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Investigation of Inflammatory and Oxidative Stress Biomarkers in Multi Vessels Minimally Invasive Coronary Artery Bypass Graft Surgery Versus Off-Pump Coronary Artery Bypass Graft

[1]**Mohammed Farouk Abdel-Hafez**, [1]**Ahmed El-Minshawy**, [1]**Ahmed M. Taha**, [2]**Ahmed Mohamed Mandour,** [3]**Mahmoud Gamal Mahmoud and** [4]**Khalid M. Mohany**

[1]*Department of Cardiothoracic Surgery, Faculty of Medicine, Assiut University, P.O. Box 71515, Assiut, Egypt*
[2]*Department of Anesthesia and Intensive Care Unit, Faculty of medicine, Assiut University, P.O. Box 71515, Assiut, Egypt*
[3]*Department of Medical Bioinformatics, Egyptian E-learning University, Egypt*
[4]*Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Assiut University, Assiut, Egypt*

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Corresponding Author:
Mahmoud Gamal Mahmoud
Department of Medical
Bioinformatics, Egyptian
Elearning University
Email: mahmoud.gamal@vet.aun.edu.eg

Abstract: Traditional Coronary Artery Bypass Graft (CABG) is currently among of the chief methods in dealing with patients suffering from atherosclerotic coronary heart disease. The current study aimed to measure and compare the levels of proinflammatory cytokines and oxidative stress marker in patients who underwent multivessels Minimally Invasive Coronary Artery Bypass Graft Surgery (MICS– CABG) versus off-pump Coronary Artery Bypass Grafting (off-pump CABG) in the cardiothoracic department, Assiut University hospitals, Upper Egypt. the study included 67 patients, all of them suffering from atherosclerotic coronary artery disease, which confirm by cardiac catheter angiography. The patients were divided randomly into two groups, first group (A) included 34 patients to whom Multi Vessels Coronary Artery Bypass Graft Surgery (MICS-CABG) under off pump had been done. The second group (B) included 33 patients whom underwent off pump Coronary Artery Bypass Grafting (off-pump CABG). Tumor Necrosis Factor-A (TNF-α), interlukin-2 (IL-2), lipid peroxides, Superoxide Dismutase (SOD), total thiols and Nitric Oxide (NO) were estimated in sera of all patients by their corresponding methods; 48 h before the operation, 15 min before the operation end and 72 h after the operation. After testing the normality, Mann-Whitney U test and Spearman correlation coefficient were used to compare the two groups and tested the variables' correlations with the duration of the operation. $p \leq 0.05$ was considered significant. Serum TNF-α, IL-2 and lipid peroxides levels were significantly higher while total thiols and SOD were significantly lower, intraoperative and postoperatively, while No was significantly higher intraoperative only, in off-pump CABG group compared to MICS-CABG group and in both groups, intraoperative and postoperatively compared to preoperative levels. Especially in the postoperative samples, TNF-α, IL-2 and NO levels correlated positively while those of SOD correlated negatively with the operation duration the clinical data obtained presented in details in the result sector and revealed that. MICS-CABG group associated with less post-operative pain, less need for blood transfusion, less hospital stays and rapid regain to normal activity. The current study revealed that MICS-CABG is an effective procedure that is associated with small surgical trauma and lower inflammations and oxidative stress compared to off-pump CABG.

Keywords: MICS - CABG, Off-Pump CABG, Inflammatory Cytokines, Oxidative Stress

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Introduction

Traditional Coronary Artery Bypass Graft (CABG) is currently among of the chief methods in dealing with patients suffering from atherosclerotic coronary heart disease. It is performed under on-pump and cardiac arrest and is associated with severe injury and a generalized inflammation with many undesired consequences postoperatively (Xu *et al.*, 2020; Bas *et al*., 2016). To minimize these adverse consequences and with the modern advancement in the vessels targeting and beating cardiac procedures, other techniques were developed. These techniques include off-pump minimal invasive Multivesseles Coronary Artery Bypass Graft Surgery (MICS-CABG) and off-pump CABG **(**Xu *et al*., 2020**)**.

