Modified Extracorporeal Membrane Oxygenation Offers Stable Hemodynamic Conditions with Less Invasiveness in Coronary Artery Bypass Grafting

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Objective: Cardiopulmonary bypass offers a stable hemodynamic condition during coronary bypass surgery, but undesirable side-effects emerge as complicating issues. We developed a minimally invasive cardiopulmonary bypass modifying extracorporeal membrane oxygenation to alleviate the side-effects of conventional cardiopulmonary bypass. Herein, we evaluated the effectiveness of the modified extracorporeal membrane oxygenation in coronary bypass surgery. **Materials and methods:** 79 patients who underwent coronary bypass surgery using cardiopulmonary bypass between January 2014 and March 2019 were divided into those using conventional cardiopulmonary bypass (n=47) and those using the modified extracorporeal membrane oxygenation (n=32). We compared the results of these groups. **Results:** The operation time in the patients with the modified extracorporeal membrane oxygenation were significantly shorter than those with conventional cardiopulmonary bypass ($p=0.001$). Heparin and priming volume were less required for the modified extracorporeal membrane oxygenation. The in-hospital mortality and morbidity were comparable between the groups. However, the length of intubation and intensive care unit stay following the operation with the modified extracorporeal membrane oxygenation were significantly shorter than those with conventional cardiopulmonary bypass ($p=0.018$ and $p=0.001$, respectively). Furthermore, the creatinine kinase MB isozyme value at the end of the operation with the modified extracorporeal membrane oxygenation was significantly lower than that with conventional cardiopulmonary bypass ($p=0.002$). **Conclusion:** Our modified extracorporeal membrane oxygenation seemed less invasive than conventional cardiopulmonary bypass because of the reduced operation time and the early postoperative recovery. This system is beneficial when performing coronary bypass surgery, especially for high-risk patients.

KEY WORDS: cardiopulmonary bypass, coronary artery bypass grafting, extracorporeal membrane oxygenation, minimally invasive extracorporeal circulation

1. Introduction

During the last decade, various modalities, such as operative techniques, surgical devices and cardiac anesthesia, have been improved, helping surgeons to perform less invasive coronary artery bypass grafting (CABG) procedures, including minimally invasive direct coronary artery bypass (MID-CAB)¹⁾, off-pump CABG²⁾ and CABG using a technique of minimally invasive cardiac surgery (MICS-CABG)³⁾. However, with the improvements in surgical management, there is an increasing proportion of pa-

tients receiving intervention who are at an older age, at a critical stage of coronary artery disease or have severe ischemic heart failure. This makes it challenging to perform less-invasive CABG. Under these circumstances, cardiopulmonary bypass (CPB) is generally used to keep hemodynamic stability during coronary bypass grafting; however, at same time, the increased invasiveness of using CPB could lead to elevated mortality, morbidity and delayed postoperative recovery, particularly in patients with the unfavorable conditions mentioned above. Based on this background, we have developed a minimally invasive CPB circuit by modifying a standard circuit of extracorporeal membrane oxygenation, which we named modified extracorporeal membrane oxygenation (mECMO), and adapted it to CABG patients who were unsuitable for the off-pump strategy. The goal was to obtain hemodynamic stability during coronary bypass grafting and to alleviate the side-effects of CPB. Potential advantages of using a closed circuit such as ECMO system include re-

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Received: January 7, 2020; Accepted: May 11, 2020

doi: 10.7793/jcad.26.20-00002

Fig. 1 Schema of the two different cardiopulmonary bypass circuits.

a: Conventional cardiopulmonary bypass circuit.

b: Modified extracorporeal membrane oxygenation circuit.

VL: venous line, CVL: cardiac vent line, SL: suction line, AL: arterial line, RP: rotary pump, VR: venous reservoir, OH: oxygenator and heat exchanger, AF: air filter, DBR: drained blood reservoir, CP: centrifugal pump, SR: soft reservoir.

quiring less priming volume⁴⁾ and avoiding blood–air interaction⁵⁾, which may contribute to alleviating the adverse effects of conventional CPB (cCPB) with an open hard-shell venous reservoir. In this study, we compared the results of CABGs using our mECMO with those using a cCPB and demonstrated the benefits of the mECMO on CABG surgery.

II. Materials and methods

1. Study design

All operations and data collection were performed in Ise Red Cross Hospital, Ise, Japan. Clinical outcome data were also obtained from hospital's patient records or by telephone interview. The ethics committee of Ise Red Cross Hospital approved this study. Between January 2014 and March 2019, we performed 230 CABG operations, of which CABGs without CPB, CABGs performed concomitant to other cardiac surgeries and CABGs performed through re sternotomy were excluded. As a result, 79 isolated CABGs using cCPB (cCPB group, n=47) or mECMO (mECMO group, n=32) were enrolled for this analysis. Regarding the assignment of the two different CPB systems, we switched the CPB system used in CABG from cCPB to mECMO after October 2016 and only used mECMO thereafter. We retrospectively reviewed the outcomes of the patients in both groups and compared both in-hospital and post-discharge results between the two groups to evaluate the effectiveness of mECMO, particularly in terms of its less invasiveness.

