ンが大きな役割を果たしている可能性が示された[13]。また，虚血心筋に対する外科的注入も報告されている[14]。

しかし，このBMMNCの血管新生効果の評価が難問であった。そこで，我々は，ブタ心筋梗塞モデルに対する骨髄細胞移植の効果について，心筋コントラストエコー法により検討した[15]。まず，NIBSブタの左前下降枝を結紮し，心筋梗塞モデルを作製した。1ヵ月後，骨髄細胞を梗塞部へ直接注入し，myocardial contrast intensity (MCI) を測定した。移植1ヵ月後に犠牲死させ，組織学的に毛細血管密度 (capillary density：CD) を測定した。その結果，MCIとCDに正の相関を認めたが，毛細血管の多くは直径10μm以下であった。移植梗塞部のMCIとCDは，非移植梗塞部よりも有意に増加した。これらより，骨髄細胞移植は，心筋梗塞部位での血流を改善し，さらに，心筋コントラストエコー法によりこの血流改善効果が非侵襲的にベッドサイドで評価し得ることが示された。

BMMNCは，細胞移植の細胞源として，採取法が確立されており，さらに培養する必要がなく用いやすい。しかし，十分な細胞数を得るには全身麻酔が必要であり侵襲が大きい。これに対し，MSCは増殖能力が高く，骨髄細胞を少量採取し，生体外で培養し，必要量が得られてから移植することが可能となる。

そこで，MSC移植による血管再生効果を，BMMNC移植と比較検討した。ラットの左総腸骨動脈の結紮・切除により下肢虚血を作製した後，同数のMSCあるいはBMMNCを移植し，未治療群と比較した。移植3週間後，移植両群は，未治療群より有意な血流増加を認めたが，MSC群がより高度な血流改善を示した。また，毛細血管数も，MSC群はBMMNC群より増加していた。さらに，両群とも移植局所に移植細胞由来と考えられる血管内皮細胞を認めたが，その数はMSC群で有意に多かった。また，MSC群では移植細胞からの血管平滑筋と壁細胞への分化を認めた。さらに，BMMNCと比較しMSCでは，vascular endothelial growth factor (VEGF)，hepatocyte growth factor (HGF)，adrenomedullin (AM) などの血管新生因子が多量に分泌していた[16]。また，低酸素状態について検討すると，*in vitro*でMSCは管腔を形成した。さらに，無血清培地培養下における低酸素状態では，MSCはBMMNCに比べてアポトーシスは少なかった。したがって，MSCは低栄養および低酸素状態においてより高率に生存し得ることから，MSC移植はBMMNC移植と比較して，同等以上の血管再生作用があると考えられた。

そこで，心筋梗塞モデルにおいてMSCの経静脈投与の効果を検討した[17]。左冠動脈結紮により作製した心筋梗塞モデルラットの頸静脈からMSCをカテーテルにより移植した。その結果，MSCの一部は梗塞巣周囲に集積し，さらに心筋細胞および血管内皮細胞に分化し，心機能を改善させた。

また，MSC細胞移植の拡張型心筋症への効果をラット心筋症モデルで検討した。近交系ラットの大腿骨より骨髄組織を取り出し，培養皿底面に付着するMSCを分離・培養した。このMSCを，ミオシン投与拡張型心筋症モデルラットの心筋壁内に心外膜より直接注入し，未治療群と比較した。4週間後における心エコーおよび心臓カテーテル検査では，未治療群と比較し，MSC移植群は左室拡張末期圧の有意な低下および左室収縮能の有意な改善を認めた。病理学的検討では，MSC移植群は心筋コラーゲン含量が減少し，さらに心筋壁内で血管内皮細胞や平滑筋細胞に分化し，管腔構造を形成した。また，免疫組織染色にて，心筋内に注入したMSCの一部はトロポニンT，desmin，およびコネキシン43が陽性であった。さらにMSCは種々の血管新生因子やアポトーシス抑制因子を分泌した。したがって，MSCは心筋細胞や血管細胞へ分化し，さらにパラクライン因子として心筋および血管再生に関与することが示唆された。次いで，ブタを用いた前臨床研究を行い，骨，軟骨，脂肪などへ分化しないこと，不整脈が出現しないことなど，MSC移植の安全性を確認した。

以上の結果を踏まえ，虚血性心疾患や拡張型心筋症などによる心不全例で，利尿剤，ACE阻害薬，β遮断薬などの既存の治療が困難な症例を対象に，患者の骨髄液15mLを採取し，体外で培養増殖させ，カテーテルを用いて心内膜側より心筋内へMSCを注入

する臨床試験を計画した。国立循環器病センター倫理委員会に「間葉系幹細胞移植による難治性心不全治療の臨床評価」の実施を申請し，承認された。これまで数例の難治性心不全症例に対して自己MSC移植を行ったが，重度の不整脈などの副作用はなく，順調に経過している。今後，補助人工心臓装着例への応用なども検討している。

内因性細胞移植(endogenous cell transplantation)

Orlicらは，2001年に急性心筋梗塞マウスモデルに顆粒球コロニー刺激因子（G-CSF）と幹細胞因子（SCF）を投与し，心機能の改善および生存率の改善が得られたことから，G-CSFとSCFによる幹細胞の賦活化を報告した[8]。しかし，再生心筋がホストの心筋由来か骨髄由来かは不明であった。我々は，この内因性幹細胞の由来を検討した。放射線照射後のC57b6マウスにGFP-BMCを移植し，キメラマウスを作製した。心筋梗塞モデルでの検討ではG-CSF投与群で心筋梗塞1ヵ月後における生存率の改善傾向を認めた[9]。また，G-CSF群では，心筋梗塞境界部のGFP-BMC数がコントロール群より有意に増加し，そのGFP-BMCのうち約20％がトロポニンI陽性細胞で，ネスチン陽性細胞も多数認めた。さらに，ドキソルビシン投与心不全モデルにおいても同様の結果であった[10]。したがって，骨髄は再生心筋の細胞源の一つで，G-CSFがその効果を増強することが示唆された。また，ヒト心筋細胞を用いた検討において，G-CSFは病的心筋に直接働き，G-CSFレセプターを介してトロポニンI陽性細胞の増殖を増強することが確認された[10]。しかし，骨髄由来の心筋細胞数が少なく，心臓ポンプ機能の改善効果には限界があった[22]。