The exposure of MICS-CABG, is done more laterally, leading to a reduction of the risk of costo-chondral or rib injury. Also, MICS-CABG allows revascularization with a similar configuration to that of a traditional sternotomy technique, by direct vision left internal mammary artery harvesting and hand sewn proximal and distal anastomosis **(**McGinn *et al*., 2009; Une *et al*., 2013). With MICS-CABG, since the technique permits access to the anterior, lateral and inferior walls of the heart with or without utilization of cardiopulmonary bypass, myocardial revascularization is achieved completely in more than 95% of cases (Detter *et al*., 2001). Also, the advantages of MICS-CABG include reduced perioperative mortality, diminished needs for blood transfusion, decreased surgical site infection rates and also early return to full physical function (McGinn *et al*., 2009; Lapierre *et al*., 2011).

The ischemia reperfusion cycles that occur during the CABG operations results in marked increase in the proinflammatory cytokines such as interleukins and Tumor Necrosis Factor Alpha (TNF-α) and oxidative stress due to imbalance between the body oxidant and antioxidants (Hirai, 2003; Dias *el al*., 2015; Perros *et al*., 2020).

The present study aimed to measure and compare the levels of proinflammatory cytokines namely TNF-α and IL-2 and oxidative stress markers namely lipid peroxides, Superoxide Dismutase (SOD), total thiols and Nitric Oxide (NO) in patients who underwent MICS- CABG versus off-pump CABG in the cardiothoracic department, Assiut University hospitals, Upper Egypt. It also tested the correlations of these proinflammatory cytokines and oxidative stress markers with the duration of the operation.

Patient and Methods

The present study was conducted in the cardiothoracic Department, Assiut university hospitals between August 2017 and August 2020. It was approved by the Assiut University Medical Ethics Committee (IRB: 17200098).

Participants

The study included 67 patients, all of them suffering from atherosclerotic coronary artery disease, which confirm by cardiac catheter angiography. The patients were divided randomly into two groups; first group (A) included 34 patients to whom Multi Vessels Coronary Artery Bypass Graft Surgery (MICS-CABG) under off pump had been done. The second group (B) included 33 patients whom underwent off pump Coronary Artery Bypass Grafting (off-pump CABG). After being acquainted with the study aim, they gave a written informed consent.

Complete medical history was taken and full examinations, electrocardiogram, chest X ray, echocardiography, abdominal sonar and Doppler US for neck, upper and lower limb vessels were done for all participants. Routine laboratory Investigations were done for all patients namely complete blood picture, random blood sugar, glycated Hemoglobin Percentage (HBA1c%), liver function tests, Hepatitis markers, renal function tests, prothrombin time and lipid profile.

Exclusion Criteria

The patient was excluded from the study when presented with sever congestive heart failure, had a history of a stroke especially those who had neurological defect and acute myocardial infarction with ST elevation (72 h before the operation). Also, the patient was excluded when his/her pericardium or pleura was opened by a previous intervention within the previous six months, when other concurrent surgical interventions were required (e.g., valve replacement), when had any contraindications for MICS-CABG and off-pump CABG, when had marked deficiency in white blood cells, platelets and red blood cells and when the patient had other non-cardiac diseases that may decrease the chance of survival (≤ 5 years) such as hepatic or renal failure.

Laboratory Analysis

Ten ml venous blood were collected from all participants preoperatively (48 h before the operation), intraoperatively (15 min before the end of the operation) and postoperatively (72 h after the operation). The samples were left for 10-15 min to be clotted and then centrifuged at 3.000×g for 15 min to collect sera. The collected sera were kept at -20°C till the assay. Enzyme linked immunosorbent assay was used to determine the levels of TNF-α (R&D systems, Inc. cat. No DTA00) and IL-2 (T cell Diagnostics Cambridge cat. No BK1010). Serum levels of Lipid peroxide were determined by the methods of Uchiyama and Mihara (1978), total thiols levels by the method of Ellman (1959), SOD by method of Misra and Fridovich (1972) and nitric oxide by the method described by Van Bexooijen *et al*. (1998) (Van Bezooijen *et al*.,1998).