2. Cardiopulmonary bypass circuit

cCPB was conducted using a centrifugal pump machine (S5 perfusion system; LivaNova PLC, London, UK). The bypass circuit consisted of a heparin-coated circuit (Cosmotec Co., Ltd.,

Tokyo, Japan) combined with an open hard-shell venous reservoir (RR30; Terumo Co., Ltd., Tokyo, Japan), a centrifugal pump (Revolution; LivaNova PLC) and a membrane oxygenator (Quadrox-I; Getinge AB, Gothenburg, Sweden). Drained blood was directly returned to the venous reservoir while the CPB was running (Fig. 1a). The solution used for priming this CPB circuit mainly comprised 6% hydroxyethylated starch and Ringer's lactate solution without any blood product.

CPB using the mECMO circuit was conducted with the same machine as with cCPB (S5 perfusion system). The bypass circuit for mECMO consisted of a heparin-coated circuit (Cosmotec Co., Ltd.) combined with a centrifugal pump (Revolution) and a membrane oxygenator (Quadrox-I). We modified this circuit by integrating a closed soft venous reservoir, which allowed for controlling the circulating blood volume by moving it upward and downward during the CPB. All these components formed a completely closed circuit. Independent of the circuit, drained blood was temporally pooled in another reservoir (XTRA; LivaNova PLC) and returned to the circuit by a rotary pump as needed (Fig. 1b). The solution used for priming the mECMO circuit was same as used in the cCPB.

3. Operative techniques

Throughout the study period, technical details of the coronary bypass surgeries in the cCPB and mECMO groups were nearly consistent. Grafts used for the coronary bypass included the left and right internal thoracic arteries and saphenous veins and were selected according to individual patient status or anastomosis sites. All operations were performed through median sternotomy. Heparin (300 IU/kg for the cCPB group and 150 IU/kg for the mECMO group) was given before the CPB with the activated

clotting time (ACT) target being 400 seconds for the cCPB group and 250 seconds for the mECMO group. ACT was measured during the CPB every hour. Arterial perfusion during the CPB in both groups was conducted via a cannula inserted in the ascending aorta or the femoral artery if severe calcification or atherosclerotic plaques were identified by epi-aortic echography. Venous drainage was conducted via the right atrium. Left ventricular venting was sometimes combined only in the cCPB group if necessary for controlling heart volume during graft anastomosis. All graft anastomoses were performed using the beating heart strategy and no cardioplegic heart arrest was combined. Static and clear operative fields for graft anastomosis were obtained with a stabilizer (Acrobat-i Stabilizer; Getinge AB, Gothenburg, Sweden) and CO₂ blower. A deep pericardial stitch was usually placed to access branches of the circumflex artery or the distal right coronary arteries. Snare stitches were placed in advance, both proximally and distally to the intended anastomosis site of the coronary artery, to block potential bleeding during graft anastomosis. An intracoronary shunt tube was exclusively used during graft anastomosis at the left anterior descending branch and the proximal right coronary artery to prevent myocardial ischemia and fatal arrhythmia. Grafts were sewn to coronary arteries using the running suture technique with 8–0 Prolene (Ethicon, Inc., Cincinnati, OH). Proximal anastomosis was conducted under partial clamping of the ascending aorta or using suture devices if the ascending aorta was inappropriate for partial clamping. After completing all anastomoses, the CPB was weaned if the hemodynamic status was stable.

4. Definitions and data collection

In-hospital and late mortality were defined as all-cause mortality following the operation before (in-hospital) and after (late) discharge. Urgent operations were defined as operations performed during unplanned admission due to a critical cardiovascular state. Postoperative stroke was defined as any brain lesion identified in the brain CT or MRI corresponding to abnormalities on physical examination. Acute kidney injury (AKI) was defined as postoperative creatinine value increasing more than 0.5 mg/dL compared with the preoperative value or a new dialysis required postoperatively. Patients who were already dependent on dialysis before the operation were excluded from the analysis of postoperative renal function. The creatinine kinase MB isozyme (CK-MB) was measured at the end of the operation, 1 day and 2 days after the operation and was compared between the two groups, except for patients who had acute myocardial infarction preoperatively; acute myocardial infarction was defined if patients had elevated CK-MB levels higher than 15 U/L before the operation and underwent the operation within seven days after the onset of acute myocardial infarction. The C-reactive protein values and the peripheral platelet counts were obtained preoperatively and

