the delivery of cardioplegia through the coronary sinus by Lillchei and colleagues in 1956 (13), many studies have been postulated to investigate its effectiveness in myocardial preservation in surgeries of cardiac valve replacement, until late in 1970s, when interest emerged in retrograde coronary perfusion in coronary surgery(14). Some studies raised concerns that the sole use of retrograde perfusion created inadequate preservation of the right ventricle in particular (15). Other studies even concluded that the combined use of antegrade and retrograde routes offered the same degree of myocardial preservation induced by the antegrade route alone, by this, they ignoring the role of the retrograde perfusion(16). Other studies reported significant differences favoring the retrograde route over the traditional antegrade route with respect to homogeneous distribution of the cardioplegia(17), myocardial recovery time (18), ease of weaning from CPB, and Swan-Ganz hemodynamic measurement on emergence from CPB. The rationale for combined antegrade and retrograde routes of cardioplegic delivery is based on anatomic and experimental arguments (19, 20). The coronary venous system is composed of two interrelated systems: the epicardial or superficial (greater) system and the endocardial or deep (lesser) system. The greater system includes the coronary sinus and its tributaries, the small cardiac vein, and the anterior cardiac vein that drain into the coronary sinus. The lesser system comprises the vessels that drain directly into the cardiac chambers. There is widespread anastomosis at all levels of the cardiac venous circulation. Thus, the myocardium may be adequately perfused retrogradely by this large venous network free of atherosclerotic changes (21). The study of the biochemical differences between both techniques opened the way to a new field of evaluation(22).

The troponin complex is the regulatory element of the myofilament, which mediates the calcium dependence of muscle contraction in both cardiac and skeletal muscle. Its three components, troponin I (TnI), troponin C (TnC), and the skeletal troponin T (TnT), interact with each other and other thin filament proteins (actin and tropomyosin) through both calcium-dependent and

independent associations (23). Hence, cardiac troponin-I is a new marker for disruption of cardiac myocytes with the potential for detection of minor differences in myocardial ischemia (24,25,26). In the present study, serum Troponin-I didn't change significantly after induction of anesthesia in the four groups of the study. However, it significantly increased in both post-declamping and post-recovery reading compared each to its post-induction reading. Within each category, the subgroup of combined antegrade and retrograde cardioplegia showed statistically significant lower readings compared to the antegrade subgroups, indicating superior myocardial protection from combined antegrade-retrograde cardioplegia that was more significant in severe coronary lesions.

CK-MB is not a specific parameter for myocardial damage or cardiac ischemic changes(27). However, in this work, it showed a significant rise in the post-declamping measurement relative to the pre-operative one within the same group, and this rise was significantly lower in the combined antegrade-retrograde cardioplegia groups relative to the antegrade groups. This reflects a better myocardial preservation when sequentially combining the two techniques rather than applying the antegrade technique alone.

In the present study, lactic acid levels were significantly increased after induction in the study groups. However, the post-declamping and post-recovery lactic acid levels were significantly higher in the antegrade groups compared to the combined antegrade – retrograde cardioplegia groups.

Lactate is an end product of anaerobic metabolism. It is one of the most common forms of metabolic acids resulting from either tissue hypoperfusion and/or hypoxemia. Measuring arterial lactate concentration is a prompt, easy and relatively non-invasive way to estimate tissue oxygen metabolism. Initial increases in the lactate level following induction of anaesthesia in the present study may be related to the stress of induction, intubation and artificial ventilation(28). Lactate levels increased significantly during post-CPB measurements in a majority of the patients. The increases in lactate levels are affected by the changes in inter-organ blood flow, blood glucose levels and/or blood pH, in addition to the effects of the CPB-priming lactated Ringer's solution(29). Studies of the lactate levels in cardiac surgeries with extracorporeal circulation (CPB) suggest that high lactate levels are indicative of inadequate oxygen delivery (DO₂), or a defect in the oxidative utilisation despite adequate DO₂ (30).

Tissue perfusion was found to be at risk during cardiac surgery with CPB and in the immediate post-

operative period. The association of low blood flows with metabolic acidosis and accumulation of lactate perioperatively has been well established. With the improvements in cardiopulmonary bypass and overall haemodynamic management, severe peri- and post-operative hypoperfusion has become rare. Despite the rarity of severe postoperative complications, several lines of evidence suggest that episodes of less severe hypoperfusion and borderline tissue oxygenation are relatively common. Measurement of blood lactate levels is widely used to assess the adequacy of tissue perfusion that apparently looked to be superior when applying the two techniques of cardioplegia rather than the antegrade technique only. However, the interpretation of elevated blood lactate levels is limited by several confounding variables including acute changes in acid-base balance, inter-organ substrate flux, peripheral and visceral tissue perfusion, and hepatic lactate uptake will all influence blood lactate levels and may occur during and after cardiac surgery with CPB (31).

Superoxide desmutase (SOD) and glutathione peroxidase (GSH-Px) are enzymes acting as free radical scavengers. Following induction of general anesthesia, levels exhibited a significant increase compared to the pre-induction levels but insignificant changes between the four groups. The readings referred as post-declamping and post-recovery levels exhibited a significant increase compared to the post-induction levels, and a significant increase of these levels in the antegrade groups compared to the combined antegrade-retrograde groups.

Evidences are accumulating that most of the degenerative diseases that affect humans have their origin in deleterious free radical reactions. The increase of the post-induction levels of all of SOD, and GSH-Px reflected the oxidative stress of induction of anaesthesia as well as endotracheal intubation that was mild and comparable in the four groups of the study.

CPB induced a significant oxidative stress. This may be attributed to the ischemic reperfusion injury caused by aortic cross-clamping, inflammatory response, cardiac neutrophil accumulation and trans-coronary neutrophil activation during clinical cardiopulmonary bypass(32) and the significant activation of antithrombotic protein C pathway during cardiopulmonary bypass, mainly during the minutes after aortic unclamping in the ischemic vascular beds. All these factors could result into an oxidative damage that may impair the post-ischemic recovery of human heart and circulation(33). The lower readings of (SOD) and (GSH-Px) in the antegrade-retrograde cardioplegia groups compared to the antegrade groups indicate less oxidative stress and better scavenging of

the free radicals. These laboratory data potentiate our previous study that analysed a number of favourable clinical end points as an evidence of adequacy of retrograde cardioplegia delivery(34).

In conclusion, coronary artery surgeries, particularly those done for severely extensive lesions exhibited better preservation of the myocardial tissue from ischemic/reperfusion insults indicated by the estimated levels of (Tn I) and (CK-MB), better tissue perfusion estimated by the level of serum lactate, and better protection from the oxidative stress by (SOD) and (GSH- Px) levels when done by a combined sequential antegrade-retrograde technique for the cardioplegia than those done with antegrade cardioplegia alone.

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