Statistical Analysis

The data was analyzed by SPSS-v. 26. The normality of the data was tested. Mann-Whitney U test was used to compare the two groups and Spearman correlation coefficient was done to evaluate the correlations of the levels of proinflammatory cytokines and oxidative stress markers with the duration of the operation. p-Values ≤0.05 were considered significant.

Results

The current study included 67 patients (57 males and 10 females), there ages ranged from 36-80 (mean ± SD 61.6±8.4) divided randomly into two groups. Group A included 34 patients (29 males and 5 females) their ages (mean ± SD was 59.29±9.71) the second group B included 33 patients (28 males and 5 females) their ages (mean ± SD was 64±6.17) with significant difference P<0.0 2. (Table 1).

The ECG finding of group A revealed old anterior Q waves in one patient in addition to sinus rhythm in another one, while the rest (32) showed no abnormality, On the other hand no abnormal ECG findings was recorded in group B patients. Regarding the myocardial markers, troponin was positive in 4 patients in group A and in 8 patients in group B. (Table 2)

The intraoperative arrhythmia was recorded in one patient in both groups A and B in the form of Ventricular Tachycardia (VT) needed to Cardioversion Defibrillation (DC). One patient in group A converted to sternotomy and one patient arrested. On the other hand, 3 patients arrested in group B. Need for Intra-aortic balloon pump IABP was recorded in 2 patients in group A and in 4 patients in group B and Cardiopulmonary Bypass (CPB) needed in 2 patients in the same group, while no mortality was recorded in the two groups. Exploration was done in group A for one patient due to avulsion of the proximal, another patient due to injury of the vein by Inter Costal Tube (ICT), third patient due to massive surgical emphysema and the fourth patient due to extension of the wound to open the sternum transversely to repair an avulsed proximal. Moreover, group B patients showed no need for re-exploration. Regarding wound infection group A showed burst chest after one month and wound reclosed with tension suture with delayed wound healing in one patient and two patients there wound reopened for reclose, where no patient in group B showed wound infection. (Table 2).

Symptoms relieved in all patients in group B immediately after operation, while only 16 patient of group A relieved and the 17 their symptoms relieved postoperative with significant difference P<0.001. One patient in group A needed revascularization within 6 months due to collapsed lung with apical pneumothorax, while no one need in group B.

The current study releaved that operation time (min) was (mean ± SD 319.03±29.22) in group a patients while (mean ± SD 226.79±13.37) in group B patients with significant difference P<0.001. (Table 2)

The mean ± SD of blood transfusion was 1.07±0.25 in group A while 1.8±0.25 in group B with significant difference P<0.001, On the other hand bleeding showed no significant difference between the two groups. The second day postoperative pain was mean ± SD 3.91±1.03 and 7.94±1.03 in group A and B respectively with significant difference P<0.001.

More over hospital stay was mean ± SD 6.24±1.78 and 10.82±1.84 in group A and B respectively with significant difference P<0.001. Group A patients regain to normal activity after mean SD 10.79±6.71 days, while Group B patients needed 50.91±8.88 days with significant difference P<0.001. (Table 2)

Finally, the fifth day postoperative pain was mean ± SD 2.18±0.72 in group A while 5.39±0.5 in group B with significant difference P<0.001) (Table 2).

Comparison between MICS-CABG and Off-Pump CABG Groups Preoperative, Intraoperative and Postoperative Levels in Laboratory Finding

In both groups, the levels of TNF-α, IL-2, NO and lipid peroxides were significantly high while the levels of SOD and total thiols were significantly low intraoperatively and postoperatively compared to the preoperative levels and intraoperatively compared to the postoperative levels (Table3).

Serum TNF-α, IL-2 and lipid peroxides levels were significantly higher while total thiols and SOD were significantly lower, intraoperative and postoperatively in off pump. No was significantly higher intraoperative only in off-pump CABG group compared to MICS-CABG group (Table 3).