at 1, 3, 7 and 14 days after the operation. The fibrinogen values were also obtained preoperatively and at 1, 3 and 7 days after the operation. The value obtained at 2 days after the operation was adopted as the value of the postoperative creatinine. After the operations, the patients were extubated if their status met our extubation criteria as follows: 1. No major bleeding, i.e., >100 ml/h. 2. Stable hemodynamic condition with mean arterial pressure controlled between 70 mmHg and 100 mmHg. 3. Sufficient recovery of respiratory function with a respiratory rate $\leq$ 20/min, vital capacity $\geq$ 8 ml/kg and blood gas analysis showing PaO₂ >80 mmHg and PaCO₂ <55 mmHg under 50% O₂ concentration. 4. Sufficient recovery of consciousness, which refers to $\geq$ 13 points in the Glasgow Coma Scale. The criteria for dismissing patients from the intensive care unit (ICU) were as follows: 1. Complete hemostasis with no more need of mediastinal and pericardial drainage. 2. Steady hemodynamic condition independent from mechanical circulatory support and persistent catecholamine administration. 3. Settled breathing with no need for ventilator support. 4. Calm mental state with no need for sedatives. These criteria for extubation and dismissing patients from the ICU were adapted to all patients throughout the study period. Major adverse cerebral and cardiovascular events (MACCE) were defined as the composite of all-cause mortality, myocardial infarction, cerebrovascular accident or stroke, or reinterventions for any coronary lesion.

5. Statistical analysis

All statistical analyses were performed using statistical software: EZR (Easy R) on R commander⁶. Continuous variables were described as the mean $\pm$ standard deviation if the data were normally distributed or as the median with the 25th and 75th percentiles if the data did not follow normal distribution. The paired Student's *t* test or Mann–Whitney *U* test was applied for comparisons of continuous variables between the groups. Categorical variables were described as numbers and percentages and the χ^2 test was applied for the group comparisons. The survival and freedom-from-MACCE rates were calculated by the Kaplan–Meier method. Differences in these rates between the groups were analyzed using the log-rank test. Multiple linear regression analysis was used as a multivariate analysis to identify the predictors for the length of ICU stay. Selection of variables for the multivariate analysis was based on significance in univariate analysis which was performed for all the available preoperative and intraoperative variables. In all statistical tests, differences between the groups were considered significant at $p < 0.05$.

III. Results

1. Patients' background

The patient characteristics are shown in Table 1. Overall, the characteristics of the patients in the two groups were compara-

Table 1 Patient characteristics

Factor	cCPB <i>n</i> =47	mECMO <i>n</i> =32	<i>p</i> value
Age	69.55 ± 9.89	70.88 ± 8.28	0.795
Male sex (%)	40 (85.1)	24 (75.0)	0.405
Obesity (%)	13 (27.7)	8 (25.0)	0.997
History of smoking (%)	32 (68.1)	20 (62.5)	0.785
Hypertension (%)	40 (85.1)	32 (100.0)	0.06
Dyslipidemia (%)	28 (59.6)	25 (78.1)	0.139
Diabetes (%)	31 (66.0)	22 (68.8)	0.988
CKD (%)	32 (68.1)	21 (65.6)	1
Dialysis (%)	8 (17.0)	7 (21.9)	0.804
Creatinine (mg/dl)	2.07 ± 2.10	2.83 ± 3.71	0.903
AMI (%)	4 (8.5)	2 (6.2)	1
CVA (%)	5 (10.6)	6 (18.8)	0.489
OMI (%)	13 (27.7)	7 (21.9)	0.751
LVEF (%)	47.6 ± 14.5	52.5 ± 15.4	0.199
LMT lesion (%)	19 (40.4)	16 (50.0)	0.542
Post-PCI (%)	14 (29.8)	7 (21.9)	0.602
NYHA class	3.06 ± 0.79	3.25 ± 0.80	0.194
CCS class	3.06 ± 0.79	3.34 ± 0.79	0.111
Urgency (%)	12 (25.5)	12 (37.5)	0.375
Preoperative ECMO support (%)	0 (0.0)	2 (6.2)	0.314
Preoperative IABP support (%)	6 (12.8)	7 (21.9)	0.446
Euro score	7.43 ± 10.52	8.44 ± 10.60	0.451

cCPB: conventional cardiopulmonary bypass, mECMO: modified extracorporeal membrane oxygenation, CKD: chronic kidney disease, AMI: acute myocardial infarction, CVA: cerebral vascular accident, OMI: old myocardial infarction, LVEF: left ventricular ejection fraction, LMT: left main trunk, PCI: percutaneous coronary intervention, NYHA: New York heart association, CCS: Canadian Cardiovascular Society, ECMO: extracorporeal membrane oxygenation, IABP: intra-aortic balloon pumping.

ble. However, relatively more patients who had hypertension were included in the mECMO group, but this difference was not statistically significant ($p=0.06$). Emergent or urgent operations were performed in 12 patients (25.5%) in the cCPB group and 12 patients (37.5%) in the mECMO group ($p=0.375$). Six patients (12.8%) in the cCPB group and seven patients (21.9%) in the mECMO group preoperatively underwent intra-aortic balloon pumping ($p=0.446$), and no patient in the cCPB group and two patients (6.2%) in the mECMO group needed preoperative ECMO support ($p=0.314$) due to hemodynamic instability. The preoperative left ventricular ejection fraction (LVEF) estimated by echocardiography was $47.6\pm 14.5\%$ in the cCPB group and $52.5\pm 15.4\%$ in the mECMO group ($p=0.199$). These differences in preoperative patient characteristic between the two groups were not statistically significant.

