

厚生労働科学研究費補助金
効果的医療技術の確立推進臨床研究事業

Prospective randomized study による人工心肺を
使用しない心拍動下冠状動脈バイパス手術の
有用性に関する研究

平成15年度 総括・分担研究報告書

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総括研究報告書

Prospective randomized study による人工心肺を使用しない 心拍動下冠状動脈バイパス手術の有用性に関する研究

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・ 研究要旨

虚血性心疾患の頻度は年々増加傾向を示し、侵襲的治療法としての冠状動脈バイパス手術（CABG）は、年間 18,000 例を超えている。中等度以上の手術リスクを有する患者に対して、人工心肺を使用しない CABG(OPCAB)が行われるようになってきた。Retrospective な研究により OPCAB は、中等度以上のリスクを有する症例では、従来の CPB を用いた CABG に比して、早期成績が良好とされている。一方、OPCAB では、バイパス本数は、通常のカABG と比べて少なく、手技的に困難なために吻合のクオリティーが落ちて、遠隔成績が不良との報告もある。そこで、Prospective な研究として、OPCAB に習熟した 5 施設において、70 歳未満の二枝病変以上の冠動脈疾患患者で、人工心肺を使用する CABG が問題ないと考えられる患者を無作為に人工心肺使用あるいは非使用の CABG に振り分けて手術を施行し、その成績を比較検討した。登録症例 141 例で、このうち、退院しデータが確認された 121 例(人工心肺非使用群 63 例、人工心肺使用群 58 例)について解析した。術前の患

患者背景等に差は認められず、両群ともに、手術死亡はなかった。手術時間、術後NSE値、最高CK-MB値、術後血小板値、S-100蛋白、入院医療費で両群間に有意差を認め、人工心肺非使用群で有意に良好な結果であった。ICU滞在期間、挿管時間、術後出血量、輸血量、術後脳高次機能、合併症の頻度では両者間に有意差を認めなかった。バイパスの本数あるいは開存等には両群間で差を認めなかった。周術期における中枢神経障害、心筋障害に関する種々の指標で、人工心肺非使用群が優れており、人工心肺を使用しない事による脳、心臓に対する低侵襲性が証明された。医療経済上も人工心肺を使用しないことで、医療費は軽減できることが明らかとなった。

- ・ 分担研究者氏名、所属機関名及び所属機関における職名 とともに、国民全体の医療費の削減に寄与することを目的とする。

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・ 研究目的

これまで本邦の心臓血管外科領域なされていなかった Prospective randomized study の手法を用いて、人工心肺使用によるリスクが少ないと考えられる患者においても、OPCABが有用であることを明らかにする。これにより OPCAB が虚血性心疾患の標準的治療法となり得るかどうかを科学的に証明し、患者の負担を軽減する

・ 研究方法

- ・ OPCAB に習熟した 5 施設において、70 歳未満の二枝病変以上の冠動脈疾患患者で、人工心肺を使用する CABG が問題ないと考えられる患者をエントリーした。症例の登録・割付を中央管理体制（インターネット）で行い、Randomized Control Trial として人工心肺使用あるいは非使用の CABG に振り分けて手術を施行した（目標症例数 300 例）。人工心肺使用および非使用群に分けて、以下の項目について比較検討した。

- ・ 1)術後早期評価
- ・ 手術時間、麻酔時間、バイパス本数、バイパスをおいた冠動脈の枝の大きさ・狭窄度、グラフト材料、挿管時間、ICU 滞在期間、術後 12 時間のドレーン排液量、輸血量、術後入院期間、術後合併症（心房細動・周術期心筋梗塞・感染症の

発生等)・入院医療費を比較した。術後 ICU 入室時に脳障害の指標である S-100 及び NSE を測定し、心筋障害の指標である CPK-MB を術後経時的に測定した。また一般血液検査、肝機能・腎機能等の一般生化学的検査を行った。