Correlations of the Studied Parameters with the Duration of the Operation

The levels of TNF-α, IL-2, NO and lipid peroxides correlated positively while SOD correlated negatively with the duration of the operation both intraoperatively and postoperatively in both MICS-CABG and off-pump CABG groups and also in the whole sample (Table 4).

Table1: Demographic data of patients group A and group B

		Group A		Group B		
		No.	%	No.	%	P. value
Sex	Male	29	85.3	28	84.8	0.959
	Female	5	14.7	5	15.2	
Age		59.29±9.71		64±6.17		0.021**

Chi-square test,
* Statistically significant difference ($p<0.05$)
****** Highly statistically significant difference ($p<0.01$)

Table 2: Clinical data of all studied cases

	Group A		Group B		
	No.	%	No.	%	P. value
ECG findings					
Old ant Q waves	1	2.9	0	0	0.368
Sinus rythem	1	2.9	0	0	
No	32	94.1	33	100	
Myocardial markers and cardiac troponin					
Positive	4	11.8	8	24.2	0.183
Negative	30	88.2	25	75.8	
Arrythmia					
interoperative VT need to DC	1	2.9	1	3	0.991
No	33	97.1	32	97	
Conversion to sternotomy.					
Yes	1	2.9	33	100	<0.001**
No	33	97.1	0	0	
Cardiac arrest.					
Yes	1	2.9	3	9.1	0.288
No	33	97.1	30	90.9	
Need for IABP.					
Yes	2	5.9	4	12.1	0.371
No	32	94.1	29	87.9	
CPB.					
Yes	0	0	2	6.1	0.145
No	34	100	31	93.9	
Mortality					
No	34	100	33	100	-
Need of exploration					
No	30	88.2	33	100	0.389
Yes due to avulsion of the proximal	1	2.9	0	0	
Yes due to injury of the vein by ICT	1	2.9	0	0	
Yes for massive surgical emphysema	1	2.9	0	0	
Yes with extension of the wound to open the sternum transversely to repair an avulsed proximal	1	2.9	0	0	
Wound infection.					
No	31	91.2	33	100	0.089
Brust chest after one month and the wound reclosed with Tension suture with delayed wound healing	1	2.9	0	0	
yes and the woud reopened for reclosure	2	5.9	0	0	
Relief of symptoms.					
Immediately after operation	16	47.1	33	100	<0.001**
Immediately post-operative	17	50	0	0	
Need for another revascularization within 6 month.					
No	33	97.1	33	100	0.321
Collapsed lumg with apical pnemuthorax	1	2.9	0	0	
Operation time. (min.)	319.03±29.22		226.79±13.57		<0.001**
Need for blood transfusion.	1.07±0.25		1.8±0.25		<0.001**
Bleeding	0.82±0.18		0.91±0.21		0.160
Pain (2nd day post op.)	3.91±1.03		7.94±1.03		<0.001**
Hospital stay.	6.24±1.78		10.82±1.84		<0.001**
Regain of normal activity_Day	10.79±6.71		50.91±8.88		<0.001**
pain (5th day post op.)	2.18±0.72		5.39±0.5		<0.001**

Table 3: Statistical analysis of all parameters studied in MICS-CABG and Off-pump CABG groups