しかし，内因性幹細胞は，障害された心筋とともに動脈硬化巣にも遊走する可能性があり[23]，心筋障害に対する効果的な内因性幹細胞を用いた治療には，内因性幹細胞の遊走に関する生理学的メカニズムの解明が望まれる。

おわりに

細胞を用いた心筋再生において，骨髄細胞は，自己細胞を用いるため拒絶反応を避けることができ，倫理的問題も少ない。さらに，心筋内に移植することで心筋と血管が同時に再生され得るため，拡張型心筋症などの難治性重症心不全に対する治療として期待される。

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第42回日本人工臓器学会大会座長報告

パネルディスカッション(4)

ハイブリッド人工臓器の現状と未来

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本パネルにおいては，生体材料を組み込んだ新たな人工臓器として期待されているハイブリッド人工臓器について，ハイブリッド人工腎臓，ハイブリッド人工肝臓，ハイブリッド人工膵臓に加え，ハイブリッド血管・心臓弁を取り上げた。

(P-4-1)「ハイブリッド人工腎臓開発の現状と課題」斉藤明(東海大学総合医学研究所分子病態学部門II)氏らは，中空糸膜モジュールと近位尿細管上皮細胞を用いたバイオ人工尿細管デバイスと持続血液濾過器により，患者血液濾過液を再生し，代謝・内分泌機能を付加して体内に戻すハイブリッド人工腎臓について報告した。持続血液濾過器としては，抗血栓性と血液適合性を得るために細胞膜のリン脂質を模したポリマーなどを用い，近位尿細管上皮細胞を単層に生着させたバイオ人工尿細管デバイスとで長期使用可能なものにすべく検討している。人工膜種により尿細管細胞の生着率や増殖能は異なった。また尿細管細胞では，生着しても重層化すると機能低下がみられることより，コンフルエントな生着後にコンタクトインヒビションを保つ尿細管細胞種を選択することが重要である。現状では，急性腎不全治療に短期間応用できるレベルであり，長期使用を可能とするために，今後の発展が期待される。

(P-4-2)「血液透析用ホロファイバー型モジュール(H)を用いたハイブリッド型人工腎臓」鶴岡秀一(自治医科大学薬理学講座臨床薬理学部門)氏らは，腎臓の機能として糸球体濾過やホルモン産生に加え，尿細管分泌に着目し，新たに作成可能となった様々な溶質をより多く分泌できる培養尿細管細胞を用いたハイブリッド人工腎臓について報告した。多剤耐性蛋白(MDR)-1遺伝子を培養尿細管細胞に導入し，細胞培養用の小型Hにコンフルエントになるまで培養したモジュールを用いることで，ジゴキシン中毒イヌの治療が可能となった。今後異なる遺伝子を用い様々な溶質除去能を持った細胞を作成することで，より生体腎に近い尿細管分泌能をもったハイブリッド型人工腎臓の開発が期待される。

(P-4-3)「ハイブリッド型人工肝臓開発の現状」中澤浩二(北九州市立大学国際環境工学部)氏らは，肝移植までのブリッジや，肝臓のもつ自己再生能を促進することで肝不全に陥った自己肝の回復を促すハイブリッド人工肝臓の開発について，細胞培養法を報告した。肝細胞の高機能発現と長期維持を実現するために三次元的な細胞組織体(オルガノイド)を形成させる培養法を確立し，2つのタイプの人工肝臓を開発検討している。一つは，加工したポリウレタン発泡体ブロックの孔内で形成される肝細胞球状組織体(スフェロイド)を利用したもので，もう一つは毛細血管に模した中空糸を微小間隔で規則的に配置し，その中空糸外部空間に遠心力を利用して形成させた肝細胞オルガノイドを利用するものである。前者は温虚血肝不全ブタを用いた前臨床試験で，後者は小動物実験において良好な救命効果を持つことが確認されている。臨床応用における問題点は細胞原であり，ブタ肝細胞とともにヒト細胞についても検討を進めている。

(P-4-4)「実用化に向けたバイオ人工肝臓・膵臓の開発」小林直哉(岡山大学大学院医歯学総合研究科・消化器・腫瘍外科学)氏らは，中空糸外細胞充填式モジュールによるバイオ人工肝臓(BAL)と膵臓(BAP)について報告した。BALには，ポリスルフォンを，BAPにはエチレンポリビニルアルコール中空糸を，細胞接着支持体にはポリアミン酸ウレタン共重合体コーティングPTFE不織布を各々用い，さらにレーヨン不織布を支持体とした簀巻状モジュールを作成した。BALとしては可逆性不死化ヒト肝細胞あるいは新鮮分離ブタ肝細胞を，BAPにはマウスインスリン分泌MIN6細胞あるいは新鮮分離ブタ膵島を各々充填した。肝不全モデルに対しBALを用いることで生存例がみられた。また，BAPに対しては糖負荷を行なったが，良好な血糖値のコントロールを示した。臨床化に向けた今後の研究が期待される。

(P-4-5)「基材として脱細胞化組織を用いたハイブリッド血管・心臓弁」藤里俊哉(国立循環器病センター再生医療部)氏

らは，脱細胞化した生体組織を用い，患者個人の細胞をハイブリッド化するテーラーメード型組織移植について報告した。この脱細胞化組織基材は，移植後，自己細胞の浸潤に伴い自己組織と置換されることが期待される。脱細胞化については，超高静水圧印加を続けて洗浄処理し，組織内の細胞を除去するパワーグラフト法を開発した。この脱細胞化基材に，回転および循環培養バイオリアクター装置を用いて血管内皮細胞を播種した。このようにして作成した血管および心臓弁をミニブタによる動物実験で検討したところでは，良好な結果を示しており，臨床化にむけて研究を進めている。