- ・ 術後 3 週間以内に心臓カテーテル検査を行い、冠状動脈及びバイパス造影を施行し、バイパスの開存性等の評価を行った。
- ・ 2)術後遠隔期評価
- ・ 術後患者に外来、郵便、電話にて調査を行った。狭心痛(CCS 分類)・心筋梗塞の有無、死亡とその原因の確認、PCI・再手術の有無、Quality of Lifeなどを調査し、術後データベースに記載した。術後 1-2 年の間に術後遠隔期の冠状動脈・バイパス造影、負荷心筋シンチ、トレッドミル負荷心電図を行いグラフト開存性、心筋虚血の有無、運動耐容能等を検査した。
- ・ (倫理面への配慮) 本研究を開始する前に、申請者の各施設の倫理委員会にて、充分検討審査を受けた。また、独立した治験管理官により、プロトコールの遂行が適正に行われているかの監査を受けた。明らかに人工心肺を用いた冠状動脈バイパス手術を受けることで手術リスクを増加させると考えられる患者は、本研究にエントリーしないことにした。人工心肺を使用しない心拍動下冠状動脈バイパス手術を受けることによる、メリッ

ト、デメリットを十分説明して、インフォームド・コンセントを得た。現時点では、人工心肺非使用群と使用群のいずれにおいても、研究を中止すべき医学的問題は生じていない。

・ 研究結果

- ・ 平成 14 年 7 月より登録を開始し、現在までに登録数は 145 例となった。このうち、退院しデータが確認された 121 例(人工心肺非使用群 63 例、人工心肺使用群 58 例)について成績を集計解析した。
- ・ 術前の患者背景等に差は認められず、選択・除外基準の遵守、両群への均等な割付が施行されていた。早期成績は、以下の通りであった。両群ともに、手術死亡はなかった。人工心肺非使用群、使用群の各で、手術時間 270±61 分、316±62 分 ($p<0.0001$)、術後 Neuron-Specific Enolase(NSE) 値 10.9±9.8 ng/ml、17.2±5.9 ng/ml ($p<0.0001$)、最高 CK-MB 値 17.3±17.4 U/L、23.7±10.5 U/L ($p<0.0001$)、術後血小板値 $9.0\pm 6.2\times 10^3/\mu\text{l}$ 、 $6.2\pm 5.7\times 10^3/\mu\text{l}$ ($p=0.002$)、S-100 蛋白 0.19±0.11 ng/ml、0.34±0.23 ng/ml ($p=0.0003$)、入院医療費(保険請求額) 270±71 万円、346±92 万円($p<0.0001$)であった。手術時間、術後 NSE 値、最高 CK-MB 値、術後血小板値、S-100 蛋白、入院医療費で両群間に有意差を認め、人工心肺非使用群で有意に良好な結果であった。ICU 滞

在期間、挿管時間、術後出血量、輸血量、術後脳高次機能、合併症の頻度では両者間に有意差を認めなかった。人工心肺非使用群、使用群の各で、バイパス本数 3.5 ± 0.9 本、 3.6 ± 0.9 本、開存率 93.9%、91.7% であり、両群間に有意差を認めなかった。

- バイパスの本数あるいは開存等には両群間で差を認めないことから、手術のクオリティーは人工心肺を使用せずとも充分保たれていることが明らかとなった。また周術期における中枢神経障害、心筋障害に関する種々の指標で、人工心肺非使用群が優れており、人工心肺を使用しない事による脳、心臓に対する低侵襲性が証明された。医療経済上も人工心肺を使用しないことで、医療費は軽減できることが明らかとなった。

• 考察

- 本研究により、OPCAB は、手術のクオリティーを落とすことなく、周術期における中枢神経障害、心筋障害を軽減させることができ、医療費も削減できることがエビデンスとして明かとなった。OPCAB は、人工心肺のために使用する高価な医療材料を削減する事ができるだけでなく、コメディカルの負担も軽減されて、クリニカル・パスにのっとり治療を効率的に進めることができ、国民全体の利益が大きいと考えられる。

- 今回得られた OPCAB の有用性のエビデンスは、早期成績に関わるものであり、遠隔期においても、OPCAB が長期にわたって人工心肺を使用した CABG よりも優れているか否かは今後の問題である。本研究を発展させるために、心事故発生率を含む遠隔成績の検討が必須と考えられる。

• 結論

- 人工心肺を使用しない心拍動下冠状動脈バイパス術により、手術のクオリティーを低下させることなく、手術時間の短縮、脳神経障害・心筋障害の軽減、手術医療費の削減を行うことが出来た。

