

に CHDF を行った症例は 10 例 (66.7%) と水元論文に比し多かったが, HD 開始日は術後 1.8 日, ICU 滞在期間は 1.3 日であり, 術後在院日数は約 10 日と短期間であった. 施設間の差はあるものの, 術後急性期に CHDF を回避することが, 在院期間や予後にどのような影響を及ぼしているかの判断はむずかしいと考える.

また自験例では全例 OPCAB 例であったが, 人工心肺を必要とする症例は術前の循環不全があったり, 心脱転時に肺動脈圧が上昇するような症例である. 術後は積極的に CHDF を行うべきであると考え.

#### 4. まとめ

近年さまざまな医療機器の出現や進歩により, 術後管理は多様化し複雑になっている. それゆえ周術期管理の簡素化や標準化により医療ミスのない安全な管理を行ってゆくことは, 医療現場ではきわめて重要なことである. 今回はその中でも維持透析患者に対する CABG の周術期透析管理に関して討論を行った. このような患者に対する CABG の予後は, CHDF と OPCAB の出現により改善されてきたが, 水元論文にあるとおり, 脳梗塞や縦隔炎などの重症合併症も決して少なくはないため, いまだ満足できるものではない. われわれは術後の積極的な CHDF が手術の安全性を高めると考えている. 近年透析回路やカテーテル

の進歩は著しく, 短期間行う持続透析のトラブルはきわめて少なく安全である. CHDF を省略することも症例によっては十分可能であるが, CHDF をいかに安全に管理するかということも大切ではないかと考える. 周術期における透析管理は個々の病状を十分に把握し, 症例ごとの病状にあったオーダーメイドの管理を行ってゆくべきであると考えている.

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## 討論 2.

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慢性透析患者の全死亡率のうち心血管イベントによる死亡は 44%にも及び, そのうちの約 20% は急性心筋梗塞であるといわれている<sup>1)</sup>. そのため, 冠状動脈病変を有する透析患者に対しても冠状動脈バイパス術 (CABG) は非常に意義のある治療法であるといえる. しかし, 腎機能障害例に対する CABG の手術成績は健常例に比較して不良とされており, 周術期管理の検討を行い, 手術成績の向上をめざす水元論文は非常に有用であるものと考えられる.

Off-pump CABG (OPCAB) は従来の人工心

肺使用 CABG と比較し, 人工心肺を使用することによる合併症を回避することができ<sup>2-4)</sup>, 透析患者においても OPCAB の有用性はすでに報告されている<sup>5,6)</sup>. そのため, 水元論文の治療方針と同様に, 可能な限り OPCAB で手術を行うことが望まれる. しかし OPCAB の欠点は, 術中の循環動態が不安定となりやすく, それを維持するために輸液が過剰となることである. とくに回旋枝領域や右冠状動脈末梢を吻合するために心臓を展開したさいに循環動態が崩れやすいが, いくら短時間で手術が終了し, 輸液量を抑えることが

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できたからといって、不完全な血行再建は術後成績を落とすといわれているため<sup>7)</sup>、当科では透析患者といえども積極的に必要な血行再建をすべきであると考えている。そういう意味で、周術期管理でもっとも重要なものは術後の水分管理、すなわち血液透析 (HD) 再開のタイミングであるといいかえられると思われる。

水元論文で述べられている見解と同様に、OPCAB では術後に BUN、血清 Cr 値は多少高値であっても問題となることはなく、高 K 血症に関しても術中の MAP 血の洗浄や GI 療法により対処可能であると思われる。しかし、術中に血液濾過 (HF) で除水ができる人工心肺使用時と違い、OPCAB では術後に輸液量を減らしたとしても、術中の輸液過剰による心不全、低酸素血症を早期に改善させるためには早期の HD 再開が必要であり、各種モニター類のある術翌日は HD を行うタイミングとしてはよい時期であると考えている。これは当院では透析センターのスタッフに ICU での HD を行ってもらえるために可能な方法なのかもしれない。

このような見解から、当院における透析患者に対する基本方針は以下のごとくである。

- 1) 定例手術では術前日に HD を行う。
- 2) OPCAB を原則とし、術中循環動態が維持できない症例、心筋梗塞急性期例、低左心機能症例 (左室駆出率 30% 未満) では人工心肺使用心拍動下で行う。ただし、低左心機能症例でも大動脈内バルーンポンピング (IABP) 挿入下で循環動態が維持できる症例は OPCAB にて行う。
- 3) 人工心肺使用時は術中に HF を行う。
- 4) 術翌日に HD を行い、その後に人工呼吸器よりの離脱を図る。
- 5) 術中・術後、循環動態が不安定な症例、緊急手術例では術日または術翌日より持続的血液濾過透析 (CHDF) を行う。
- 6) 輸血はセルセーバーにより洗浄し行う。

次に当院の現状を示す。1998 年 6 月～2006 年 6 月の単独 CABG 例 798 例中、術前からの血液透析例は 47 例あった。そのうちの人工心肺使用例は 5 例 (すべて心拍動下) で、OPCAB 例は 42 例あった。人工心肺使用例の 3 例に、OPCAB 例の 34 例に対し術翌日に HD を行った。OPCAB 例のうち 1 例は術翌日の透析中に心室細動

となり、経皮的心肺補助 (PCPS)、CHDF を必要としたが、翌日に HD を行えたその他の症例での術後人工呼吸器時間、術後 ICU 滞在日数、術後在院日数はそれぞれ  $13.5 \pm 7.2$  時間、 $2.6 \pm 3.4$  日、 $23.4 \pm 11.3$  日であった。また、術後に CHDF を必要とした症例は 9 例あり、透析再開までの CHDF 使用期間は平均  $5.7 \pm 3.5$  日であった。CHDF は循環動態の変動が少ないという利点はあるが、そのために臥床期間も長くなり、患者の負担も増えることを考えると、HD を行い早期離床に努めることのほうがより患者に対してもよいものと思われる。

当科の経験では、術翌日に透析を行うことで出血に難渋したということではなく、nafamostat mesilate を使用し、嚴重に凝固時間をコントロールすることで出血の増悪を抑えることは可能であると考えている。また、CHDF と違い長時間のカテーテル挿入が必要でないため、カテーテル感染のリスクを減らすことができる。この方法は患者の早期回復だけでなく入院期間を短縮することができ、さらには医療費の軽減にもつながるのではないかとわれわれは考えている。

以上より、水元論文と同様の見解ではあるが、より早期の HD 再開が患者の QOL の向上にもつながるものと考えている。

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## 求人・募集案内

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■ (財)日本心臓血圧研究振興会附属 榊原記念病院では心臓血管疾患の診断および治療などの専門的な臨床研修を希望する若手医師のために専修課程があり、出身大学・所属医局を問わず広く専修医を募集しています。

1. 応募資格：日本国医師免許を取得していて、2年以上(小児科は3年以上)の臨床経験を有する若手医師
2. 募集人員：循環器内科・心臓血管外科・循環器小児科 各数名
3. 研修期間：原則として、内科・外科は3年間、小児科は2年間(応相談)
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## 左前下行枝 (LAD) 1 枝バイパス例： MIDCAB と OPCAB の比較検討

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左前下行枝 (LAD) 1 枝バイパス例に対する off-pump CABG (OPCAB) について検討した。1997 年 3 月から 2000 年 2 月までの 30 例を対象とし、MIDCAB 群 22 例 (左前胸部小切開法)、OPCAB 群 8 例 (胸骨正中切開法) の 2 群に分けた。緊急手術症例は OPCAB 群で多く (OPCAB 群 75% : MIDCAB 群 27.3%)、手術時間は MIDCAB 群で延長していた (OPCAB 群 2.1 時間 : MIDCAB 群 3.9 時間)。全死亡、心臓死回避率 (5 年) は OPCAB 群で 100%、MIDCAB 群で 86.4% とやや OPCAB 群のほうが良好だった。OPCAB は、手術時間も短く、遠隔成績も良好と、1 枝 CABG の手技として有用と考えられた。日心外会誌 36 巻 5 号 : 245-247 (2007)

Keywords : OPCAB, MIDCAB, 1 VD, LAD

### The Long-Term Results of Left Internal Thoracic Artery Grafting in the Left Anterior Descending Artery with Either a Sternotomy or an Anterior Minithoracotomy