Follow-up was completed for 94.9% of the patients. The mean follow-up period for both groups was 24.6 ± 18.7 months. However, there was a difference in the follow-up period between the cCPB group (31.3 ± 21.0 months) and the mECMO group

(14.8 ± 7.6 months) ($p<0.001$) because the first patient in the mECMO group was enrolled in October 2016.

2. Operative data

Table 2 shows all operative data. The mean number of distal anastomoses in the two groups were comparable: 3.53 ± 0.88 in the cCPB group and 3.41 ± 0.71 in the mECMO group ($p=0.686$). However, both the operation time and the CPB time in the mECMO group (334 ± 68 min. and 159 ± 57 min., respectively) were significantly shorter than those in the cCPB group (394 ± 80 min. and 187 ± 45 min., respectively) ($p=0.001$ and $p=0.014$, respectively). The mean priming volume in the mECMO group (879 ± 111 ml) was significantly lower than that in the cCPB group (1084 ± 164 ml) ($p<0.001$). The heparin dosage was reduced in the mECMO group (214.5 ± 66.2 IU/kg) compared with the cCPB group (387.5 ± 133.1 IU/kg) ($p<0.001$), which was resulted in the shorter ACT during the CPB in the mECMO group. Although difference in the amount of bleeding between the two groups did not reach significance, the amount of transfusion was significantly less in the mECMO group (1500 ± 680 ml) com-

Table 2 Operative data

Factor	cCPB <i>n</i> =47	mECMO <i>n</i> =32	<i>p</i> value
Operating time (min)	394 ± 80	334 ± 68	0.001
CPB time (min)	187 ± 45	159 ± 57	0.014
Priming volume (ml)	1084 ± 164	879 ± 111	<0.001
Heparin dose (IU/kg)	387.5 ± 133.1	214.5 ± 66.2	<0.001
Bleeding (ml)	1322 ± 839	1284 ± 689	0.811
ACT (sec)			
Before heparinization	153 ± 27	151 ± 22	0.905
Maximum value during heparinization	548 ± 159	385 ± 74	<0.001
Mean value during heparinization	461 ± 113	316 ± 46	<0.001
Transfusion (ml)	1927 ± 944	1500 ± 680	0.031
Total fluid balance (ml)	2213 ± 1455	2228 ± 1254	0.952
Bodyweight increment at POD#1 (%)	5.17 ± 4.28	5.54 ± 2.83	0.873
Number of distal anastomoses	3.53 ± 0.88	3.41 ± 0.71	0.686
Use of UITA (%)	23 (48.9)	16 (50.0)	1
Use of BITA (%)	23 (48.9)	15 (46.9)	1
Use of SVG (%)	44 (93.6)	31 (96.9)	0.900

cCPB: conventional cardiopulmonary bypass, mECMO: modified extracorporeal membrane oxygenation, CPB: cardiopulmonary bypass, ACT: activated clotting time, POD: postoperative day, UITA: unilateral internal thoracic artery, BITA: bilateral internal thoracic artery, SVG: saphenous vein graft.

pared with the cCPB group (1927±944 ml) ($p=0.031$), which seemed to be attributed to less hemodilution, which was achieved by mECMO with a low priming volume.

3. In-hospital results

Table 3 summarizes the in-hospital outcomes. In-hospital death occurred in four patients in the cCPB group, the causes of which were low output syndrome in two patients, bleeding in one patient and fatal arrhythmia in one patient. However, no in-hospital deaths occurred in the mECMO group. Although in-hospital deaths occurred only in the cCPB group, the difference in the in-hospital mortality rate between the cCPB and mECMO groups did not reach statistical significance ($p=0.242$). The incidence of postoperative stroke, re sternotomy due to postoperative bleeding, low output syndrome requiring sustained ECMO support and AKI were all comparable between the two groups. However, some parameters associated with postoperative recovery indicated the superiority of mECMO; the mean intubation time was significantly shorter in the mECMO group (32.3 hours) compared with the cCPB group (46.0 hours) ($p=0.018$), the length of ICU stay was significantly shorter in the mECMO group (3.8 days) compared with the cCPB group (6.4 days) ($p=0.001$), and the percentage of patients who could discharge within 2 weeks after the operation was higher in the mECMO group (37.5%) compared with the cCPB group (19.1%) ($p=0.12$). Furthermore, use of mECMO was an independent predictor for shorter ICU stay by the multiple linear regression anal-

ysis (Table 4). Considering quality of the anastomoses, the rate of the patent bypass grafts confirmed by coronary CT or coronary angiography following the operation was similar between the two groups (97.8% in the cCPB group and 96.2% in the mECMO group; $p=0.706$).

Fig. 2 shows parameters related to invasiveness of the operation. Among these results, the CK-MB level was significantly lower in the mECMO group at the end of the operation (48.4±74.0 U/L) and the next day (37.8±77.1 U/L) compared with the cCPB group (63.3±61.9 U/L at the end of the operation, 42.6±38.2 U/L the next day) ($p=0.002$ and $p=0.007$, respectively) (Fig. 2a). However, there was no difference in the C-reactive protein levels at any time point between the groups (Fig. 2b). The values of the peripheral platelet count and the fibrinogen in the mECMO group tended to be higher throughout the postoperative course than those in the cCPB group, with the significance at the postoperative day 7 in the peripheral platelet counts (22.0±8.4 ×10⁴ cells/mm³ vs. 18.3±8.3 ×10⁴ cells/mm³; $p=0.049$) and at the postoperative day 3 in the fibrinogen values (448±66 mg/dL vs. 371±109 mg/dL; $p=0.002$) (Fig. 2c, d).