• 研究発表

1. 論文発表

別紙参照

2. 学会発表

別紙参照

• 知的財産権の出願・登録状況

1. 特許取得 なし

2. 実用新案登録 なし

現在の進行状況

2004年2月17日現在

症例の登録開始(2002年7月より)

登録数

141例

人工心肺非使用群

71例

人工心肺使用群

70例

集計・解析数

121例

人工心肺非使用群

63例

人工心肺使用群

58例



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結果

術前患者背景	非使用群	使用群	p值
年齡	58 ± 7歲	58 ± 7歲	NS
性別(男:女)	55:8	52:6	NS
病變枝數	42(67%) 21(33%) 26(41%) 44(70%) 39(62%)	42(72%) 16(28%) 32(55%) 41(71%) 40(69%)	NS NS NS NS NS
糖尿病	1(2%)	0(0%)	NS
高脂血症	0(0%)	1(2%)	NS
高血壓	3(5%)	4(7%)	NS
腦血管病變	1(2%)	1(2%)	NS
末梢血管病變	1(2%)	1(2%)	NS
呼吸機能障害	1(2%)	1(2%)	NS
肝機能障害	1(2%)	0(0%)	NS
腎機能障害	1(2%)	0(0%)	NS



手術成績	非使用群	使用群	p値
手術時間	270 ± 61 分	316 ± 62 分	0.0001
バイパス本数	3.5 ± 0.9 本	3.6 ± 0.9 本	NS
吻合グラフト	212	206	
左内胸動脈	73(34%)	63(31%)	
右内胸動脈	20(9%)	38(18%)	
撓骨動脈	89(42%)	81(39%)	
胃大網動脈	17(8%)	18(9%)	
動脈グラフト	199(94%)	200(97%)	
静脈グラフト	13(6%)	6(3%)	NS
術中合併症	5(8%)	5(9%)	NS
術中輸血量	4.0 ± 0 (*4)単位	5.7 ± 3.9 (*4)単位	NS

注: (*)内数値は中央値



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手術成績	非使用群	使用群	p値
ICU滞在期間	31 ± 19 (*21)時間	33 ± 25 (*21)時間	NS
挿管時間	10.0 ± 34.5 (*4)時間	6.5 ± 9.6 (*5)時間	NS
術後出血量	485 ± 286 (*412) ml	516 ± 381 (*412.5) ml	NS
術後輸血量	5.7 ± 3.7 (*4)単位	4.4 ± 2.0 (*4)単位	NS
脳高次機能検査	41.4 ± 34.1 (*65)	45.6 ± 36.5 (*65)	NS
S-100 蛋白	0.19 ± 0.11 ng/ml	0.34 ± 0.23 ng/ml	0.0003
Neuron-Specific Enolase	10.9 ± 9.8 ng/ml	17.2 ± 5.9 ng/ml	0.0001
血小板値	9.0 ± 6.2 ×10 ³ /μl	6.2 ± 5.7 ×10 ³ /μl	0.002
最高CK-MB	17.3 ± 17.4 U/L	23.7 ± 10.5 U/L	0.0001
術後合併症(心房細動)	13(21%)	17(29%)	NS
開存率	93.9%	91.7%	NS
入院医療費	270 ± 71万円	346 ± 92万円	0.0001
死亡	0	0	NS

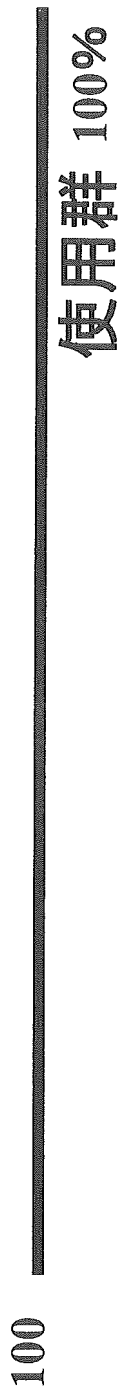
注:(*)内数値は中央値



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心事故回避率曲線

非使用群 100%



0

6

12

17

months



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An Early Outcome of A Randomized Comparison of Off-Pump and On-pump Multiple Arterial Coronary Revascularization

Running head: randomized comparison of off-pump vs. on-pump CABG

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Key words: coronary disease, revascularization, angiography

Abstract

Objective: Previous randomized comparisons of off-pump versus on-pump coronary artery bypass grafting (CABG) have yielded controversial results about cardiac and neurological protection, and graft patency. In addition, these studies were composed of CABG mainly with LITA and saphenous vein grafts. We performed a prospective randomized controlled study to compare off-pump and on-pump CABG with multiple arterial grafts.