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The main objective of this study was to describe the long-term results of left internal thoracic artery grafting of the left anterior descending artery with a sternotomy or anterior minithoracotomy without using extracorporeal circulation. From March 1997 to February 2000, a median sternotomy was performed in 8 patients and a minithoracotomy in 22 patients. We compared and analyzed the findings of these groups. An emergency operation was performed in 75% of the patients in the median sternotomy group and in 27.3% of those in the minithoracotomy group ( $p=0.03$ ). The operation time was 2.1 h in the median sternotomy group and 3.9 h in the minithoracotomy group ( $p<0.01$ ). The early graft patency rate was 100% in the median sternotomy group and 90.4% in the minithoracotomy group (NS). The five-year actuarial survival rate was 100% in the median sternotomy group and 86.4% in the minithoracotomy group. The five-year cardiac event free rate was 100% in the median sternotomy group and 86.4% in the minithoracotomy group. In conclusion, the results for the median sternotomy group were comparatively better than for minithoracotomy group. Minithoracotomy and median sternotomy have differences in operation time, early graft patency and early outcome. The median sternotomy technique therefore remains an invaluable operative modality for the treatment of one-vessel disease. Jpn. J. Cardiovasc. Surg. 36 : 245-247 (2007)

近年、1 枝病変についても人工心肺非使用冠動脈バイパス術 (off-pump CABG) が盛んに行われるようになったが、施設によって小切開低侵襲冠動脈バイパス術 (MIDCAB) と胸骨正中切開 off-pump CABG (OPCAB) がさまざまに選択されている。今回われわれは、左前下行枝 (LAD) 1 枝バイパス例に対する off-pump CABG 30 例について検討し、今後の 1 枝病変に対する off-pump CABG の方向性を検討した。

#### 対象と方法

1997 年 3 月から 2000 年 2 月までに同一術者によって施行された LAD 1 枝に対する off-pump CABG 施行例 30 例を対象とし、MIDCAB 群 22 例 (左前胸部小切開法 ; 平

均年齢 67.1 歳, 男女比 16 : 6)、OPCAB 群 8 例 (胸骨正中切開法 ; 平均年齢 69.0 歳, 男女比 7 : 1) の 2 群に分けて、術前因子、術中因子、術後経過、遠隔成績について統計学的検討を行った。なお、症例はすべて内科で、完全閉塞、びまん性病変、ステント留置後の再狭窄などにより、冠動脈形成術 (PCI) 不可能と判断されたものである。手術方法において、MIDCAB の内胸動脈 (ITA) 採取は、右半側臥位で胸腔内 3 カ所に胸腔鏡用 port の挿入後、胸腔鏡下にハーモニックスカルペル (Ethicon 社製) を使用して第 1 肋間まで胸腔側のみ剝離し、そののち第 4 肋間に約 5 cm の切開をして Thoralfit (Auto Suture 社製) を挿入し、直視下で採取した。冠動脈の吻合では、1997 年 8 月より Mini-CABG システム (Auto Suture 社製) の開胸器と、stabilizer を使用し、心臓を軽度圧迫して静止野を得た。冠動脈吻合は 8-0 ポリプロピレン糸を用い、連続縫

合であった。OPCAB群では、胸骨正中切開ののち、電気メスとハーモニックスカルペルによりITAを直視下で採取した。冠動脈の吻合はオクトパス-2 (Medtronic社製)を使用し、心臓を軽度圧迫して静止野を得た。冠動脈吻合は8-0ポリプロピレン糸連続縫合で行った。

統計学的検定は、 $\chi^2$ 検定、Fisherの直接法検定、*t*-検定、Mann-Whitney's U test, Log-rank testを用い、 $p < 0.05$ で有意差とした。

## 結 果

術前因子では、不安定狭心症の症例がOPCAB群で7例(87.5%;  $p < 0.01$ )と多かった以外は、年齢、性別、LVEF、陳旧性心筋梗塞、腎不全、呼吸器障害、糖尿病、術前脳障害、大動脈石灰化、Euro scoreなどに両群間で有意差は認められなかった(表1)。

術中因子では、手術時間でOPCAB群が126分と、MIDCAB群の234分に比し、有意に減少していた。MIDCAB群での手術時間の延長は、胸腔鏡下で内胸動脈の剝離を行ったためである。当科の方針として、正中切開による内胸動脈と同じ質のグラフトを採取するには、内胸動脈を鎖骨下動脈分岐部まで剝離する必要があると考えている。

出血量ではOPCAB群は正中切開にもかかわらず、MIDCAB群と比して有意差はなかった。また、OPCAB群は輸血症例もなかった。

開存率はMIDCAB群で90.4%、OPCAB群で100%と有意差はないものの、OPCAB群で良い傾向であった(表2)。

術後因子では、ICU滞在、術後在院、人工呼吸時間、出血再開胸に有意差は認めなかった。IABPの挿入、脳障害の発生、病院死亡は両群とも認めなかった。遠隔期再手術を1例、遠隔死亡を5例、MIDCAB群で認めたが、OPCAB群では認めなかった(表3)。

表1 術前因子

	M群 (n=22)	O群 (n=8)	p-Value
年齢	67.1	69.0	NS
男女比	16/6	7/1	NS
病変枝数(枝)	1.6	1.0	NS
不安定狭心症(例)	16	7	0.0094
LVEF(%)	64.0	63.7	NS
陳旧性心筋梗塞(例)	10	1	NS
腎不全(例)	5	0	NS
呼吸機能障害(例)	4	0	NS
糖尿病(例)	13	2	NS
脳障害(例)	1	0	NS
大動脈石灰化(例)	4	0	NS
Euro score(点)	6.5	8.3	NS

M群：MIDCAB群(左前胸部小切開法)、O群：OPCAB群(胸骨正中切開法)。

全死亡回避率は、OPCAB群の5年生存率は100%、MIDCAB群でも5年生存率は86.4%と良好であったが、OPCAB群に比してやや低めであった(図1)。

心臓死回避率は、OPCAB群は5年で100%、MIDCAB群は5年で86.4%と両群とも良好であったが、MIDCAB群で4例の心死亡を認めた(図2)。心死亡の内訳は、MIDCAB群で術後0.95年と2.36年で心筋梗塞による死亡の2例、術後1.2年で突然死の1例、術後7.5年で心室細動による死亡の1例であった。

## 考 察

Off-pump CABGは、従来はhigh risk症例に行われていた<sup>1,2)</sup>。しかしMIDCABの開発により、LAD1枝バイパスによる完全血行再建の可能な症例では全身状態に関係なくMIDCABの適応とするなどoff-pump CABGの適応は拡大されてきた<sup>3)</sup>。この結果、MIDCABは人工心肺を使用しないことや小さな手術切開創などにより、さまざまな施設で行われるようになった<sup>4)</sup>が、視野の展開が不十分、吸着型スタビライザー(オクトパス-2)の挿入が難しいなどの問題があり、現在はOPCABに移行しつつあるものと考えられる<sup>5)</sup>。そこでわれわれは、LAD1枝バイパスについてのMIDCABとOPCABの2群比較を行い比較検討した。結果としてOPCABはMIDCABに比して、手術時間の短縮と緊急手術例増加を認めた。時間短縮の理由としては、やはり内胸動脈の採取の方法があげられる。OPCABは胸骨正中切開であるため、通常どおり

表2 術中因子

	M群 (n=22)	O群 (n=8)	p-Value
緊急手術(例)	6	6	0.0342
動脈グラフト使用(本)	0.9	0.9	NS
手術時間(分)	234	126	0.0001
出血量(ml)	284.4	243.3	NS
輸血(例)	4	0	NS
開存率(%)	90.4	100	NS

M群：MIDCAB群(左前胸部小切開法)、O群：OPCAB群(胸骨正中切開法)。

表3 術後因子

	M群 (n=22)	O群 (n=8)	p-Value
ICU滞在(日)	1.2	1.3	NS
術後在院日数(日)	19.4	15.3	NS
術後人工呼吸時間(分)	150	912	NS
出血再開胸(例)	0	1	NS
IABP(例)	0	0	NS
術後脳障害(例)	0	0	NS
遠隔期再手術(例)	1	0	NS
病院死亡(例)	0	0	NS