4. Late outcome

During the follow-up period, nine late mortalities occurred in the cCPB group, four of which were cardiovascular related, while three late mortalities occurred in the mECMO group, two of which were cardiovascular related. Overall, the survival rate in the mECMO group was better than that in the cCPB group,

Table 3 In-hospital results

Factor	cCPB <i>n</i> =47	mECMO <i>n</i> =32	<i>p</i> value
In-hospital mortality (%)	4 (8.5)	0 (0.0)	0.242
Stroke (%)	1 (2.1)	2 (6.2)	0.733
LOS requiring ECMO support (%)	1 (2.1)	1 (3.1)	1
Postoperative IABP support (%)	10 (21.3%)	6 (18.8%)	1
Resternotomy due to postoperative bleeding (%)	0 (0.0)	0 (0.0)	NA
AKI (%)	11 (28.2)	4 (16.0)	0.411
New dialysis requirement (%)	7 (14.9)	2 (6.2)	0.409
Postoperative creatinine (mg/dl)	1.20 (0.94, 2.84)*	1.32 (0.86, 2.68)*	0.936
Duration of intubation (hours)	8.0 (5.0, 14.0)*	5.0 (4.0, 10.3)*	0.018
Catecholamine-dependent days	2.0 (1.0, 4.5)*	2.00 (1.0, 3.0)*	0.169
ICU stay (days)	5.0 (3.0, 5.5)*	3.00 (2.0, 4.0)*	<0.001
Early discharge within 14 days (%)	9 (19.1)	12 (37.5)	0.12
Number of patent grafts (%)	136 (97.8)	101(96.2)	0.706

cCPB: conventional cardiopulmonary bypass, mECMO: modified extracorporeal membrane oxygenation, LOS: low output syndrome, ECMO: extracorporeal membrane oxygenation, NA: not available, AKI: acute kidney injury, ICU: intensive care unit, *: Values are expressed as median (25th and 75th percentiles).

Table 4 Predictors for duration of ICU stay

Factor	Univariate		Multivariate		<i>p</i> value
	<i>p</i> value	Coefficient	95%CI		
			Lower limit	Upper limit	
Preoperative					
Age	0.363				
Male sex	0.244				
Smoking	0.100				
CKD	0.049	1.755	-1.513	5.022	0.288
CVA	0.948				
Dyslipidemia	0.144				
Diabetes	0.538				
Dialysis	0.679				
Hypertension	0.061				
Obesity	0.151				
OMI	0.945				
LVEF	0.275				
NYHA class	0.040	0.829	-1.566	3.214	0.491
CCS class	0.062				
Urgency	0.008	4.171	-0.098	8.441	0.055
Intraoperative					
mECMO	<0.001	-3.212	-6.353	-0.072	0.045
Total fluid balance	0.904				
Bleeding	0.173				
Operating time	0.510				
CPB time	0.419				

ICU: intensive care unit, CI: confidence interval, CKD: chronic kidney disease, CVA: cerebral vascular accident, OMI: old myocardial infarction, LVEF: left ventricular ejection fraction, NYHA: New York heart association, CCS: Canadian Cardiovascular Society, mECMO: modified extracorporeal membrane oxygenation, CPB: cardiopulmonary bypass.

Fig. 2 Parameters related to invasiveness of the operation.

a: Creatinine kinase MB isozyme.

b: C-reactive protein.

c: Peripheral platelet count.

d: Fibrinogen.

CK-MB: creatinine kinase MB isozyme, POD: postoperative day, cCPB: conventional cardiopulmonary bypass, mECMO: modified extracorporeal membrane oxygenation, CRP: c-reactive protein, PLT: platelet, FIB: fibrinogen, *: $p < 0.01$, #: $p < 0.05$.

The level of each time point shows the mean value. The error bars indicate standard deviation.

although the difference analyzed by the log rank test was not statistically significant ($p = 0.115$) (Fig. 3a). Regarding freedom from MACCE, there was no difference between the two groups ($p = 0.698$) (Fig. 3b).

IV. Discussion

CPB support allows for complete revascularization in CABG surgery under stable a hemodynamic condition, but it is more invasive compared with off-pump strategies. Possible adverse side-effects of the CPB include a systemic inflammatory response and subsequent organ dysfunction triggered by complement system activation through foreign surfaces, priming volume, and blood–air interaction in the open reservoir^{4, 5, 7}. To avoid these cCPB side-effects, minimally invasive extracorporeal

circulation (MiECC) technologies have been developed and applied not only to CABG surgery but also to other cardiovascular surgeries in the last decade^{8, 9}. The MiECC generally consists of a closed circuit integrating an oxygenator and a centrifugal pump and is characterized with its markedly reduced length, which allows for running the CPB with low a priming volume. The closed circuit has the advantage of avoiding blood–air interaction which is believed to activate a systemic inflammatory response⁵ and the coagulation cascade¹⁰. In addition, a low priming volume contributes to less blood transfusion⁴. All these factors suggest that MiECC is less invasive compared with cCPB. In fact, we obtained superior results in CABG surgery with our MiECC system, mECMO, in terms of postoperative recovery, compared with that using cCPB.