本パネルにおいては，基材に各種人工臓器あるいは脱細胞化組織を用い，適当な細胞を付加することで，期待する機能を得ようとする各種ハイブリッド人工臓器が報告された。共通した問題点は，用いる細胞種の確保であり，今後の研究の進展が期待された。

CHD

Fontan operation with a viable and growing conduit using pedicled autologous pericardial roll: Serial changes in conduit geometry

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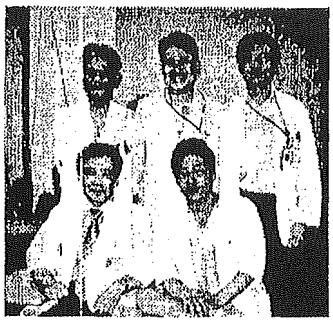

Kagisaki, Hagino, Ishizaka (*top, from left*) Yagihara, Adachi (*bottom, from left*)

Supplemental material is available online.

Objective: We sought to examine midterm results of the Fontan operation with an extracardiac conduit using pedicled autologous pericardial roll, with special attention to angiographic evaluation of serial changes in conduit geometry.

Methods: Of 202 patients subjected to the Fontan operation since 1996, the conduit was used in 28 patients who had intact pericardium. We retrospectively reviewed a consecutive series of these patients, and serial changes in conduit geometry were accessed in 16 patients who underwent catheter examinations twice at 1.1 ± 0.4 and 4.5 ± 1.4 years postoperatively.

Results: There was one early and one late death. Except for a patient with apicocaval juxtaposition in whom a conduit occlusion developed caused by compression between the vertebral bodies and the ventricle, there were no important complications. Angiographically, conduit volume, estimated by using the MULTI-SLICE method, increased significantly (3490 ± 2166 to 5426 ± 3081 mm^3, $P < .001$), whereas the volume per body weight remained unchanged. Conduit diameter increased significantly at both the inferior vena caval end (16.8 ± 4.8 to 19.8 ± 4.8 mm, $P < .001$) and the pulmonary artery end (11.9 ± 3.8 to 14.2 ± 4.2 mm, $P < .001$), whereas the diameter indexed to the normal right pulmonary artery remained unchanged. The cross-sectional area of the conduit increased in parallel with that of the normal right pulmonary artery. The ratio of the widest to the narrowest diameter of the conduit exhibited no significant change.

Conclusions: Midterm results of the Fontan operation with pedicled autologous pericardial roll were favorable. Proportional increase of conduit size was demonstrated, with its shape preserved. This suggested a potential of the conduit to grow and that growth correlated with somatic development.

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Received for publication April 9, 2005; revisions received April 9, 2005; accepted for publication April 9, 2005.

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J Thorac Cardiovasc Surg 2005;130:1517-22

0022-5223/$30.00

doi:10.1016/j.jtcvs.2005.07.050

Surgical repair with native tissue has widened the indications of congenital cardiovascular surgery and has gained increasingly widespread application to various reconstructive procedures. Autologous pericardium has been used for construction of a cavopulmonary connection in the Fontan operation, with the expectation of possible growth ability and less thrombogenicity of the conduit.[1-6] Although favorable midterm outcomes have been reported,[7] no clinical study has quantitatively evaluated serial changes in conduit shape and size. Our objective was to examine midterm results of the Fontan operation using a pedicled pericardial conduit, with special attention to angiographic evaluation of serial changes in conduit geometry.

Patients and Methods

Patient Population

Since 1996, we have used the Fontan operation with an extracardiac conduit constructed with pedicled autologous pericardial roll (PAPR) in patients with an intact pericardium. Of 202

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Abbreviations and Acronyms
IVC = inferior vena cava
PA = pulmonary artery
PAPR = pedicled autologous pericardial roll
SVC = superior vena cava

patients subjected to the Fontan operation between January 1996 and February 2005, a PAPR conduit was used in 28 patients. The median age at operation was 1.3 years (range, 0.8-19.7 years), and median body weight was 8.5 kg (range, 4.6-51.3 kg). The primary diagnosis was tricuspid atresia in 10, unbalanced common atrioventricular canal in 5, double-inlet left ventricle in 4, atrioventricular discordance with double-outlet right ventricle in 2 and with hypoplastic right ventricle in 1, pulmonary atresia with intact ventricular septum in 3, mitral atresia in 1, double-inlet right ventricle in 1, and double-outlet right ventricle with noncommitted ventricular septal defect in 1. Atrial arrangement was situs solitus in 22, right isomerism in 4, and situs inversus in 2. Concomitant procedures were as follows: pulmonary artery (PA) plasty in 8; enlargement of atrial septal defect, ventricular septal defect, or both in 6; additional aortopulmonary anastomosis in 2; mitral valve plasty in 1; and cryoablation of the right atrium in 1. Of the 28 patients, 19 had previously undergone palliative operations, and 2 had a history of median sternotomy.

Information regarding the late status of patients was obtained from medical records. Median duration of follow-up was 5.5 years (range, 1.2-8.4 years). All surviving patients have been followed up postoperatively in our outpatient clinic.

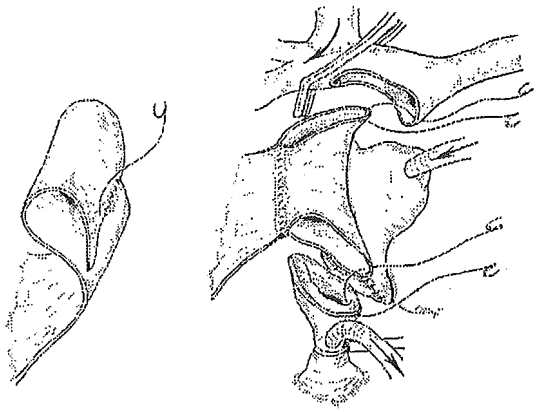

Figure 1. A, A sufficiently large rectangular flap of pericardium was cut, leaving it pedicled so as to preserve its vascular connections, and the flap was then rolled into a tube shape. B, The schema of extracardiac grafting with a pedicled autologous pericardial roll (PAPR) conduit with the aid of a temporary bypass from the inferior vena cava (IVC) to the atrium. The left pulmonary artery was clamped to control retrograde blood return (not depicted for simplicity). The venoatrial junction was divided obliquely to obtain an adequate orifice for anastomosis between a PAPR conduit and the IVC, leaving a small sleeve of atrial musculature around the IVC.