M群：MIDCAB群(左前胸部小切開法)、O群：OPCAB群(胸骨正中切開法)。

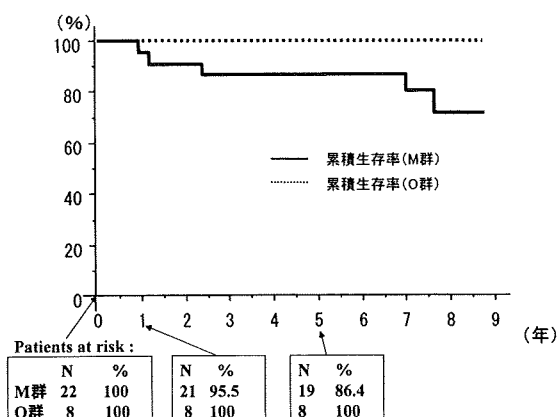


図1 全死亡回避率

M群：MIDCAB群（左前胸部小切開法），O群：OPCAB群（胸骨正中切開法）。全死亡回避率は、O群（5年）で100%、M群（5年）で86.4%と良好であったが、O群に比してやや低めであった。

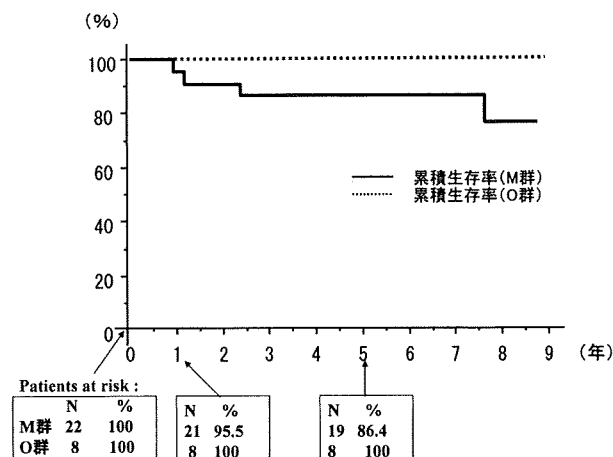


図2 心臓死回避率

M群：MIDCAB群（左前胸部小切開法），O群：OPCAB群（胸骨正中切開法）。心臓死回避率は、O群（5年）で100%、M群（5年）で86.4%と良好であったが、O群に比してやや低めであった。

の採取が可能であるが、MIDCABはITAの剥離が不十分な場合には、肺による内胸動脈の圧迫や運動による内胸動脈の損傷が報告されている<sup>6)</sup>ため、渡邊ら<sup>4)</sup>や、Benettiら<sup>7)</sup>の報告にしたがい胸腔鏡を使用して採取を行った。内視鏡による剥離を始めた当初は、内胸動脈の採取に2時間を要したが、20例を超えてきた時点では40分で剥離できるようになっていた。ただし、それでも直視下に採取する場合と比較すると2倍以上の時間が必要とされ、その結果、手術時間の平均はOPCABの約2倍要したものと考えられた。また、MIDCABでは視野の展開の不十分なこと、吸着型スタビライザーの使用不可など<sup>5)</sup>により、開存率も94%と有意差はないものの低くなりがちである。さらに手術時間の延長もあってMIDCABでの緊急手術はOPCABに比し少ないものと思われた。土肥らもMID-

CABでの冠動脈露出は不十分であり、OPCABに移行していると報告している<sup>8)</sup>。

術後因子の検討でも、すべての因子において両群に有意差は認めず、遠隔期の成績でも全死亡回避率、心臓死回避率が両群とも良好であったが、OPCAB群で死亡例がないため、統計学的検討ができないものの、OPCAB群で良い傾向がみられた。

以上よりOPCABはMIDCABに比して高侵襲とはいえず、MIDCABよりも良好なグラフト開存が期待できるため、現状では1枝バイパス例に対するoff-pump CABGはOPCABが現実的な手技であると思われ、とくに緊急症例や複雑病変などに対する多様性があると考えられる。現在海外ではダ・ビンチなどのロボット手術によるCABGの成績も報告されるようになってきており<sup>9)</sup>、今後わが国でもロボット手術は発展していくものと思われる。しかし、内視鏡下ロボット手術による低侵襲手術は現状ではなかなか導入が難しく、かなりの時間のランニングカーブが必要であり、安易に導入できない現状があり、手術を安全かつ確実に行うためには、1枝バイパス例に対するOPCABを現段階では有用と考える。

結 語

胸骨正中切開 off-pump CABG は、手術時間も短く、遠隔成績も良好であり、現状では1枝CABGの手技として有用と考えられた。

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## Living-donor single-lobe lung transplantation for bronchiolitis obliterans in a 4-year-old boy

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Drs Shiraishi and Shirakusa (left to right)

A single-lobe lung transplantation from a living donor was performed in a 4-year-old boy. The transplantation was successful, and the patient recovered smoothly despite severe volume mismatch between the lung allograft and the recipient chest cavity. To our knowledge, this case represents the youngest recipient of a living-related single-lobe transplantation ever reported.

### Clinical Summary

This male patient's history included diagnosis of juvenile myelomonocytic leukemia at 1 year 3 months, with subsequent peripheral blood stem cell transplantation from his mother. He later had bronchiolitis obliterans develop, and his respiratory condition progressively deteriorated thereafter. Mechanical ventilation was instituted at 4 years 10 months because of the onset of carbon dioxide narcosis. Chest computed tomography (CT) demonstrated bilateral diffuse emphysema and severe lung overexpansion.

Transplantation from a cadaveric donor is considered impossible within a limited time frame; therefore, the only realistic transplant option was considered a living-related single-lobe lung transplantation (because of the recipient's small stature). The potential donor was his mother. The heights and weights of the recipient and donor were 98 cm and 13 kg and 159 cm and 58 kg, respectively.

The left lower lobe was determined to be an acceptable lobe for transplantation on the basis of 3-dimensional CT volumetric evaluation of both recipient and donor, which indicated the recipient's left chest cavity to be 768 mL and the donor's left lower lobe to be 906 mL. The uncertain result of this transplantation was repeatedly discussed with the recipient's family, who were willing to proceed with this plan. The Ethical Committee of Fukuoka University approved this surgery with an understanding of the experimental nature of this transplantation.

Four weeks after mechanical ventilation was started, at the age of 4 years 11 months, the patient underwent left single-lobe transplantation through a bilateral thoracosternotomy. The surgical aspects of the living-related lobar transplantation procedure have been previously described.<sup>1,2</sup> The implantation was completed uneventfully.

Chest CT on day 1 demonstrated a well-inflated lung allograft without obvious atelectasis (Figure 1). The patient was weaned from the ventilator on day 10. A 3-dimensional CT on day 44 demonstrated the lung allograft volume to be 427 mL, as opposed to its 906 mL original size before transplantation (Figure 2). This finding suggests that an oversized lung graft can work adequately, despite severe compression resulting in a graft 47% of the original size.

### Discussion

In the history of living-related lung transplantation, a single donor was used in the beginning. Starnes and colleagues<sup>3</sup> demonstrated the first successful single-lobe lung transplantation for a 12-year-

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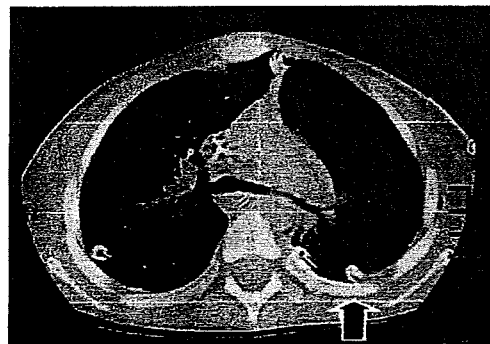
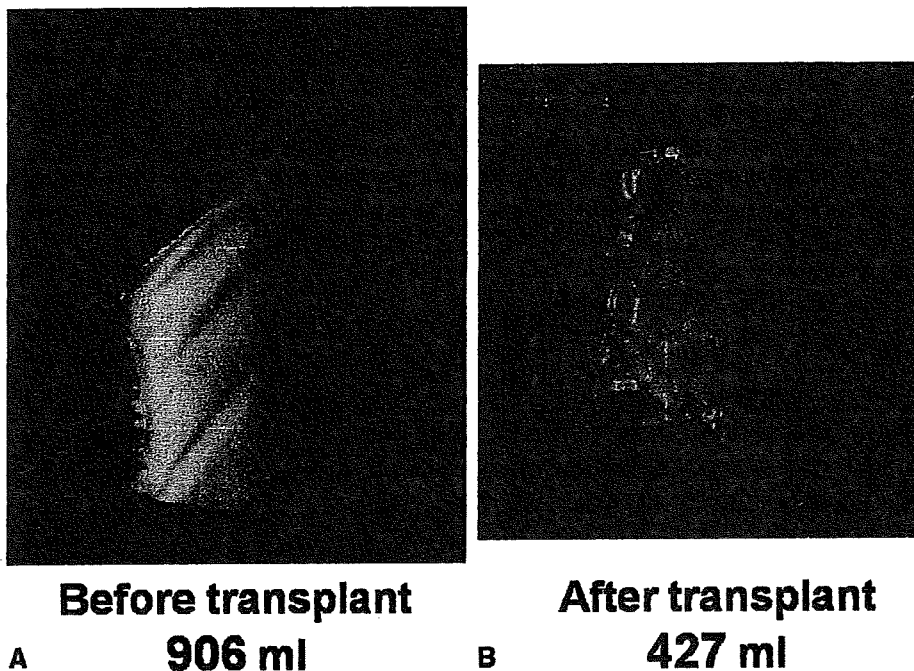