			P-Values								
				MICS-CABG(GA)				Off-pump CBAG(GB)			
	MICS-CABG (GA) n = 34	Off-pump CBAG (GB) n = 33	GA*Vs* GB	Pre Vs intr Vs Pos	Pre Vs Intr	Pre Vs Pos	Intra Vs Pos	Pre Vs intr Vs Pos	Pre Vs Intr	Pre Vs Pos	Intra Vs Pos
Cholesterol (mg/dl)	215.9±21.0	216.1±27.4	0.972								
Triacylglycerol(mg/dl)	192.1±20.3	191.1±32.4	0.892								
HDL-c (mg/dl)	46.5±6.7	48.8±7.5	0.268								
LDL-c (mg/dl)	130.9±23.7	129.2±31.8	0.822								
Glucose (mg/dl)	119.6±24.4	123.6±8.4	0.442								
HbA1c% (mg/dl)	6.5±0.3	6.6±0.3	0.290								
TNF-α (pg/ml) (pr)	28.6±6.4	30.4±8.2	0.415	<0.001	<0.001	0.002	0.010	<0.001	<0.001	<0.001	<0.001
TNF-α (pg/ml) (intr)	40.0±7.4	55.8±14.4	<0.001								
TNF-α (pg/ml) (pos)	35.0±6.7	42.6±13.7	0.014								
IL-2 (pg/mL) (pr)	87.4±11.5	91.2±11.3	0.245	<0.001	<0.001	<0.001	0.031	<0.001	<0.001	0.001	<0.001
IL-2 (pg/mL) (intr)	109.2±11.0	129.0±16.7	<0.001								
IL-2 (pg/ml) (pos)	102.5±10.0	114.8±13.8	<0.001								
NO (µmol/L) (pr)	4.8±0.7	4.9±0.7	0.688	<0.001	<0.001	0.001	0.001	<0.001	<0.001	<0.001	0.004
NO (µmol/l) (Intr)	6.4±0.8	8.2±1.4	<0.001								
NO (µmol/l) (pos)	5.6±0.8	5.8±1.0	0.488								
SOD (U/ml) (pr)	1.9±0.8	1.5±0.4	<0.001	0.203	0.199	0.659	0.087	<0.001	<0.001	<0.001	<0.001
SOD (U/ml) (Intr)	1.6±0.8	1.3±0.7	<0.001								
SOD (U/ml) (pos)	1.8±0.4	1.4±0.3	<0.001								
Total thiol (µmol/l) (pr)	5.7±0.6	5.8±1.0	0.258	0.010	0.003	0.298	0.047	<0.001	<0.001	<0.001	0.345
Total thiol (µmol/l) (intr)	4.7±1.2	4.2±0.4	<0.001								
Total thiol (µmol/l) (pos)	4.5±0.9	4.1±0.5	0.004								
Lipid peroxide (nmol/l) (pre)	3.8±0.9	4.5±0.9	0.068	0.011	0.579	0.139	0.044	<0.001	<0.001	<0.001	0.002
Lipid peroxide (nmol/l) (intr)	4.4±0.9	6.5±1.1	<0.001								
Lipid peroxide (nmol/l) (pos)	3.9±0.6	5.6±1.1	<0.001								

SD: Standard Deviation, HDL-c: High Density Lipoprotein cholesterol, LDL-c: Low Density Lipoprotein cholesterol, HBA1c%: glycated hemogolbin percentage, TNF-α: Tumor Necrosis Factor alpha, pr: Preoperative, intr: Intraoperative, **pos:** Postoperative, IL-2: Interleukin-2, NO: Nitric oxide, SOD: Superoxide Dismutase

Table 4: correlations between the duration of the operation and intra- and postoperative levels of TNF-α, IL-2, NO·, SOD, total thiols and lipid peroxides

		Duration of the operation (hours)		
		MICS-CABG(GA)	Off-pump CBAG(GB)	Whole sample (GA&GB)
TNF-α (pg/ml) (intr)	*C*	0.487	0.738	0.625
	P	0.013	<0.001	<0.001
TNF-α (pg/ml) (pos)	*C*	0.431	0.591	0.530
	P	<0.001	<0.001	<0.001
IL-2 (pg/mL) (intr)	*C*	0.429	0.426	0.363
	P	<0.001	<0.001	<0.001
IL-2 (pg/mL) (pos)	*c*	0.503	0.651	0.583
	P	0.010	<0.001	<0.001
NO (µmol/l) (Intr)	*c*	0.481	0.731	0.490
	P	0.015	<0.001	0.004
NO (µmol/l) (pos)	*c*	0.424	0.699	0.580
	P	0.035	<0.001	<0.001
SOD (U/ml) (Intr)	*c*	-0.527	-0.681	-0.603
	P	0.007	<0.001	<0.001
SOD (U/ml) (pos)	*c*	-0.256	-0.579	0.367
	P	0.009	<0.001	0.001
Total thiol (µmol/l) (intr)	*c*	-0.219	0.199	0.099
	P	0.293	0.341	0.495
Total thiol (µmol/l) (pos)	*c*	0.162	0.314	0.167
	P	0.438	0.126	0.246
Lipid peroxide (nmol/l) (intr)	*c*	0.616	0.585	0.571
	P	<0.001	<0.001	<0.001
Lipid peroxide (nmol/l) (pos)	*c*	0.435	0.705	0.588
	P	0.030	<0.001	<0.001