Fig. 3 Kaplan–Meier curves for comparison of late outcome between the two groups.

a: Overall survival.

b: Freedom from MACCE.

cCPB: conventional cardiopulmonary bypass, mECMO: modified extracorporeal membrane oxygenation, MACCE: major adverse cerebral and cardiovascular events.

Anastasiadis et al. categorized the MiECC system into four types according to its components¹¹. According to their categorization, mECMO can be assigned to the type III MiECC system, which allows for controlling circulating blood volume. The detailed features of mECMO system are as follows: First, a soft reservoir is integrated into the bypass circuit. Controlling heart capacity is vital to achieving satisfactory distal anastomosis to the coronary vessels because a larger heart may restrict the view for the distal anastomosis, especially to the circumflex artery or the posterior descending artery. The soft reservoir integrated in to the circuit allows circulating blood volume and heart capacity to be easily controlled and is helpful in performing high-quality anastomosis. Second, mECMO circuit was developed by modifying an ordinary ECMO circuit. Advantages of using an ordinary ECMO scircuit include it being possible to make the system simple and cost-effective. Finally, mediastinal drainage blood can be returned quickly to the main circuit through another circuit with a rotary pump. cCPB could return drained blood quickly to systemic circulation and easily maintains the hemodynamic condition, but the standard ECMO generally lacks a shed-blood suction component and cannot handle an unexpectedly large amount of bleeding. To resolve this concern associated with standard ECMO, we added an extra circuit and a reservoir where drained blood temporally pools, then directly returns to the main bypass circuit as needed. Another possible option for reusing drained blood is to process it using a cell-saver device. According to previous reports, the concentration of inflammatory cytokines in mediastinal drainage blood is reduced by treatment with a cell-saver device, and using cell-saver processed blood is help-

ful in maintaining systemic vascular resistance¹². In another report, Teligui et al. observed that low systemic heparinization is only safe in combination with separation of mediastinal drainage blood from the systemic circulation using a cell-saver device in case of generating clots in the drained blood¹³. However, because there is a time-lag to process drained blood with the cell-saver device, it is probably difficult to address an unexpectedly large amount of bleeding. In addition, the plasma component containing the coagulation factors and the platelets are completely removed by the cell-saver process, which might cause coagulopathy and require transfusion of the plasma component. Considering the contamination risk for the blood clots without using a cell-saver device, the risk seems low because we always added heparinized saline to the drained blood through a two-lumen suction tube when draining the leaked blood besides systemic heparinization. In addition, the drained blood was filtered through a filter included in the blood reservoir. As a result, we did not experience any complication regarding the direct return of mediastinal drainage blood.

One concern associated with a closed circuit is how to remove air that might be mixed within the circuit. Although secure surgical techniques are mandatory to prevent air aspirated from the venous cannula, the oxygenator generally has the capacity to remove some air. In addition, we combined an air trapping filter in the main bypass circuit before the arterial cannula, which seemed to be sufficient for preventing air embolism in case of accidental air contamination.

According to the operative data in this study, mECMO led to a shorter operation time and CPB time regardless of the similar

number of the distal anastomoses between the two groups. One reason for this finding is that the mECMO system was simpler than that of cCPB because it did not have a cardiac vent route or multiple suction tubes, and the time for establishing and withdrawing the system was thus reduced. Another reason may be that the time for hemostasis was reduced in the mECMO group owing to a preserved coagulability attributed to a lower heparin dosage and milder hemodilution. The shorter CPB time in the mECMO group was likely because patients in the mECMO group could be weaned from CPBs more easily. In contrast, patients in the cCPB group took longer to wean from CPBs, probably because of their decreased cardiac function. Five patients in the cCPB group required additional IABPs for weaning from CPBs; these IABPs were all introduced while the CPBs were running. Additionally, some other patients in the cCPB group underwent secondary CPBs after completing all the anastomoses and the initial CPBs. However, only one patient in the mECMO group required an additional IABP while the CPB was running. This difference in weaning from CPB was considered to have influenced the CPB time in the two groups.

Other remarkable findings concerning the operative data were that mECMO required a lower dosage of heparin and a lower priming volume, contributing to less transfusion in the mECMO group. In addition, MiECC is considered to be associated with reduced coagulation activation and causes less thrombin formation owing to better biocompatible surfaces and the elimination of the blood–air interaction^{10, 14}. These features also may have helped to achieve less transfusion in the mECMO group.