Figure 1. Chest computed tomographic scan 1 day after transplantation. Lung allograft (arrow) was well aerated, without any abnormal compression or atelectasis



**Figure 2.** Three-dimensional computed tomographic scans of lung allograft before (A) and 44 days after (B) transplantation. Three-dimensional computed tomographic scan in end-inspiratory point taken on day 44 after transplantation (B) showed left lung graft volume to be 427 mL, as opposed to its 906 mL original size before transplantation (A). This finding suggests that oversized lung graft can work adequately despite severe compression resulting in graft only 47% of its original size.

old girl. Similar successes were reported for teenaged recipients.<sup>3-5</sup> A 4-year-old recipient with Eisenmenger syndrome, however, died immediately after transplantation of severe pulmonary edema in the allograft.<sup>3</sup> The standard technique for this surgery is now double-lobe transplantation with right and left lower lobe grafts from two donors. Single-lobe transplantation is, however, considered when the recipient is a small child or only one donor is available.

The 3-dimensional CT showed the donor's left lower lobe to be 118% the size of the recipient's left thoracic cavity. Because the recipient's chest cavity was abnormally expanded, it was unclear whether the allograft could work. We therefore considered the possibility of a right lung volume reduction after implantation to extend the "working space" for the lung allograft if it could not ventilate. This, however, was not necessary.

Interestingly, the allograft volume gradually declined after weaning from the ventilator with the recovery of the chest wall and diaphragm toward to their original status, and the graft size finally decreased to 47% of its original. The patient recovered well, however, and his physical status continued to improve. This indicated that an overexpanded chest cavity with severe emphysematous lung may be able to accept a fairly oversized lung.

Theoretically, the recipient was "chimeric" with the lung donor because of the previous engraftment with peripheral blood stem cells. Therefore no immunosuppression might be required to control rejection, but it turned out that low-dose immunosuppression

(FK506 maintained with a trough level of 5 ng/mL and prednisolone) was necessary to control smoldering graft-versus-host disease in the liver induced by peripheral blood stem cell transplantation. No acute rejection on the allograft was found during the entire observation period. The patient recovered well and was discharged from the hospital on the 53rd day after transplantation.

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Ticlopidine 投与中の OPCAB 施行例に対して  
aprotinin を使用した 1 例\*

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はじめに 薬剤溶解性ステント (DES) は近年カテーテルインターベンション (PCI) にて多く使用されているが, DES を使用するには, ticlopidine 内服を 3 ヶ月は継続する必要がある<sup>1)</sup>. Ticlopidine の効果が消失するには内服中止後約 10 日かかるといわれており<sup>2,3)</sup>, ticlopidine 投与中の手術は大量出血を伴い難渋するとされている<sup>4-6)</sup>. 今回われわれは, ticlopidine 投与中の患者の緊急冠状動脈バイパス術 (CABG) 中に aprotinin を投与することにより出血を最小限にコントロールできたので報告する.

## 症 例

症 例 65 歳, 男.

主 訴: 胸部不快感.

家族歴: 特記すべきことはない.

既往歴: 胃潰瘍, 高血圧, 高脂血症.

現病歴: 2005 年 1 月ごろより労作時に胸部不快感が出現し, 近医を受診した. 左前下行枝 (LAD) #6, 左回旋枝 (Cx) #13 に DES 挿入を考慮され ticlopidine 200 mg/日を 2 週間投与後, 冠状動脈造影 (CAG) を受けた. 冠状動脈病変は 3 枝病変で, DES 挿入を試みたが CAG 中に胸痛発作が出現し, 大動脈内バルーンポンピング (IABP) を挿入され当科に緊急入院した.

入院時所見: 心胸郭比 60.4%, 心電図では心拍数 66 回/分, 洞調律であった. 心臓超音波検査で左室駆出率は 60%, 僧帽弁閉鎖不全 (MR) I 度, 大動脈弁閉鎖不全 (AR) I 度を認めた.

血液学的検査所見: WBC 8,000/ $\mu$ l, Hb 13.6 g/dl, HCT 39.8%, PLT 18.4/ $\mu$ l, T-Bil 0.9 mg/dl, GOT 14 IU/l, GPT 18 IU/l, LDH 178 IU/l, CPK 42 IU/l, BUN 9 mg/dl, Cr 0.9 mg/dl, Na 141 mEq/l, K 3.7 mEq/l, Cl 107 mEq/l, Ca 8.6 mg/dl, CRP 3.2 mg/dl であった.

CAG 所見: LAD#6 に 99%, #8 に 75%, 対角枝 (Dx1) #9 に 90%, Dx2#10 に 75%, Cx #11 に 75%, #13 に 75%, 右冠状動脈 #1 に 75%, #2 に 90%, #4PD に 75% の狭窄の 3 枝病変であった.

以上より, 手術による出血をできるだけ減らすことを考え, 人工心肺非使用 CABG (OPCAB) を行い, 手術開始時に aprotinin 50 万単位, 冠状動脈吻合後に 50 万単位を投与することとした.

手術所見: 全身麻酔下に胸骨正中切開を行った. この段階で aprotinin を 50 万単位単回投与した. ハーモニックスカルペル (Johnson & Johnson 社, ニューブランズウィック) を使用してスケルトナイズ法で左右内胸動脈 (LITA, RITA) と左橈骨動脈 (RA) を採取した. LITA は中枢側の性状がよくなかったため, 遊離グラフトとして使用することとした. 大伏在静脈は通常法にて採取した. 心膜を切開後, あらかじめ右開胸を行い, LIMA スーチャーをかけて心臓を挙上<sup>7,8)</sup>, スタビライザーは Octopus IV (Medtronic 社, ミネアポリス) を使用した. 全身ヘパリン投与後, RITA は *in situ* にて LAD#7 に 8-0 ポ

キーワード: DES, OPCAB, ticlopidine, aprotinin

\* 要旨は第 100 回日本循環器学会九州地方会において発表した.

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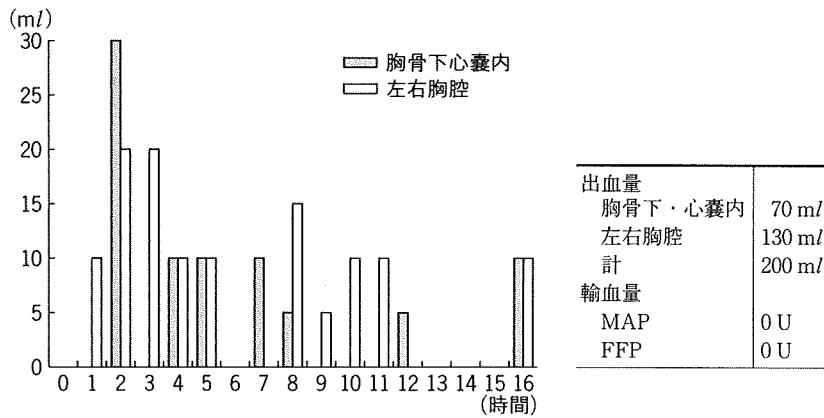