Methods: Between July 2002 and September 2004, 167 consecutive unselected patients referred for elective primary CABG were randomly assigned to undergo multiple arterial off-pump CABG (n=81) or on-pump CABG (n=86). Clinical outcomes, S-100 protein, neuron specific enolase, and maximum CK-MB level were compared. Early graft patency was examined within 3 weeks after the operation by angiography.

Results: The number of grafts performed per patient (3.5 ± 1.0 for off-pump CABG and 3.6 ± 0.9 for on-pump CABG) and number of arterial grafts performed per patient (3.3 ± 1.0 for off-pump CABG and 3.4 ± 0.9 for on-pump CABG) were similar. Completeness of revascularization (completed grafts / planned grafts) was both 98%. There was no hospital death in both groups. Operation time was significantly ($p<0.001$) shorter in the off-pump group than in the on-pump group (267 ± 60 minutes vs. 307 ± 59 minutes). The incidence of perioperative complications was similar. No transfusion was possible more frequently in off-pump group than on-pump group (80% vs. 55%, $p<0.001$). S-100 protein levels at the ICU admission were significantly ($p<0.001$) lower in the off-pump group than in the on-pump group (0.20 ± 0.11 ng/ml vs. 0.34 ± 0.22 ng/ml). Neuron specific enolase levels at the ICU admission were significantly ($p<0.001$) lower in the off-pump group than in the on-pump group (10.4 ± 9.0 ng/ml vs. 16.9 ± 6.9 ng/ml). Maximum CK-MB levels were significantly ($p=0.046$) lower in the off-pump group than in the on-pump group (17.1 ± 16.7

IU/L vs. 21.5 ± 10.6 IU/L). Early graft patency with or without stenosis (93% and 98% for off-pump CABG vs. 96% and 98% for on-pump CABG) was similar.

Conclusions: Off-pump CABG with multiple arterial grafts was as safe as conventional on-pump CABG with similar completeness of revascularization and early graft patency. Less myocardial injury and less neurological damage were achieved with off-pump CABG.

Off-pump coronary artery bypass grafting (OPCAB) has become an established method of coronary artery bypass grafting (CABG), and the advantage of OPCAB over standard CABG with cardiopulmonary bypass (CPB) has been reported¹⁻³ in many retrospective studies. Previous randomized controlled studies also showed a shorter postoperative ICU and hospital stay, a reduced postoperative bleeding, a reduced use of blood products, and reduced morbidity⁴⁻⁹. However, there remained controversies regarding atrial fibrillation, cardiac and neurological protection, an incidence of recurrence of angina and reintervention. In addition, these comparative studies were composed of CABG mainly with only left internal thoracic artery (LITA) to left anterior descending artery (LAD) and saphenous vein grafts. Recent analyses showed significantly better outcomes when both ITAs were used compared with a single ITA^{10, 11}. Radial artery (RA) as a second arterial conduit in LITA to LAD opposed to vein graft has also achieved improved long-term outcomes probably because of better graft patency^{12, 13}. The quality and completeness of revascularization has been a major concern of OPCAB. Suboptimal anastomoses and incomplete revascularization may cause poor graft patency and long-term results after OPCAB. In the present study, we compared an early outcome of off-pump and on-pump CABG with multiple arterial grafts in a prospective randomized controlled trial.

Methods

Study Design and Patients

The JOCRI study (Japanese Off-pump Coronary Revascularization Investigation) was designed to compare off-pump and on-pump coronary revascularization with regard to completeness of revascularization, clinical outcomes, and 3-year late outcomes after CABG. This was a prospective randomized controlled multicenter trial performed in 5 centers. Surgeons have experienced more than 200 OPCAB before this study, and more than 90% of CABG was performed in 2001 before the study period. In an effort to minimize bias by the

operator, all procedures were performed by a single surgeon in each hospital. Patients who were referred for isolated, first-time CABG due to at least two vessel diseases were eligible for the study. Exclusion criteria were as follows: an age of more than 70 years; an indication for additional surgical procedures; documented history of stroke; severe ascending aortic calcification by CT scan; carotid arterial stenosis of more than 75% by Duplex scanning; acute Q-wave myocardial infarction which necessitates emergent operation; left ventricular ejection fraction of less than 30%; serum creatinine level of higher than 2.0 mg/dl; liver cirrhosis; chronic obstructive pulmonary disease who needs medication; pulmonary hypertension; other comorbidity which is not appropriate for cardiopulmonary bypass such as anomalous coagulation, cancer, and an inability to provide written informed consent.