Surgical Procedure

The chest was opened through a median sternotomy, and the pleural space of the corresponding side was opened widely. A sufficiently large rectangular flap of pericardium was cut, leaving it pedicled to preserve its vascular connections, with care taken not to injure the phrenic nerve. The flap was then rolled into a tube shape with a running suture of 6-0 polypropylene with minimal tension and relatively rough pitch to maintain the blood supply to PAPR (Figure 1, *A*). Intraoperative measurements of PAPR diameter in the 28 patients were 16 mm in 2, 17 mm in 2, 18 mm in 12, 19 mm in 1, 20 mm in 8, 22 mm in 2, and 26 mm in 1. The length of the PAPR conduit was determined on the basis of the distance between the inferior vena cava (IVC) and the PA.

Subsequent to injection of 0.15 mL/kg heparin, the superior vena cava (SVC) was connected to the upper surface of the PA by means of bidirectional Glenn anastomosis in all but one patient, who had undergone bidirectional Glenn anastomosis previously. In 19 patients a temporary bypass from the SVC to the atrium was used when cross-clamping the SVC, whereas in the other 9 patients cardiopulmonary bypass was used because of either intracardiac procedures or extended PA plasty. The temporary bypass was a circuit placed between the caval veins and the atrium for venous drainage and it consisted of 2 cannulae and a short connector with a device for air trapping.[8] The PAPR conduit was anastomosed to the lower surface of the PA by using a temporary bypass from the IVC to the atrium in cases without cardiopulmonary bypass. The venoatrial junction was divided obliquely to obtain an adequate orifice for anastomosis between the PAPR conduit and the IVC, leaving a small sleeve of atrial musculature around the IVC. The proximal stump of the atrial side was oversewn, and the distal stump of the IVC side was anastomosed to the PAPR conduit, which had been trimmed and tailored (Figure 1, *B*). In 2 patients a fenestration was placed by interposing a 5-mm Gore-Tex tube graft between the PAPR conduit and the atrium because of relatively high pulmonary vascular resistance (3.0 and 2.8 μm^2, respectively). In addition to routine monitoring of SVC pressure through a percutaneously placed catheter, femoral venous pressure was confirmed not to exceed 20 mm Hg during IVC clamping in cases without cardiopulmonary bypass.

Anticoagulation

Anticoagulation therapy with warfarin sodium and dipyridamole was continued until 1 year postoperatively. The international normalized ratio was maintained at around 2.0. The duration of dipyridamole administration was determined by the patient's personal pediatrician, although indefinite continuation of dipyridamole was recommended when compliance could be predicted and there were no obvious contraindications.

Angiographic Evaluation

Of the 28 patients with the PAPR conduit, 16 underwent catheter examinations twice at 1.1 ± 0.4 and 4.5 ± 1.4 years postopera-

tively. During this period, their body weight and body surface area increased significantly (body weight: 12.4 ± 2.6 to 19.1 ± 3.4 kg, $P < .001$; body surface area: 0.5 ± 0.1 to 0.8 ± 0.1 m^2, $P < .001$). PAPR diameter, cross-sectional area, and volume were measured, and serial changes of these parameters were compared with somatic growth. As control subjects, 18 patients with an artificial graft as an extracardiac conduit who underwent postoperative catheter studies twice were evaluated. Graft volume was estimated by using the MULTI-SLICE method, which is usually used for ventricular volumetry. Each graft was traced in both frontal and lateral views, and the selected structure was divided into 32 cross-sections (Figure E1). Finally, cross-sectional areas of each slice were integrated to calculate graft volume. The ratio of the widest to the narrowest diameter of the PAPR conduit was estimated in either the frontal or lateral view to determine proportional change in the PAPR conduit (Figure E2). Three individuals (I.A., T.Y., and K.K.) determined the measurement points individually to eliminate subjectivity of examiner measurements. Furthermore, all procedures of measurement, such as diameter calculation and graft tracing, were repeated 3 times in each case to minimize potential sources of error from manual maneuvers, and mean values of the 3 measurements were used as final discrete values. All angiographic measurements were performed with DCM View3 angiogram software (Climb Medical System).

Statistical Analysis

Means and standard deviations were calculated for continuous variables. Comparisons were made between values obtained postoperatively at the 2 angiographies by using a paired t test. All analyses were performed with StatView statistical software (Abacus Concepts).

Results

Mortality and Morbidity

There was 1 (3.6%; 95% confidence interval, 0.6%-17.7%) early death caused by cerebral infarction. Because the patient had no fenestration and was hemodynamically stable after the operation, embolic infarction during cardiopulmonary bypass was suspected. There was 1 late death 18 months after the Fontan operation caused by viral pneumonia. Although postmortem examination was not performed for this patient, echocardiography revealed no cardiac or conduit-related problems. Except for a patient with apicocaval juxtaposition in whom conduit occlusion developed as a result of compression between the vertebral bodies and the ventricle, there were no important complications. The median durations of mechanical ventilation, intensive care unit stay, and chest tube drainage among hospital survivors were 1 day, 6 days, and 6 days, respectively. Two patients required prolonged chest tube drainage (>2 weeks) but exhibited spontaneous resolution. One patient had phrenic nerve palsy on the side opposite the pericardial harvest, which could be observed conservatively. There was no conduit-related reoperation in any patient except for 1 patient in whom conduit occlusion developed, as mentioned above. Of the 27 patients who survived the Fontan completion, all remain in sinus rhythm, with an adequate rate at their latest follow-up without prescription of antiarrhythmic drugs. Patients were otherwise free of any other late complications.