図1. 術後出血量の推移  
ICU 退出までの16時間の出血総量は200 mlである。

リプロピレン糸連続縫合で吻合した。上行大動脈には術中エコー上、後面に内膜肥厚を認めたものの前面は問題なかったため、Enclose II (Novare Surgical Systems 社, クパチーノ) を使用して3カ所に中枢吻合を行った。その後LITA-LAD#8, RA-Dx-鈍角枝(OM)を吻合した。端側吻合には8-0 ポリプロピレン糸連続縫合にて吻合し、側々吻合はU-クリップ (Medtronic 社) 2個と8-0 ポリプロピレン糸を結節吻合するダイヤモンド吻合を行った<sup>7)</sup>。大伏在静脈グラフト(SVG)-左左室後側壁枝(LPL)-右左室後側壁枝(RPL)-右後下行枝(RPD)は端側吻合には7-0 ポリプロピレン糸連続縫合で吻合し、側々吻合はU-クリップ2個と7-0 プロリンを結節吻合するダイヤモンド吻合を行った<sup>7)</sup>。冠状動脈吻合後、IRIS-IV (ベリタス社, 東京) を用いて術中にグラフトの赤外線撮影を行い、グラフトの開存を確認後、protamine にてヘパリンを中和した。その後、aprotinin を50万単位投与し、新鮮凍結血漿(FFP) 6U, 血小板(PC) 20Uを輸血した。出血が落ちついてきたところで閉胸し手術を終了した。出血量330 ml, セルセーバー処理量5,354 ml, 同返血量1,545 ml, 手術時間は6時間であった。

**術後経過:** 手術後のドレーンからの出血は10~50 ml/時と少なく、血行動態も良好であったため、術後2.5時間でIABPより離脱した。術後11時間で抜管を行い、術翌日にはICUを退出した。術後13日目に退院となった。手術終了からICU退出までの総出血量は200 mlで、輸血は

必要なかった(図1)。今回の全体の輸血総量はFFP 6U, PC 20Uであった。

#### 考 察

われわれは、以前にDES挿入後ticlopidine内服中の患者に対して緊急CABGを行い出血に難渋した症例を経験している。このような症例は海外でも報告があり、海外ではclopidogrelが用いられているが、術中・術後の出血に難渋している<sup>4-6)</sup>。しかしaspirinについては、術前の継続投与に関して出血量の増加はあまりなく、術後の合併症の軽減にもなるとの報告<sup>9)</sup>もあり、当科においては継続投与のまま手術を行っている。

DESは2004年8月以降よりPCIにて多く使用されており、ここ1年間で約10万本が日本において使用されている。報告では、Cypher (Johnson & Johnson 社) の再狭窄率は3.2%ともいわれており<sup>10)</sup>、左主幹部(LMT)を含めた病変においても積極的に使用されるようになってきている<sup>11)</sup>。その結果、ticlopidineを内服する患者は増加の一途をたどっている。今後はticlopidine投与中の患者が外科に回されてくることは確実である。Ticlopidineは投与後2日目で血小板凝集の抑制は最大効果をきたし<sup>12)</sup>、投与中止後も血小板凝集能の回復に10日間がかかる<sup>2,3)</sup>とされている<sup>2,3)</sup>。しかもDES挿入後は最低3ヵ月以上の投与が必要とされている<sup>1)</sup>。DES挿入後の患者がCABG予定手術となっても、ticlopidineの10日間の休薬とそのかわりにヘパリンの投与を考慮

しなければならない。しかも DES に対するヘパリンの効果は確立されておらず、ステント内血栓形成 (SAT) を引き起す可能性もある。Ticlopidine の効果が持続したままの緊急手術に対する対応は、さらにむずかしくなることが予想される。

また、今後は日本においても clopidogrel が使用頻度を増すものと考えられる。Clopidogrel は、ticlopidine と同系統の thienopyridine 誘導体で、血小板凝集阻害作用を有する。Clopidogrel の作用の減弱に CABG 中の aprotinin 投与が有効との報告がある<sup>13,14)</sup>。その方法とは、200 万単位を手術直前に単回投与し、200 万単位を人工心肺 (CPB) 中に入れ、さらに 50 万単位/時で手術中に持続投与するというもの<sup>13)</sup>と、200 万単位を手術直前に単回投与し、200 万単位を CPB 終了時に単回投与するというものであった<sup>14)</sup>。Aprotinin 液はウシの肺抽出物で抗プラスミン作用を示すその作用は強力で、プラスミノゲンからプラスミンへの活性化を阻害するだけでなく、すでに活性化されたプラスミンをも阻害する<sup>15)</sup>とされ、血液凝固、線溶系酵素を阻害することにより凝固・線溶異常を改善する。これらのことから、clopidogrel と同じ臨床系統の誘導体の ticlopidine も aprotinin の投与が有効であるかもしれないと考えられ、その投与に踏み切った。今回の投与量は、OPCAB に対し手術開始時に aprotinin 50 万単位、冠状動脈吻合後に aprotinin 50 万単位を投与とした。結果として手術中の出血は 330 ml と平穏であり、術後の出血も少なく血行動態も安定し、よい結果が得られた。ただし、今回は OPCAB に対するものであり、人工心肺を使用するさいにはさらに投与量を検討すべきであろうと考えられる。

おわりに 今回われわれは、ticlopidine 投与中に緊急 OPCAB を行った 1 例を経験した。手術中は aprotinin 総量 100 万単位の投与を行うことにより止血に難渋することなく、良好な手術を行うことができた。DES の登場によりこのような症例は増加することが考えられるため、今後の対策として aprotinin 投与は有用であろうと思われた。

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## SUMMARY

### Aprotinin Reduces Bleeding during Off-pump Coronary Artery Bypass Grafting in A Patient on Ticlopidine ; Report of a Case

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A 65-year-old man was admitted to a local hospital with symptoms of unstable angina pectoris. He was administered ticlopidine before drug eluting stent (DES) stenting for 2 weeks. Coronary angiography showed 3 vessel diseases. He was then admitted to our hospital due to a sudden onset of unstable angina following shock during the percutaneous coronary intervention (PCI) procedure, emergency off-pump coronary artery bypass grafting (OPCAB) was thus performed. He received aprotinin 5 hundred thousand KIU just at the start of surgery and 5 hundred thousand KIU after undergoing anastomosis of the coronary artery. Postoperatively, only some minor bleeding was observed. Aprotinin reduces bleeding, the transfusion requirements of packed red blood cells, platelets, and the total blood units in patients on ticlopidine who undergo emergency OPCAB.

### KEY WORDS

DES/OPCAB/ticlopidine/aprotinin

\* \* \*

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<ul style="list-style-type: none"> <li>■ 特集「胸部外科10年の進歩と将来展望」によせて .....幕内晴朗/近藤 丘</li> <li>■ 癌の外科治療における分子生物学</li> <li>■ 心臓血管外科における再生医療と分子生物学</li> <li>■ 人工心臓</li> <li>■ 同種移植と異種移植</li> </ul>		<ul style="list-style-type: none"> <li>■ 胸部外科の診療システムの課題と展望 —日本胸部外科学会からのメッセージ</li> <li>■ 胸部外科の魅力ある卒前・卒後教育</li> <li>■ 胸部外科と専門医制度—心臓血管外科</li> <li>■ 胸部外科医と専門医制度—呼吸器外科</li> <li>■ 胸部外科における国際交流</li> </ul>	

# New Method of Thermal Coronary Angiography for Intraoperative Patency Control in Off-Pump and On-Pump Coronary Artery Bypass Grafting

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**Background.** We evaluated the effectiveness of a new thermal coronary angiogram system using intraoperative imaging with an infrared camera for coronary artery bypass grafting.

**Methods.** The thermal coronary angiograms of 51 patients who underwent a total of 107 coronary artery bypass grafts were evaluated. Thermal coronary angiograms were obtained after completing distal anastomoses by the injection of cold saline solution into the vein grafts or free arterial grafts or by reperfusion with warmer blood in the internal thoracic artery grafts. Temperature differences of greater than 0.1°C between the injectant and the epimyocardium resulted in high-contrast images.

**Results.** Thermal coronary angiograms were obtained from 107 coronary artery bypass grafts; 103 grafts were patent (96.3%), and 2 internal thoracic artery grafts were

occluded. After reanastomoses, thermal coronary angiograms were again obtained, and all grafts appeared to be patent. Four grafts did not clearly show hemokinesis because of an intramyocardial segment or circumferential fat surrounding the artery.

**Conclusions.** Thermal coronary angiograms cannot show hemokinesis clearly in cases with an intramyocardial arterial segment or in patients in whom the grafts are surrounded by fat. Therefore, thermal coronary angiograms are considered to play a valuable role in confirming the success or failure of myocardium revascularization because this diagnostic modality does not interfere with the surgical procedures, is noninvasive, and can be both quickly and easily performed.