Institutional review board and ethical committee in each hospital approved the study. Written informed consent was obtained from the patient and family. Patients were randomly assigned by means of a computer access to internet assignment in equal proportions to undergo off-pump or on-pump CABG. Surgical plan was decided by coronary angiography before randomization. Randomization was performed according to the method of minimization. Randomization was stratified according to age (< 60 years old, 60 to 65 years, 65 to 70 years), gender, coronary artery diseases (two vessel disease, three vessel disease, and left main trunk lesion), and institutes to insure roughly equal numbers of patients within strata defined by these characteristics.

Study Protocols

Patients participating in the JOCRI study had the same anesthetic protocols, the same CPB, and the same postoperative care protocols as non-randomized patients in each hospital. The heart was exposed through a median sternotomy incision. A stabilizer and an apical suction device were used for OPCAB. Surgical technique and strategy of OPCAB was previously reported¹⁴. On-pump CABG was done in standardized fashion with ascending

aortic cannulation and single venous cannulation of the right atrium. Body temperature was kept between 32 and 34 °C. Intermittent tepid blood cardioplegia was delivered ante- and retrograde. A standardized protocol of antiplatelet therapy (daily dose of aspirin 81-200mg) was used. CK-MB was measured every 8 hours after admission to ICU until 24 hours as a marker of cardiac damage. Maximum CK-MB higher than 100 U/L with ECG change was assessed as perioperative myocardial infarction. S-100 protein and neuron specific enolase were measured as markers for neurological damage when the patient was admitted to ICU.

All patients underwent postoperative angiography to evaluate graft patency within 3 weeks after CABG. Interventional cardiologists were blinded as to group assignment for angiographic evaluation. Graft patency was defined when the anastomosed site and graft was opacified by contrast medium either via conduit or native coronary artery. Flow competition or string sign was not defined as occlusion. The quality of the grafts was assessed using the criteria of FitzGibbon¹⁵.

Follow-up

Pre and postoperative data acquisition were performed in each hospital to fulfill case report forms. All data were transferred to the data center and analyzed independently. Follow-up was completed in the outpatient clinic or telephone interview every 3 months. Adverse events, admission due to angina, myocardial infarction, and reintervention were recorded for all patients.

Testing Statistical Hypothesis and Statistical Analysis

The sample size calculation was based on the assumptions that the actuarial freedom from cardiac event rate at 3 years after standard CABG is 95% and that OPCAB did not decrease the rate more than 10%. The α error was set at 0.05 and β error was set at 0.20. The required sample size was 141 in each group for a total of 282. All values are expressed

as mean \pm standard deviation or percentage. Continuous variables were compared by the Wilcoxon rank sum test, while the discrete variables were analyzed with Fisher's exact test. Differences were considered statistically significant when the p value was less than 0.05. All data analysis was according to intent to treat. Interim analyses were carried out annually to detect safety.

Results

This is the second interim analysis of early outcomes. Between July 2002 and September 2004, total of 1538 patients underwent isolated CABG, and 302 patients were eligible for this study. Of those, 167 patients (55%) underwent randomization after informed consent was obtained. They were assigned to undergo off-pump CABG (n=81) and on-pump CABG (n=86). One patient in on-pump group was found to have severe ascending aortic calcification after randomization and decided to undergo OPCAB. There was no patient who was converted from off-pump to cardiopulmonary bypass. All patients were completely followed up more than 30 days after the operation.