Angiographic Evaluation

PAPR volume increased significantly (3490 ± 2166 to 5426 ± 3081 mm^3, $P < .001$), whereas artificial graft volume decreased significantly (6210 ± 2795 to 5853 ± 2481 mm^3, $P = .026$). PAPR volume per body weight remained unchanged (286 ± 173 to 282 ± 155 mm^3/kg, $P = .775$). PAPR diameter increased significantly at both the IVC and PA ends (IVC: 16.8 ± 4.8 to 19.8 ± 4.8 mm, $P < .001$; PA: 11.9 ± 3.8 to 14.2 ± 4.2 mm, $P < .001$). However, when PAPR diameter was indexed to normal right PA diameter, it remained unchanged at both the IVC and PA ends (IVC: 162% ± 46% to 160% ± 35%, $P = .722$; PA: 114% ± 36% to 114% ± 31%, $P = .963$). The ratio of the widest to the narrowest diameter of the PAPR conduit exhibited no significant change in either the frontal or lateral view (frontal: 2.0 ± 0.8 to 1.9 ± 0.7, $P = .495$; lateral: 1.9 ± 0.7 to 2.0 ± 0.6, $P = .759$; Figure 2). The cross-sectional area of the narrowest portion of the PAPR conduit increased in parallel with that of the normal right PA (Figure 3). Neither aneurysmal change nor stenosis of the PAPR conduit was observed, and no pressure gradient was detected across the PAPR conduit in any patient except for 1 patient in whom conduit occlusion developed.

Discussion

Since Fontan and Baudet[9] described the first successful right-sided heart bypass operation in patients with single-ventricle physiology, several modifications have been developed to obtain better quality of circulation and ease of surgical procedures. Of such modifications, the extracardiac Fontan operation has been widely accepted as a technique of choice because of its several advantages, although concern remains regarding the risk of thrombosis and lack of growth ability of the artificial graft in the systemic venous pathway. In 1992, Hvass and colleagues[1] first reported their successful use of a pedicled pericardial tube for construction of a Fontan pathway, and similar reports have since been published,[2-6] with midterm results that appear to be equivalent to those of the extracardiac Fontan operation with an artificial graft.[7] Pathway connection with autologous pericardium might have additional potential advantages over that with an artificial graft. Of such advantages, growth potential is theoretically a significant one because Fontan completion has recently been performed much earlier.[10] In 1997, Gundry and associates[4] described in their report that serial follow-up echocardiograms showed continued growth of the extracardiac lateral tunnels constructed with pedicled pericardium in length and width. However, no previous clinical

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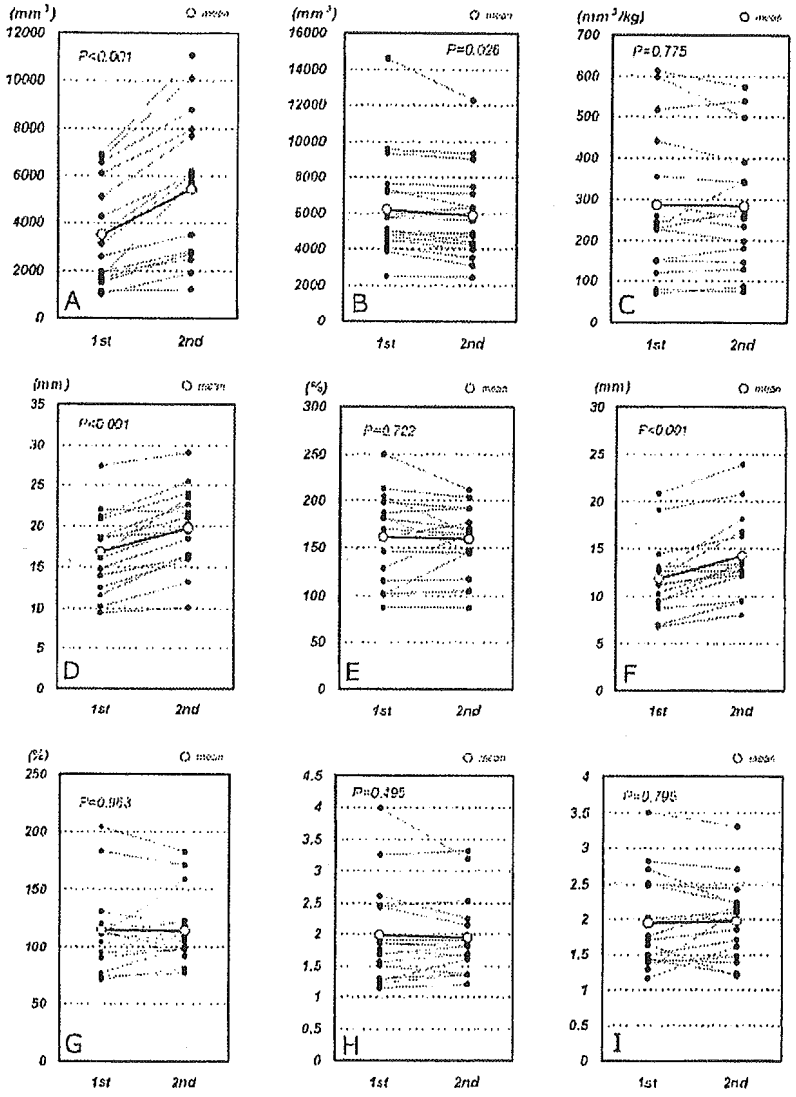

Figure 2. Serial changes in pedicled autologous pericardial roll (PAPR) volume (A), artificial graft volume (B), PAPR volume indexed to body weight (C), PAPR diameter at the inferior vena caval (IVC) end (D), PAPR diameter at the IVC end indexed to normal right pulmonary artery (PA) diameter (E), PAPR diameter at the PA end (F), PAPR diameter at the PA end indexed to normal right PA diameter (G), widest/narrowest ratio in PAPR (frontal view; H), and widest/narrowest ratio in PAPR (lateral view; I).