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**G**raft patency control is important in the sequence of coronary artery bypass grafting (CABG). Early graft failure is often associated with technical failure, and it should therefore be avoided as much as possible. We evaluated the effectiveness of a new thermal coronary angiogram system named IRIS-III using intraoperative imaging with an infrared camera for on-pump or off-pump CABG.

## Patients and Methods

### Patients

Between September 1999 and July 2000, thermal coronary angiograms of 51 patients who underwent a total of 107 CABGs were evaluated. Twenty-four patients (mean age, 61.5 years; 19 men and 5 women) who had 46 grafts underwent on-pump CABG, and 27 patients (mean age, 65.7 years; 19 men and 8 women) who had 61 grafts underwent off-pump CABG.

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### Methods

A new thermal coronary angiogram system using intraoperative imaging with an infrared camera for CABG named IRIS-III (Thermatrek, Dusseldorf, Germany) has been used since September 1999. This system consists of two mobile parts, a camera and a console. The console contains a video recorder and control unit. The camera unit contains an infrared imager, a charge-coupled device camera, and two monitors (Fig 1). The console can be placed anywhere. As a result, the camera unit is easily placed over the heart from the surgeon's side or the anesthesiologist's side. Thermal coronary angiograms were obtained after completing distal anastomoses by the injection of cold saline solution (30°C, 3 to 5 mL) into the vein grafts or free arterial grafts or by reperfusion with warmer blood (about 5 seconds) in the internal thoracic artery (ITA) and gastroepiploic artery graft after epicardial cooling by sprinkling cold saline solution (30°C, 1 to 2 mL).

The temperature of warmer blood is about 37°C during on-pump or off-pump CABG. Temperature differences of greater than 0.1°C between the injectant and the epimyocardium resulted in high-contrast images [1]. Thermal coronary angiograms were performed immediately after

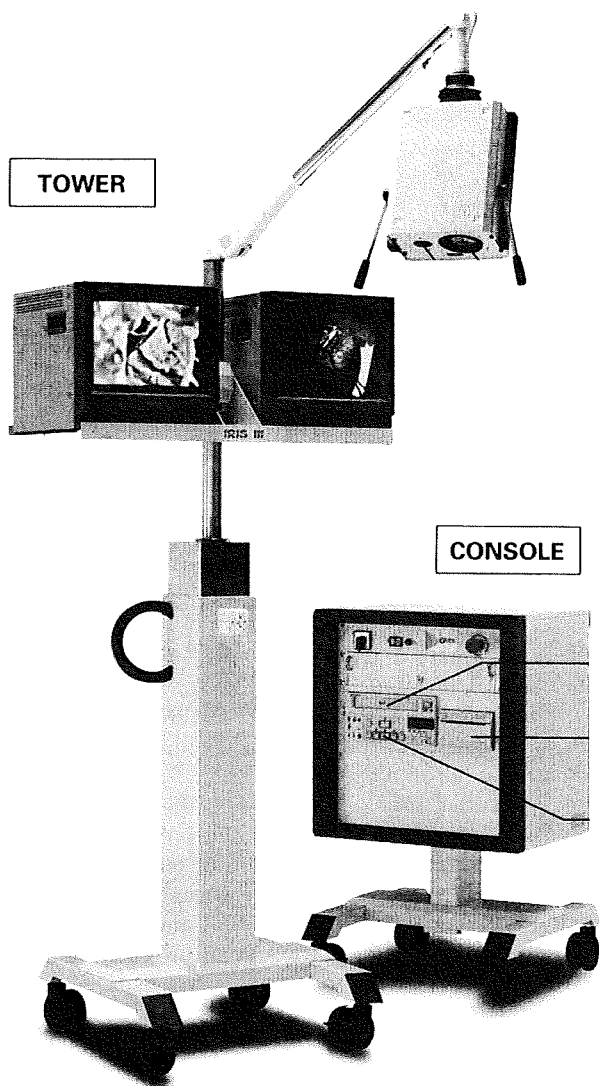


Fig 1. A new thermal coronary angiogram system using intraoperative imaging with an infrared camera for coronary artery bypass grafting named IRIS-III (Thermatrek, Dusseldorf, Germany). This system consists of two mobile parts, a camera and a console. The console contains a video recorder and control unit. The camera unit contains an infrared imager, a charge-coupled device camera, and two monitors.

distal graft anastomoses but before protamine was given in all cases.

Between 7 and 10 days after surgery, postoperative angiography was performed in all patients. The results of the thermal coronary angiograms were compared with postoperative angiography. A statistical analysis was performed using Fisher's exact test. Statistically significant differences were assumed to exist at a value of  $p$  less than 0.05.

### Results

Thermal coronary angiograms were obtained from 107 grafts; 103 grafts were patent (96.3%), whereas 2 ITA grafts were occluded. We found 2 occluded grafts by the IRIS-III in the operation. Immediately after reanastomoses were performed, thermal coronary angiograms were again obtained and all grafts appeared to be patent in the same operation. Therefore, the postoperative angiography was performed in 107 grafts. The results of the thermal coronary angiograms were compared with postoperative angiography. Four grafts did not clearly show hemokinesis because of an intramyocardial segment or circumferential fat surrounding the artery. In four grafts, we could see clear images produced by the IRIS-III. However, these grafts were subsequently revealed to not be patent by postoperative angiography, which was performed because of the occurrence of early graft thrombosis (Table 1).

The graft patency rate of the IRIS-III was 96.3%. In contrast, the postoperative patency rate for angiography was 95.3%. No significant differences in the total grafts performed were observed between the two groups (Table 2). In addition, no significant differences in the left anterior descending artery area (Table 3), the circumflex artery area (Table 4), and the right coronary artery area (Table 5) graft patency variables were observed between the two groups.

We now have two effective cases of intraoperative thermal coronary angiograms in CABG. In the first case, Iwahashi and colleagues [1] reported that the left ITA was grafted to the obtuse marginal artery. Just after complet-

Table 1. Data Mismatch Between Thermal Coronary Angiogram (IRIS-III) and Postoperative Angiography

Anastomotic Site	IRIS-III	Postoperative Angiography	Reason
SVG-OM	not detected	patent	Surrounded by fat
SVG-LPL-RPD	not detected	patent	Surrounded by fat
LITA-LAD	not detected	patent	Surrounded by fat
LITA-FRITA-OM	not detected	patent	Surrounded by fat
SVG-PL1	detected	not patent	Graft thrombosis
SVG-RPD	detected	not patent	Graft thrombosis
LITA-LAD	detected	not patent	Graft thrombosis
SVG-RPD	detected	not patent	Graft thrombosis

FRITA = free right internal thoracic artery; IRIS-III = intraoperative thermal coronary angiography; LAD = left anterior descending; LITA = left internal thoracic artery; LPL = left posterior lateral; OM = obtuse marginal; PL1 = posterior lateral 1; RPD = right posterior descending; SVG = saphenous vein graft.

Table 2. Total Cases

Postoperative Angiography	IRIS-III		Total
	Detect	Not Detect	
Patent	98	4	102
Not patent	5	0	5
Total	103	4	107

Fisher's exact probability test;  $p = 0.82$ .  
IRIS-III = intraoperative thermal coronary angiography.

ing the anastomosis, we performed thermal coronary angiography by IRIS-III. The left ITA to obtuse marginal artery appeared to not be patent on thermal coronary angiography. After a reanastomosis at the left ITA to obtuse marginal artery, thermal coronary angiography was again performed and the left ITA to obtuse marginal artery anastomosis was thus found to be patent. The postoperative course was uneventful, and all grafts were patent on postoperative angiography.

In the second case, the left ITA was grafted to the left anterior descending coronary artery. The left ITA to left anterior descending coronary artery was not patent on thermal coronary angiography by IRIS-III because of graft occlusion. Therefore, a reanastomosis was done at a saphenus vein graft to left anterior descending coronary artery; thermal coronary angiography was then reperformed, and the saphenus vein graft to left anterior descending coronary artery anastomosis was subsequently found to be patent (Fig 2).