In the cCPB group, a relatively higher rate of in-hospital mortality was observed. Among the four patients with in-hospital mortality in the cCPB group, three underwent emergent CABG operations because of their severely deteriorated hemodynamic conditions caused by acute myocardial ischemia. The remaining patient had a vulnerability in her vascular system, including coronary arteries and bypass grafts, which required repeated anastomoses in one anastomosis site. This caused prolonged operation time and increased bleeding. These undesirable factors may have contributed to her early postoperative mortality. Although a similar number of emergent operations were also performed in patients with deteriorated preoperative hemodynamic conditions in the mECMO groups, no early mortality was fortunately observed in the mECMO group. This difference in early mortality rates seems to be attributed to the difference in the invasiveness between the two CPB systems; i.e., the deleterious effects of cCPB may further have affected the patients' postoperative status, which was already impaired preoperatively.

Considering other in-hospital outcomes, there was no significant difference in in-hospital morbidity between the cCPB and mECMO groups. However, the results showed the superiority of

mECMO in some parameters related to postoperative recovery. For example, the mean length of intubation was significantly shorter in the mECMO group. Consistent with our results, Boven, et al reported that postoperative respiratory function was confirmed to be preserved following CABG with a fluid restrictive closed circuit by measuring the lung-specific biomarker, lung clara cell 16 (CC16) protein¹⁵. Although there seem to be multiple factors for the length of intubation after an operation: e.g., preoperative respiratory function, history of smoking, depth of the anesthesia and inflammatory cytokine level¹⁶, the operation time and CPB time are particularly important and can markedly influence the length of the postoperative intubation¹⁷. The length of the ICU stay for patients in the mECMO group was also shorter than that for patients in the cCPB group, which was also considered to be evidence that mECMO was preferable for postoperative recovery. In addition, multiple linear regression analysis revealed that mECMO was an independent predictor for shorter ICU stay. The better outcome in the mECMO group continued early after hospital discharge; the survival rate in the mECMO group tended to be better than that in the cCPB group, and the MACCE remained similar between the two groups.

Among all findings in this study, the most interesting result was that the postoperative CK-MB value was significantly lower in the patients who received mECMO, compared with the cCPB group patients, regardless of both methods having the same operative strategy of not initiating cardioplegic heart arrest during the coronary bypass graft anastomosis. Although several researchers have shown the efficacy of MiECC compared with cCPB over the last decade, the myocardial protective effect of MiECC has not been mentioned to date. Generally, CABG with the beating heart strategy is protective against ischemic reperfusion injury in the cardiac muscle compared with the cardioplegic arrest strategy. In this study, it was shown that mECMO further prevented the cardiac muscle from leaking cardiac enzymes. One possible reason for mECMO being protective toward myocardial injury is the lower inflammatory response to mECMO compared with cCPB. Proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin (IL)-6 and IL-8, are associated with myocardial dysfunction and hemodynamic instability¹⁸, and there is a report showing that such proinflammatory cytokines' level and neutrophil activation was alleviated with the use of MiECC¹⁹. Instead of those proinflammatory cytokines, we measured C-reactive protein, peripheral platelet number and fibrinogen to see the postoperative inflammatory status. As already known, peripheral platelet number and fibrinogen value also represent not only coagulability but also inflammatory status of patients, and they correlate with the degree of inflammation²⁰. However, compared with the cCPB group, all these parameters were not reduced in the mECMO group, but inversely, the plate-

let counts and the fibrinogen values in the mECMO were relatively higher throughout the postoperative courses. Because platelet count and fibrinogen value can be influenced by other factors such as hemodilution, consumption, and degradation during operations²⁰, this result can explain that mECMO helped more highly preserve the level of platelet number and fibrinogen and contributed to their early recovery thereafter. Therefore, further investigations are necessary to conclude that mECMO has advantage in reducing inflammatory response. Another possible reason for the lower CK-MB level in the mECMO group might be that mECMO could maintain a higher mean arterial pressure and require a lower dosage of vasoactive drugs, which was helpful in maintaining adequate peripheral perfusion and protective against myocardial ischemia. Taken together, although the reason has not fully been elucidated yet, the lower CK-MB level following CABG with mECMO can indicate that mECMO is less invasive in terms of being protective against myocardial injury.

Finally, several limitations must be mentioned in the present study. First, this study was designed as a retrospective study, which can contain a selection bias or inherent heterogeneity in the comparison groups. However, we only used cCPB until mECMO was first introduced in October 2016 and we mainly used mECMO thereafter, which suggests that the bias for patient selection should be minimized. In addition, to the best of our knowledge, no apparent difference in the baseline characteristics in the two groups was recognized. Second, as already mentioned in the Methods, we switched the CPB system used in CABG from cCPB to mECMO after October 2016; therefore, there were differences in when the operation was performed and follow-up length between the two groups. That could suggest that the operative results may be affected by surgeons' and surgical teams' experience. However, we found no apparent technical inferiority in the operations in the cCPB group and anastomosis time did not differ greatly between the two groups. Additionally, operative techniques other than circulatory support systems and patient management were barely changed throughout the study period. We therefore consider that when the operation was performed has only slightly affected the operative results. Finally, the study was performed with a relatively small sample. Therefore, the study lacks the power to detect statistical significance in the differences in outcomes for dichotomous variables, such as rate of mortality, stroke, or AKI between the comparison groups, and conversely, the differences may appear more significant than they are expected. Thus, care should be taken in the interpretation of the data.