study has quantitatively evaluated serial changes in conduit shape and size with time, although the ability of pedicled pericardium to grow has been clearly shown in an experimental animal study.[11]

In our study significant increases in PAPR volume and diameter between the 2 postoperative angiographies were demonstrated quantitatively. However, when these values were indexed to somatic parameters, the indexed values

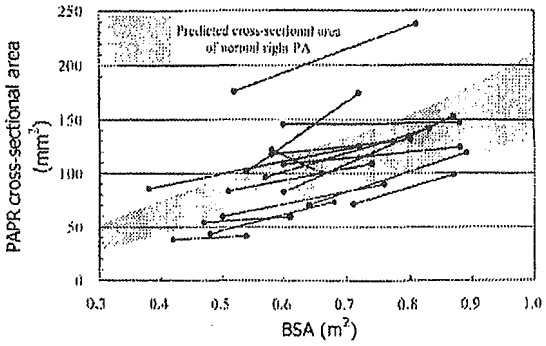

Figure 3. Relation between cross-sectional area of pedicled autologous pericardial roll *(PAPR)* and body surface area *(BSA)*. *PA*, Pulmonary artery.

remained unchanged. The cross-sectional area of the PAPR conduit increased nearly in parallel with that of the normal right PA. These findings indicated that a significant increase in PAPR size was correlated with somatic development. Furthermore, invariability of PAPR proportion was demonstrated, although in previous studies use of autologous pericardium as an implant for vascular substitute yielded mixed results, including shrinkage caused by fibrosis with retraction or thinning with dilatation.[12] Despite the difficulty in clearly distinguishing between growth and mere dilatation, the potential of the PAPR conduit to grow was suggested by the proportional increase in conduit size with preservation of shape.

Some discrepancy was found in PAPR conduit diameters between angiographic examination and intraoperative findings. The angiographic mean value of the PA end diameter at the first catheter examination (11.9 ± 3.8 mm) was 36% less than the intraoperative measurement (18.6 ± 1.3 mm). This phenomenon can be regarded as a result of pericardial remodeling rather than shrinkage because a significant increase in diameter was demonstrated over time. In other words, we might observe the intrinsic adjustability of the PAPR conduit, which has the ability to vary its own shape in response to the flow amount passing through it.

The obvious disadvantage of this modification is its limited application. In fact, we could use the technique in less than 14% (28/202) of patients undergoing Fontan completion over the 9-year period of this study because of the lack of intact pericardium. There were no other anatomic limitations that prevented us from using this technique in the majority of our patients undergoing the Fontan operation. However, apicocaval juxtaposition might be considered as a contraindication of this technique because PAPR was more vulnerable to external compression than a rigid artificial graft.

A potential disadvantage of the geometric approach to measuring graft volume on angiographic studies is possible variability in calculated volume from observer to observer when the graft region of interest is drawn manually or when the anastomotic lines of the graft are defined manually. This is a major problem in the type of angiographic examinations performed in the present study because of the inherently overly smooth anastomotic lines resulting from construction of pathways using only native tissue. Three individuals determined the measurement points individually in the present study to eliminate subjectivity of examiner measurement, and as a result, there was little interobserver variation. Furthermore, little intraobserver variability was noted, although all procedures of measurement, such as diameter calculation and graft tracing, were repeated 3 times in each case to minimize potential sources of error from manual maneuvers.

In conclusion, midterm results of the Fontan operation with a PAPR conduit were favorable. Proportional increase of conduit size was demonstrated, with its shape preserved. This suggests a potential of the conduit to grow and that growth correlated with somatic development.

We wish to express our appreciation for the excellent technical assistance of Akiko Kada (General Clinical Research Unit, National Cardiovascular Center, Japan) in the statistical analysis.

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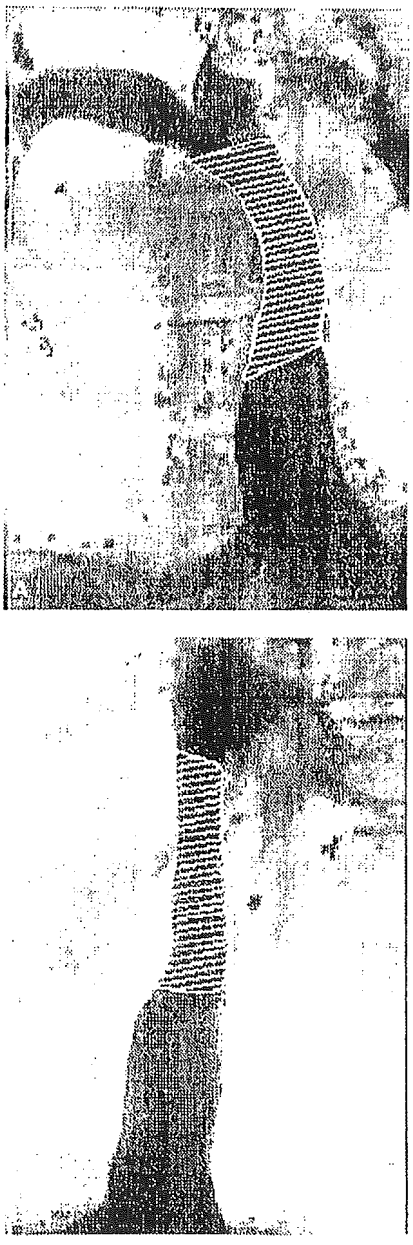

Figure E1. Each graft was traced in both frontal (A) and lateral (B) views, the selected structure was divided into 32 cross-sections, and the cross-sectional areas of each slice were integrated to calculate graft volume (MULTI-SLICE method).