**Comment**

We evaluated the effectiveness of a new thermal coronary angiogram system (IRIS-III) using intraoperative imaging with an infrared camera for CABG. The graft patency rate of the IRIS-III was 96.3%. In contrast, the postoperative patency rate of angiography was 95.3%. No significant differences in the total graft variables were observed between the two groups. Therefore, a thermal coronary angiogram is considered to be better than a postoperative angiogram. Thermal coronary angiography can be performed just after completing distal anastomoses and we can observe it in real time. In addition, temperature differences of greater than 0.1°C between the injectant and the epimyocardium resulted in high-contrast images. A thermal coronary angiogram does not

Table 3. Left Anterior Descending Coronary Artery

Postoperative Angiography	IRIS-III		Total
	Detect	Not Detect	
Patent	48	1	49
Not patent	1	0	1
Total	49	1	50

Fisher's exact probability test;  $p = 0.98$ .  
IRIS-III = intraoperative thermal coronary angiography.

Table 4. Circumflex Artery

Postoperative Angiography	IRIS-III		Total
	Detect	Not Detect	
Patent	30	3	33
Not patent	2	0	2
Total	32	3	35

Fisher's exact probability test;  $p = 0.83$ .  
IRIS-III = intraoperative thermal coronary angiography.

use the contrast medium. As a result, if the bypass graft is not patent, then a reanastomosis can be performed immediately. Because thermal coronary angiograms do not show clearly hemokinesis because of either the presence of intramyocardial arterial segments or circumferential fat surrounding the artery, another method (eg, flowmeter) would therefore be helpful in such conditions.

Up to now, several studies on intraoperative coronary assessment of anastomotic quality have been reported on the development of techniques to verify graft patency. In one method, intraoperative angiography is the gold standard for assessing anastomotic quality, but this is an invasive method that is also expensive and time-consuming [2]. In a second method, angioscopic evaluation is another alternative to assess the quality of anastomosis [3, 4]. However, it has the potential danger of causing intimal injury, and it is not feasible for in situ grafts and has never had wide acceptance. In a third method, Louagie and associates [5] and Merin and co-workers [6] reported on the use of an electromagnetic flowmeter. The determined values based on such measurements are not absolute. In a fourth method, Sakakibara and colleagues [7] reported using intraoperative echocardiography. However, their method was not very clearly described [8], and this tool is nether cost-effective nor practical [9].

In a fifth method, high-frequency epicardial echocardiography was used to detect anastomotic failures by some authors [10, 11]. However, segmental calcifications on the arteries may cause some artifacts that may complicate an accurate assessment and prolong the investigation time.

In a sixth method, the ultrasound-based transit-time flow has been used as a method to measure graft flow [12]. Intraoperative measurements have been reported to

Table 5. Right Coronary Artery

Postoperative Angiography	IRIS-III		Total
	Detect	Not Detect	
Patent	20	0	20
Not patent	2	0	2
Total	22	0	22

Fisher's exact probability test;  $p = 1.0$ .  
IRIS-III = intraoperative thermal coronary angiography.

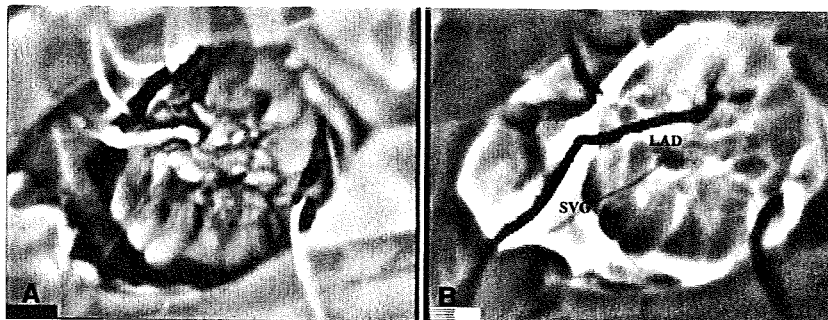


Fig 2. (A) The left internal thoracic artery to left anterior descending coronary artery anastomosis was not patent on thermal coronary angiography by intraoperative imaging with an infrared camera because of graft occlusion. (B) After a reanastomosis at a saphenous vein graft (SVG) to left anterior descending coronary artery (LAD), thermal coronary angiography was performed again and the saphenous vein graft to left anterior descending coronary artery anastomosis was subsequently found to be patent (black line).

result in a revision of 9.9% of the distal anastomosis constructed during off-pump CABG [13]. However, comparing the intraoperative ultrasound-based transit-time flow and postoperative angiogram, the transit-time flow could not identify any significant lesions in the arterial or vein grafts, and the interpretation of the flow measurement alone should therefore be done cautiously [14].

Falk and coworkers [15] reported that a thermal coronary angiogram was an ideal, noninvasive method to immediately document the success or failure of myocardial revascularization. Friedrich and associates [16] reported a thermal coronary angiogram to be both clinically relevant while also helping to improve the decision making during CABG.

The current models of thermal coronary angiograms need temperature differences between 0.2 and 0.4°C [15]. In contrast, the new thermal coronary angiogram needs only a 0.1°C temperature difference [1]. Therefore, we can use the new thermal coronary angiogram system more easily.

We are presently trying to develop a new system to analyze the blood flow using a thermal coronary angiogram system. If such a system can be developed, then thermal coronary angiograms could thus be performed anywhere. In the near future, it may therefore no longer be necessary to perform postoperative angiograms.

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## The CA-1 Test as a New Method for Monitoring Liver Dysfunction

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**Abstract :** Recent studies have focused on the fact that liver dysfunction is associated with the prothrombin time (PT) and hepaplastintest (HPT). We developed a new test to determine the prothrombin levels using the Carinactivase-1 (CA-1) test for liver dysfunction. Total plasma samples were assayed for the CA-1 test, PT and HPT. This prospective randomized study was carried out in 47 samples. The samples were divided into 2 groups. Group 1 included 20 samples and group 2 included 27 samples. Group 1 consisted of samples from individuals with no liver dysfunction, while Group 2 comprised samples from patients with liver dysfunction. The mean prothrombin levels(CA-1 score)were measured using the CA-1 test in groups 1 and 2. The mean value was 119.4  $\mu\text{g/ml}$  in group 1 and 95.8  $\mu\text{g/ml}$  in group 2. The CA-1 score of group 2 decreased more significantly than in group 1 ( $p < 0.05$ ). Even the prothrombin time international normalized ratio (PT-INR) decreased more significantly in group 2 than in group 1. Therefore, the HPT was not significantly different between groups 1 and 2. Consequently, the CA-1 test is a quantitative analysis. In contrast, the PT and HPT are qualitative analyses. Therefore, the CA-1 test is considered to be superior to the PT and HPT. The CA-1 test is therefore considered to be more useful for monitoring liver dysfunction than HPT.

**Key words :** Liver dysfunction, Prothrombin time, Carinactivase-1, Hepaplastin test

### Introduction

The prothrombin time international normalized ratio (PT-INR) and Hepaplastin test (HPT) are major methods for monitoring liver dysfunction. However, as the titer of reagents used to measure the PT-INR and the HPT differs from manufacturer to manufacturer, and thus the determined values based on such measurements are not absolute. Therefore, the establishment of new and more accurate monitoring methods is required. With this purpose in mind, we tried to establish a new test to determine the prothrombin levels using a  $\text{Ca}^{2+}$ -dependent prothrombin activator, which was designated as the Carinactivase-1(CA-1) test.

### Patients and methods

#### Patients

This prospective randomized study was carried out using 47 samples obtained from the Fukuoka University Hospital Department of Cardiovascular Surgery between May 1997 and December 1998. The samples were prospectively randomized to receive either a non-liver dysfunction or a liver dysfunction group.

Group 1 included 20 samples while group 2 included 27 samples. Group 1 had no samples from individuals with liver dysfunction. (mean age 63.2 years, gender 12 males and 8 females). Group 2 had samples from patients with liver dysfunction. (mean age 65.9 years, gender 15 males and 12 fe-

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males) (Table 1)

### Methods

All samples were measured using the CA-1 test, PT-INR and HPT. For comparisons of the two groups, we performed statistical analysis.

### Liver dysfunction

In this study, the liver dysfunction definition is the aspartate aminotransferase (AST)  $\geq 35$  IU/L and/or alanine aminotransferase (ALT)  $\geq 35$  IU/L and/or  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GTP)  $\geq 49$  IU/L. Neither abdominal echography nor the CT scanning data were considered in this study.