Most baseline demographic data were similar in two groups (Table 1). The number of grafts performed per patient (3.5 ± 1.0 for off-pump CABG and 3.6 ± 0.9 for on-pump CABG) and number of arterial grafts performed per patient (3.3 ± 1.0 for off-pump CABG and 3.4 ± 0.9 for on-pump CABG) were similar (Table 2). Arterial grafts were used in 94% of total grafts in off-pump group and 97% in on-pump group. Completeness of revascularization (completed grafts / planned grafts) was both 98% (Table 3). Operation time was significantly ($p < 0.001$) shorter in the off-pump group than in the on-pump group (267 ± 60 minutes vs. 307 ± 59 minutes). There was no hospital death in both groups (Table 4). There was no difference in the incidence of intraoperative complications such as arrhythmia and bleeding between two groups. The incidence of postoperative complications such as atrial fibrillation, infection, stroke, bleeding, and perioperative myocardial infarction

was also similar. No transfusion was possible more frequently in off-pump group than on-pump group (80% vs. 55%, $p < 0.001$). S-100 protein levels at the ICU admission were significantly ($p < 0.001$) lower in the off-pump group than in the on-pump group (0.20 ± 0.11 ng/ml vs. 0.33 ± 0.24 ng/ml). Neuron specific enolase levels at the ICU admission were significantly ($p < 0.001$) lower in the off-pump group than in the on-pump group (10.7 ± 9.5 ng/ml vs. 16.7 ± 5.8 ng/ml). Maximum CK-MB levels were significantly ($p = 0.046$) lower in the off-pump group than in the on-pump group (15 ± 14 IU/L vs. 22 ± 11 IU/L).

The early graft patency with or without stenosis was similar (off-pump 93% and 98% for off-pump group vs. 96% and 98% for on-pump group). The early graft patency with or without stenosis according to graft material and bypass sites were shown in Table 5. There was no difference in the stenosis free graft patency according to graft material, graft sites, and with or without cardiopulmonary bypass (Table 5). Graft patency of gastroepiploic artery and graft to right coronary territory were slightly worse in off-pump group although statistically not significant.

Discussion

OPCAB has become an established method of CABG, and the advantage of OPCAB over standard CABG in high risk patients has been reported¹⁻³. On the other hand, LITA is widely recognized as the ideal graft to LAD, and the bilateral use of ITA further improved the long-term results compared with the single use of ITA^{10,11}. Bilateral use of ITA may not be enough for complete revascularization because of the length of the conduit even if skeletonized technique was applied for harvesting. RA has been also used as a free graft with increasing frequency instead of saphenous vein because of easy harvesting and handling¹⁶, and superior late outcomes compared with saphenous vein¹³. Composite RA grafts make more efficient use of the conduit by placing the inflow close to coronary arteries. Complete arterial revascularization with LITA and RA composite has been reported^{14,17}.

The advantage of LITA as inflow of RA over ascending aorta was also speculated. As partial aortic cross clamp may cause atheromatous emboli¹⁸, OPCAB without aortic manipulation is feasible to reduce the incidence of stroke. Thus, coronary revascularization with in-situ and composite arterial graft is optimal to reduce neurological complication in OPCAB. In this randomized controlled study, arterial grafts were used in 94% of total grafts in off-pump group and 97% of on-pump group. In the previous randomized studies, the frequency of arterial graft use ranged from 41% to 66%⁴⁻⁹. Therefore, our multiple arterial revascularization strategy should be the most frequent use of arterial grafts, which must be an ultimately ideal option in OPCAB and should be compared with on-pump CABG.

The quality and completeness of revascularization has been a major concern of OPCAB. As OPCAB with arterial grafts are thought to be technically demanding, suboptimal anastomoses and incomplete revascularization with poor long-term results after OPCAB is suspected. This study was undertaken after operating surgeons in each hospital had experienced more than 200 OPCAB cases with multiple arterial grafts. Thus complete multiple arterial coronary revascularization without CPB was possible in almost all cases. Graft patency with or without stenosis was almost the same irrespective of CPB use. Stenosis free graft patency of the gastroepiploic arteries to the right coronary area was slightly lower in off-pump group than in on-pump group though statistically not significant. There may be two reasons. One is that the target right coronary artery is sometimes very thick and calcified compared to other territory of coronary branches, which are not suitable for OPCAB. The graft patency of RITA as in-situ graft to right coronary artery was reported worse than that of LITA to LAD in standard CABG¹⁹. The other possibility was the characteristics of gastroepiploic artery. According to our experience, it has a lot of size variety, and difficulty of handling for sequential bypass grafting.