C: Spearman correlation coefficient, TNF-α: Tumor Necrosis Factor alpha, pr: Preoperative, intr: Intraoperativr, pos: Postoperative, IL-2: Interleukin-2, NO: Nitric Oxide, SOD: Superoxide Dismutase

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Discussion

According to our best knowledge we could trace few papers compared the oxidative stress between off-pump CABG and MICS-CABG.

In patient underwent, MICS-CABG and off-pump CABG, the increased levels of TNF-α, IL-2, NO and lipid peroxides and the decreased levels of SOD and total thiols that were found intraoperative and postoperatively compared to the preoperative levels in the current study are in accordance with the results reported by many previous studies.

The present study revealed significantly high intra operative and post-operative levels of TNF-a in off-pump CABG group compare to MICS- GABA. In both groups TNF-a levels were significantly higher intraoperative than preoperative and post- operative level.

A major source of TNF-α is ischemia-reperfusion cycle during CABG and left ventricle dysfunction aggravates the condition (Hirai, 2003; Perros *et al*., 2020). Diegeler *et al.* (2000) in his non-randomized study reported that TNF-α soluble receptors increased significantly and persist for 48 h after CABG surgery, while only post-operative rise showed in off-pump CABG and no change reported in MICS- CABG (Diegeler *et al*., 2000). Schulze *et al*. (2000) reported a rise in the circulating levels of TNF-α in both CABG and off-pump CABG groups of patients but the rise was more in CABG group throughout the study period (Schulze *et al*., 2000). In contrast, Matata *et al*. (2000) did not reported any early change in TNF-α levels in off-pump CABG while significant increase in CABG after 48 h postoperatively (Matata *et al*., 2000).

Also, the current study found significantly higher intra operative levels of IL-2 in off-pump CABG group compared to MICS-CABG group. In both groups, these levels were significantly higher intraoperative than pre-operative and post-operative levels and postoperatively than preoperative levels.

Regarding the proinflammatory cytokine; IL2, the results of many previous studies reported an increase in the levels of IL-2 and its receptors in both CABG and off-pump CABG procedures with more rise in CABG **(**Xu *et al*., 2020; Perros *et al*., 2020; Schulze *et al*.,2000). The MICS-CABG unlike traditional revascularization techniques, which are highly invasive due to the use of large incision (sternotomy), has a limited invasiveness and so avoid ischemia perfusion cycles and diminishes release proinflammatory cytokines such as TNF-α and interlukin-2 (Kayatta *et al*., 2018).

Lipid peroxides showed significantly higher intra- and post-operative levels in off-pump CABG group compared to MICS-CABG group. In the off-pump CABG group the lipid peroxide levels were significantly higher intraoperative than preoperative and postoperative levels and also postoperatively than preoperative levels. MICS CABG group showed significant higher levels of Lipid peroxides intra operatively than postoperative levels while no significant difference was found between preoperative and postoperative levels. Zakkar *et al.* (2015) reported that atherosclerotic coronary artery disease interaction is associated with oxidative stress prior the surgery which markedly increased during cardiopulmonary bypass and when the condition was associated with coexisting morbidities such as diabetes mellitus, renal or lung diseases (Zakkar *et al*., 2015). The authors also reported that off-pump procedures are associated with lower degree of oxidative stress than on-pump surgery (Zakkar *et al*., 2015). Gerritsen *et al.* (2001) reported that off-pump CABG was associated with significant lower levels of urinary malondialdehyde during the first 24 h after surgery (Gerritsen *et al*., 2001). Matata *et al.* (2000) showed that in the early hours after surgery off-pump CABG patients have significant lower levels of lipid hydroperoxide, protein carbonyls and nitrotyrosine compared to on-pump coronary artery bypass with beating heart and without cardioplegia **(**Matata *et al*., 2000). The authors added that the coronary arteries were clamped only for the time needed to perform distal anastomosis in both group which means equal degree of myocardial ischemia perfusion in both group (Matata *et al*., 2000).