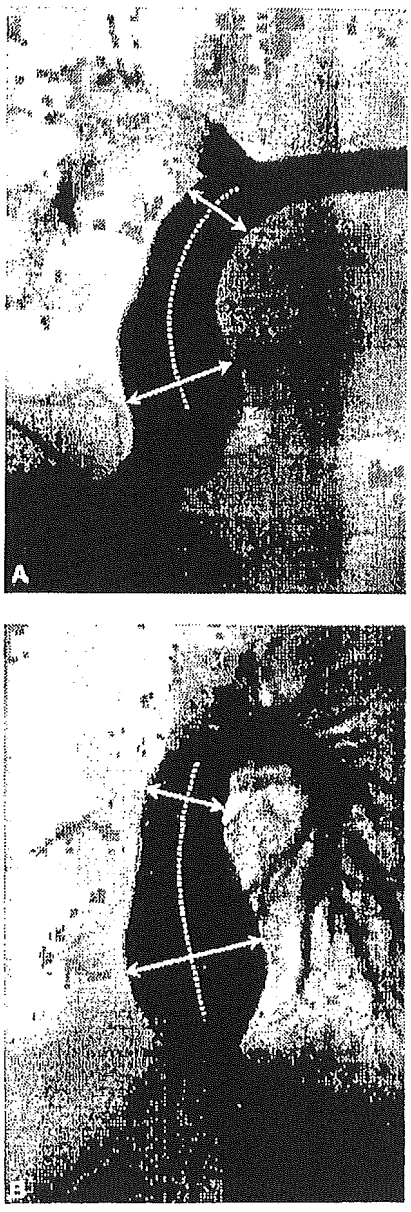

Figure E2. The ratio of the widest to the narrowest diameter in the pedicled autologous pericardial roll conduit was estimated in either the frontal (A) or lateral (B) view to determine proportional change in conduit shape.

ORIGINAL ARTICLE

Early Results of Off-pump Coronary Artery Bypass Grafting for Patients on Chronic Renal Dialysis

Objective: Renal dialysis is one of the independent risk factors for coronary artery bypass graft surgery. Off-pump coronary artery bypass grafting (OPCAB) may become a good option for these patients. In this study, early results as well as surgical techniques of OPCAB in dialysis patients were analyzed compared with non-dialysis patients. *Methods:* Between July 1997 and December 2002, 471 consecutive patients who underwent OPCAB were enrolled in this study. Among them, 20 patients (4.2%) had received hemodialysis regularly for more than 3 months until the operation. Severity of coronary artery disease or clinical presentations had no significant difference, however, left ventricular function was significantly impaired in dialysis patients. *Results:* The average number of anastomosis was 2.8±1.0 in the dialysis group and 3.2±1.0 in the non-dialysis group (p=0.056). Twelve patients (60.0%) received 3 or more bypass grafts in the dialysis group. Among them, 6 patients were revascularized only by *in-situ* or composite arterial conduits using bilateral internal thoracic arteries with or without the gastroepiploic artery. No patients required aortic clamping in the dialysis group. There was no mortality or morbidity in dialysis patients. Perioperaitve bleeding and mechanical ventilation time in the intensive care unit was similar in both groups. No dialysis patients required prolonged mechanical ventilation and hemodialysis from the beginning of the operation to extubation. *Conclusion:* The rationale for OPCAB for dialysis patients has been established. Total arterial revascularization without aortic clamping is applicable for dialysis patients who require multivessel bypass grafts.
(Jpn J Thorac Cardiovasc Surg 2005; 53: 186–192)

Key words: off-pump, hemodialysis, aorta no-touch technique, arterial conduit

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Renal dialysis is one of the independent risk factors for coronary artery bypass graft surgery.[1] Complicated perioperative body fluid control, frequently associated systemic atherosclerotic diseases, impaired coagulant function, or impaired immune systems may induce operative mortality or morbidity, especially when cardiopulmonary bypass (CPB) is used during the operation. Off-pump coronary artery bypass grafting (OPCAB) has become an established method,[2-5] and early advantages of OPCAB for dialysis patients over conventional bypass using CPB have been reported.[6,7] However, whether renal dialysis may become a surgical risk factor or may prolong recovery time in off-pump surgery is still unclear. In OPCAB the selection of graft is also controversial for these patients, because the radial artery needs to be preserved for the shunt formation for hemodialysis.

In our institution, OPCAB with extensive use of arterial conduit has been applied for over 5 years to improve both early and late results.[8,9] In this study, early results as well as surgical techniques of OPCAB in dialysis patients were analyzed compared with patients without dialysis.

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Received for publication March 1, 2004.
Accepted for publication November 4, 2004.
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Subjects and Methods

Patient population. Between July 1997 and December 2002, 471 consecutive patients who underwent OPCAB were enrolled in this study. Among them, 20 patients (4.2%) had received hemodialysis

Table I. *Patients' demographics*

Variables	*Dialysis (n=20)*	*Non-dialysis (n=451)*	*p value*
Age	63.9±8.0	67.2±8.9	0.103
Gender: Male	17 (85.0%)	368 (81.6%)	0.700
Diabetes	13 (65.0%)	243 (53.9%)	0.281
Hypertension	16 (80.0%)	302 (67.0%)	0.329
Cerebrovascular disease	9 (45.0%)	112 (24.8%)	0.043
Serum Hb level (g/dl)	10.2±0.8	13.2±1.8	<0.0001
Triple vessel disease	16 (80.0%)	315 (69.8%)	0.455
LMT≧50% stenosis	8 (40.0%)	159 (35.3%)	0.664
CCS angina grading≧3	3 (15.0%)	119 (26.4%)	0.309
Preoperative IABP	0	17 (3.8%)	1.000
LVEF	37.5±11.3	49.4±11.9	0.0002
LVEF<30%	5 (25.0%)	22 (4.9%)	0.004
≧Moderate ischemic MR	4 (20.0%)	54 (12.0%)	0.293

Plus minus values are mean±SD.
Hb, Hemoglobin; *LMT*, left main trunk; *CCS*, Canadian Cardiovascular Society; *IABP*, intraaortic balloon pumping; *LVEF*, left ventricular ejection fraction; *MR*, mitral regurgitation.

regularly for more than 3 months until the operation. During the same period, 473 patients were assigned for coronary artery bypass using CPB. From July 1997 to February 2000, application of OPCAB had been limited to patients with severe surgical risk factors such as renal failure, severe atherosclerotic disease, or being over 80 years of age. Since March 2000, the off-pump technique has been utilized in all patients who received isolated coronary artery bypass.[8,9] Therefore, in 1997, the number of dialysis/non-dialysis cohort receiving OPCAB was 0/2 patients, in 1998, 2/5 patients, in 1999, 1/6 patients, in 2000, 2/93 patients, in 2001, 7/176 patients, and in 2002, 8/169 patients.