### CA-1 test

Carinactivase-1 (CA-1),  $Ca^{2+}$ -dependent prothrombin activator which was isolated from the venom of *Echis carinatus leucogaster*, was used in this study. The CA-1 test is performed as follows: Blood samples (3 ml) were withdrawn from all patients and then were kept in a vacuum tube containing citric acid as anticoagulant. The blood was centrifuged for 10 min at 3000 r.p.m., and the plasma separated. Aliquots of plasma (10  $\mu$ l) were diluted 10-fold with 20 mM Tris-HCl 140 mM NaCl pH 7.5 (Tris-buffered saline; TBS) containing 1 mg/ml bovine serum albumin (TBS/BSA), and

then were mixed with 80  $\mu$ l of 3 mM  $CaCl_2$  and 0.31 mM t-butoxycarbonyl (Boc)-Val-Pro-Arg-p-nitroanilide (pNA) (Seikagaku Corporation, Tokyo, Japan) and incubated at 37°C for an appropriate time (5 min). Next, 10  $\mu$ l of 2.5 nM CA-1 were added. The amount of thrombin generated was quantified by measuring the initial velocity of p-nitroaniline at 405 nm, using kinetic plate reader, with pure human prothrombin as a standard. This method was reported by Yamada *et al.* for the first time in 1996.<sup>1)</sup>

### PT and HPT

The PT and HPT were all measured using the CA-5000 (Sysmex, Kobe, Japan). The PT-INR reagent used in this study was Thromborel-S (ISI: 1.08) (Sysmex, Kobe, Japan). The HPT reagent was determined using the Hepaplastin test (Eisai, Tokyo, Japan).

### Statistical analysis

A statistical analysis was performed using the Mann-Whitney U-test. Statistically significant differences were assumed to exist at a value of  $P < 0.05$ . The mean value was taken as the mean  $\pm$  standard deviation.

### Results

After comparing the demographics of the samples in group 1 and group 2, no significant difference was observed in the two populations (Table 1).

Table 2 shows the pre-measure CA-1 test variables. Even the AST, ALT and  $\gamma$ -GTP decreased more significantly in group 2 than in group 1.

Table 3 shows the CA-1 test variables. The mean prothrombin levels (CA-1 score) of group 1 was  $119.4 \pm 44.3$   $\mu$ g/ml. In contrast, the mean CA-

Table 1

	Group 1	Group 2
Cases	20	27
Male/female	12/8	15/12
Mean age (years)	63.2 $\pm$ 13.0	65.9 $\pm$ 14.1

Group 1 had no samples from individuals with liver dysfunction.

Group 2 had samples from patients with liver dysfunction.

Table 2

	Group 1	Group 2	p-value
AST (IU/L)	19.7 $\pm$ 5.3	83.1 $\pm$ 115.6	<0.0001
ALT (IU/L)	13.6 $\pm$ 6.3	33.0 $\pm$ 29.6	0.0002
$\gamma$ -GTP (IU/L)	23.2 $\pm$ 9.9	82.5 $\pm$ 18.4	0.0002

Group 1 had no samples from individuals with liver dysfunction.

Group 2 had samples from patients with liver dysfunction.

AST: Aspartate aminotransferase, ALT: alanine aminotransferase,  $\gamma$ -GTP:  $\gamma$ -glutamyl transpeptidase.

Table 3

	Group 1	Group 2	p-value
CA-1 score ( $\mu\text{g/ml}$ )	119.4 $\pm$ 44.3	95.8 $\pm$ 29.4	0.0402
PT-INR	1.0 $\pm$ 0.1	1.1 $\pm$ 0.1	0.0486
HPT (%)	101.8 $\pm$ 25.4	94.4 $\pm$ 32.9	NS

Group 1 had no samples from individuals with liver dysfunction.

Group 2 had samples from patients with liver dysfunction.

CA-1 score : Normal prothrombin levels, PT-INR : Prothrombin time-international normalized ratio, HPT : Hepaplastin test.

1 score of group 2 was 95.8 $\pm$ 29.4  $\mu\text{g/ml}$ . The CA-1 score of group 2 decreased more significantly than in group 1 based on the above findings.

Table 3 shows the PT-INR variables. The mean PT-INR of group 1 was 1.0 $\pm$ 0.1. In contrast, the mean PT-INR of group 2 was 1.1 $\pm$ 0.1. The PT-INR of group 2 decreased more significantly than in group 1 based on the above findings.

Table 3 showed the HPT variable. The mean HPT of group 1 was 101.8 $\pm$ 25.4%. In contrast, the mean HPT of group 2 was 94.4 $\pm$ 32.9%. No significant differences in the HPT variables were observed between the 2 groups.

### Discussion

This prospective randomized study was carried out in 47 samples. The mean prothrombin levels (CA-1 score) were measured using the CA-1 test. The mean value of CA-1 score was 119.4  $\mu\text{g/ml}$  in the control group and 95.8  $\mu\text{g/ml}$  in the liver dysfunction group. The prothrombin levels of the liver dysfunction group decreased more significantly than in the control group.

Therefore, no significant difference in the HPT level was observed between the 2 groups.

Prothrombin is coagulation factors that is made in liver. Prothrombin has 72kDa polypeptide and single chain.<sup>2)</sup> The volume of prothrombin from the liver demonstrates a higher quantity than another vitamin-K dependent coagulation factors.<sup>2)</sup> Measuring the prothrombin level is therefore considered to be a good measurement of the liver function. The CA-1 test activates only the prothrombin levels<sup>1)</sup>. This test is not only a qualitative analysis but also a quantitative analysis. The CA-1 test requires only 10  $\mu\text{l}$  of diluted blood plasma.<sup>3)</sup> Each examination took only

about 30 minutes, and neither EDTA nor heparin affected the normal prothrombin level obtained by the CA-1 test. Therefore, the CA-1 test is thus considered to be an accurate monitoring system.<sup>2)</sup>

In the present study, the PT and HPT were measured to demonstrate their levels in the liver.

PT examines coagulant factors II, V, VII, X and fibrinogen. In addition, the HPT examines the Vitamin K-dependent coagulant factors II, VII, and X. It is said that the prothrombin induced by vitamin K absence (PIVKA) does not affect HPT, and it is also considered to be superior to PT for monitoring liver dysfunction.<sup>4)5)</sup> However, as the titer of reagents used to measure the PT-INR and the HPT differ from manufacturer to manufacturer. The determined values based on such measurements are not absolute. Therefore, both the PT and HPT are not accurate monitoring systems. In addition the PT and HPT can not measure the coagulation activity of plasma sample anticoagulated by heparin and EDTA.<sup>5)</sup> Therefore, the HPT can not monitor anticoagulant therapy patients treated by heparin. In contrast, the CA-1 test can measure such patients. In this study, the CA-1 score of the liver dysfunction group decreased more significantly than in the control group. In contrast, no significant differences in the HPT variables were observed between the 2 groups. Consequently, the CA-1 test is therefore considered to be superior to the PT and HPT.

Camacho-Lobato L et al<sup>6)</sup> reported that they observed a prolonged prothrombin fragment 1+2 in early liver dysfunction in schistosomiasis as the albumin levels tended to be normal. However, the prothrombin fragment 1+2 needs a long measurement time, while, in addition, this method is also difficult to perform and expensive.<sup>7)</sup> In addition, the thrombin-antithrombin III complex (TAT) is

used to analyze for liver dysfunction.

However, the TAT takes three hours to perform and it is also expensive.<sup>8)</sup>

Singer AM<sup>9)</sup> reported about "increased transaminase levels in patients with acetoaminophen-induced liver dysfunction". In such cases, the CA-1 test is therefore considered to be an appropriate analytical test.

Furie et al.<sup>10)</sup> developed a new radioimmunoassay to analyze normal prothrombin levels.

Kornberg et al.<sup>11)</sup> developed an assay for the prothrombin levels by using ELISA. These studies clearly indicated that the prothrombin levels reflected the clotting activities of plasma samples. However, an assay to determine the prothrombin levels is difficult because it requires a Ca<sup>2+</sup>-dependent anti-human prothrombin antibody which recognizes the Ca<sup>2+</sup>-bound conformation of the Gla-domain. In contrast, the CA-1 test is a highly sensitive chromogenic microplate assay that easily quantifies normal prothrombin.<sup>1)</sup>

### Conclusions

This study shows that the CA-1 test can be used to easily and rapidly determine the prothrombin levels in plasma specimens from liver dysfunction patients. The sensitivity of the CA-1 test is higher than the HPT. Neither EDTA nor heparin affected the normal prothrombin levels obtained by the CA-1 test. In addition, the CA-1 test is also a more accurate monitoring system than PT and HPT. Based on these preliminary data, we therefore recommend the use of the CA-1 test to measure the prothrombin levels as an effective new method for monitoring liver dysfunction.

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