V. Conclusion

The present study showed that CABG using mECMO achieved a reduced operation time and CPB time, resulted in

early recovery from the operation, and alleviated myocardial injury. Although further investigation is necessary, mECMO can offer hemodynamic stability during coronary revascularization with fewer deleterious side-effects usually associated with CPB. Such characteristics of mECMO may also be beneficial for more challenging cases, such as those with severely impaired cardiac function or complex coronary lesions. mECMO may even be appropriate for other cardiac procedures, including minimally invasive cardiac surgery.

Acknowledgement

None.

Disclosure statement

None of the authors has conflict of interest.

References

- 1) Repossini A, Di Bacco L, Nicoli F, et al: Minimally invasive coronary artery bypass: Twenty-year experience. *J Thorac Cardiovasc Surg* 2019; **158**: 127–138. e1
- 2) Shroyer AL, Grover FL, Hattler B, et al: On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med* 2009; **361**: 1827–1837
- 3) Nambiar P, Kumar S, Mittal CM, et al: Minimally invasive coronary artery bypass grafting with bilateral internal thoracic arteries: Will this be the future? *J Thorac Cardiovasc Surg* 2018; **155**: 190–197
- 4) Ellam S, Pitkanen O, Lahtinen P, et al: Impact of minimal invasive extracorporeal circulation on the need of red blood cell transfusion. *Perfusion* 2019; **34**: 605–612
- 5) Schönberger JP, Everts PA, Hoffmann JJ: Systemic blood activation with open and closed venous reservoirs. *Ann Thorac Surg* 1995; **59**: 1549–1555
- 6) Kanda Y: Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant* 2013; **48**: 452–458
- 7) Edmunds LH: Inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg* 1998; **66** (5 Suppl): S12–16; discussion: S25–28
- 8) Immer FF, Ackermann A, Gygas E, et al: Minimal extracorporeal circulation is a promising technique for coronary artery bypass grafting. *Ann Thorac Surg* 2007; **84**: 1515–1520; discussion: 1521
- 9) Liebold A, Albrecht G: Minimized extracorporeal circulation in non-coronary surgery. *J Thorac Dis* 2019; **11** (Suppl 10): S1498–S1506
- 10) Ovrum E, Holen EA, Tangen G, et al: Completely heparinized cardiopulmonary bypass and reduced systemic heparin: clinical and hemostatic effects. *Ann Thorac Surg* 1995; **60**: 365–371
- 11) Anastasiadis K, Murkin J, Antonitsis P, et al: Use of minimal invasive extracorporeal circulation in cardiac surgery: principles, definitions and potential benefits. A position paper from the Minimal invasive Extra-Corporeal Technologies international Society (MiECTiS). *Interact Cardiovasc Thorac Surg* 2016; **22**: 647–662
- 12) Westerberg M, Gäbel J, Bengtsson A, et al: Hemodynamic effects of

- cardiotomy suction blood. *J Thorac Cardiovasc Surg* 2006; **131**: 1352–1357
- 13) Teligui L, Dalmayrac E, Mabilieu G, et al: An ex vivo evaluation of blood coagulation and thromboresistance of two extracorporeal circuit coatings with reduced and full heparin dose. *Interact Cardiovasc Thorac Surg* 2014; **18**: 763–769
- 14) Wippermann J, Albes JM, Hartrumpf M, et al: Comparison of minimally invasive closed circuit extracorporeal circulation with conventional cardiopulmonary bypass and with off-pump technique in CABG patients: selected parameters of coagulation and inflammatory system. *Eur J Cardiothorac Surg* 2005; **28**: 127–132
- 15) van Boven WJP, Gerritsen WB, Driessen AH, et al: Minimised closed circuit coronary artery bypass grafting in the elderly is associated with lower levels of organ-specific biomarkers: A prospective randomised study. *Eur J Anaesthesiol* 2013; **30**: 685–694
- 16) Kern H, Redlich U, Hotz H, et al: Risk factors for prolonged ventilation after cardiac surgery using APACHE II, SAPS II, and TISS: comparison of three different models. *Intensive Care Med* 2001; **27**: 407–415
- 17) Reddy SLC, Grayson AD, Griffiths EM, et al: Logistic risk model for prolonged ventilation after adult cardiac surgery. *Ann Thorac Surg* 2007; **84**: 528–536
- 18) Wan S, Izzat MB, Lee TW, et al: Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. *Ann Thorac Surg* 1999; **68**: 52–56; discussion: 56–57
- 19) Ohata T, Mitsuno M, Yamamura M, et al: Minimal cardiopulmonary bypass attenuates neutrophil activation and cytokine release in coronary artery bypass grafting. *J Artif Organs* 2007; **10**: 92–95
- 20) Aljassim O, Karlsson M, Wiklund L, et al: Inflammatory response and platelet activation after off-pump coronary artery bypass surgery. *Scand Cardiovasc J* 2006; **40**: 43–48