The levels of superoxide dismutase were significantly higher in the Off-pump CABG group compared to MICS-CABG group intra and postoperative. Off-pump CABG group showed significant higher levels of superoxide dismutase preoperatively than intraoperative and post-operative levels and higher postoperatively than intraoperative. In contrast, no significant different recorded between pre, intra and post- operative levels in MICS-CABG group.

It had been reported that reperfusion after a period of ischemia induces oxidative stress by initiating a series of biochemical events that result in the generation of excessive amount of reactive oxygen species **(**Zakkar *et al*., 2015**)**. Also, Biglioli *et al.* (2003) reported that off-pump CABG seemed to be associated with significant lower degree of oxidative stress with respect to CABG. They added that co-morbidities such hypercholesterolemia, hypertension, DM and chronic illness worsened this stress (Biglioli *et al*., 2003).

The current study revealed significantly higher intra operative levels of NO in CABG group compered to MICS-CABG group.

In addition, the current work revealed significantly higher levels of nitric oxide, in both groups, preoperatively than intraoperative and postoperative levels and also, postoperative than intraoperative levels. L-Arginine act as precursor for the synthesis of Nitric Oxide (NO). It was reported that the addition of

L-Arginine to cardioplegia solutions in patients undergoing CABG, it increased the myocardial O_2 uptake and reduced lipid peroxides. Also, the use of minimal bypass could attenuate the production of lipid peroxides and nitric oxide **(**Andrews *et al*., 2012).

Total thiols level was significantly lower in CABG group than MICS-CABG group intra and post-operative while in both groups total thiols level was significantly lower intra and post-operative compere to preoperative and intraoperative compere to postoperative.

Total thiols act as scavenger of free radical in our body and the used of exogenous antioxidant is very helpful in such condition.

The levels of TNF-α, IL-2, NO and lipid peroxides correlated positively while SOD correlated negatively with the duration of the operation both intraoperatively and postoperatively in both MICS-CABG and off-pump CABG groups and also in the whole sample (table 4).

in spite of the longer duration of MICS-CABG group still the levels of the oxidative stress are significantly lower compere to the off-pump CABG.

Since the two procedures in the present study are off-pump, the major causes of difference in the inflammatory reaction maybe due to the surgical trauma and its complications (sternotomy in off-pump CABG) (Xu *et al*., 2020).

Conclusion

The current work revealed that MICS-CABG is an effective procedure that is associated with small surgical trauma and lower inflammations and oxidative stress compared to off-pump CABG and it is preferred to be used when possible.

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Author Contribution’s

Mohammed Farouk Abdel-Hafez: Performed the experiment wrote the paper performed the surgeries.

Ahmed El-Minshawy: Conceived and designed the experiments. Performed the surgeries.

Ahmed Mohamed Taha: Performed the surgeries.

Ahmed Mohamed Mandour: Performed the anesthesia and follow up.

Mahmoud Gamal Mahmoud and [4]Khalid Mohamed Mohany: Performed the biochemical and statistical analysis. Wrote the paper.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved

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Abbreviations

MICS- CABG:	Group A multi vessels minimally invasive coronary artery bypass graft surgery
CABG:	GROUP B pump coronary artery bypass grafting
TNF-α:	Tumor necrosis factor- alpha
IL-2:	Interleukin-2,
NO:	Nitric oxide,
SOD:	Superoxide dismutase
VT:	Ventricular tachycardia
DC:	Cardioversion Defibrillation
IABP:	Intra-aortic balloon pump
CPB:	Cardiopulmonary bypass
ICT:	Inter costal tube