Patients' demographics are shown in Table I. Thirteen patients on dialysis (65.0%) had diabetic nephropathy. The incidence of diabetes mellitus was not significantly different between the two groups. Preoperative serum hemoglobin level was significantly low in dialysis patients. There was no significant difference in severity of coronary artery disease or clinical presentations. Left ventricular function was significantly impaired in dialysis patients. Poor left ventricular function (ejection fraction<30%) was present in 5 patients (25.0%) on dialysis, which is a significantly higher incidence than patients not on dialysis (22 patients, 5.1%).

Surgical technique. Our surgical technique for OPCAB has been based upon total arterial complete revascularization with the aorta no-touch technique.[8,9] Complete revascularization was defined as constructing one graft or more per coronary system (left anterior descending, circumflex, right) which had significant stenosis at not less than one branch. The precise technique of OPCAB was described previously.[8,9] Briefly, a standard median sternotomy was used in all patients. A single or bilateral internal thoracic artery (ITA) was dissected in the semi-skeletonized fashion. Targeted coronary arteries were revascularized in the order of left anterior descending, diagonal, circumflex, and right coronary artery branches after administration of heparin (1.0–1.5 mg/kg). Proper positioning and stabilization of the heart was obtained with pericardial sutures, surgical sponges and the Octopus III stabilizer (Medtronic) with a deep Trendelenburg position and rotation of the operative table toward the surgeon. Possible hemodynamic changes were strictly checked not only by routine vital signs but also by using transesophageal echocardiography and pulmonary artery pressure monitoring. A clear operative field was kept using Retract-O-Tape (Quest Medical), a carbon dioxide blower (Visuflo, Edwards Lifesciences), and an internal shunt (Anastaflo, Edwards Lifesciences; Clear View, Medtronic).

Total arterial bypass graft has been attempted as much as possible using a single or bilateral ITA and a composite radial artery connected to the side or the end of the ITA since the start of OPCAB. The gastroepiploic artery (GEA) was used when we preferred to avoid bilateral use of the ITA because of the sternal wound healing problem. Saphenous vein graft was mainly applied for over 80-year-old patients using an Aortic Connector

(Symmetry). For patients with chronic renal failure, graft selection is more complicated in cases requiring systematic revascularization, because multivessel bypasses must be accomplished without the use of the composite radial artery. We initially had applied Y-composite graft using the saphenous vein connected to the side of the left ITA for these patients. However, one of them presented with recurrent angina caused by occlusion of the saphenous vein just 3 months after the surgery due to accelerated vein graft disease.[10] After this experience, since December 2000, we have applied *in situ* or Y-composite grafting only with bilateral ITAs for patients requiring 3 or more bypass grafts.

Perioperative care for patients on renal dialysis. All patients on renal dialysis received routine dialysis on the day before the surgery. Intraoperative continuous hemodialysis was not scheduled in any patients. Perioperative infusion volume was reduced as little as possible by adequate use of catecholamine or the Trendelenburg position. Serum potassium ion level was strictly measured every hour from the beginning of the surgery, and glucose-insulin therapy was performed first for progressive hyperkalemia. The protocol of anticoagulant therapy was the same in dialysis patients as in non-dialysis patients. Protamine sulfate was given intraoperatively to neutralize the systemic heparinization during anastomosis, then heparin was re-started after hemostasis was secured until the next morning in the intensive care unit (ICU). Half dose of antibiotics was administered at the beginning of surgery in dialysis patients. Maintenance dialysis was planned to re-start the day after the operation or the following day.

Angiographic study. Coronary and graft angiography were performed in 18 dialysis patients (90.0%) and 401 non-dialysis patients (88.9%) within 2 to 3 weeks after the surgery. Cardiologists independently assessed graft patency and stenosis.

Data collection and follow-up. We retrospectively reviewed the data from the operation notes, anesthesia records, clinical histories, laboratory investigations and cardiac catheterization. Follow-up data were collected from the National Cardiovascular Center records of outpatient visits and correspondence with referring physicians. All clinical characteristics were accumulated as a computerized database and analyzed.

Statistical analysis. All values are expressed as mean value±standard deviation. Comparisons between the two groups are established with unpaired t tests for continuous variables and with the χ^2 and Fischer exact tests for discrete variables. Differences were considered statistically significant when the p value was less than 0.05.

Results

Operative technique (Table II). The number of anastomosis was similar in both groups. The average number of anastomosis was 2.8±1.0 in the dialysis group and 3.2±1.0 in the non-dialysis group (p=0.056). Twelve patients (60.0%) received 3 or more bypass grafts in the dialysis group. Among them, five patients received composite grafting using the ITA and saphenous vein. One patient received an *in-situ* ITA graft and saphenous vein graft from the ascending aorta using an Aortic Connector (Symmetry). The other 6 patients received total arterial revascularization. Four received *in-situ* ITA's with or without a GEA graft, and the other two received a Y-composite graft using bilateral ITA's.

The left anterior descending artery was revascularized in all dialysis patients by *in-situ* ITA grafting. Complete revascularization was achieved less in dialysis patients (55.0%), though this is not significant (p=0.063). All dialysis patients who did not receive complete revascularization had diabetic nephropathy and ungraftable diffuse narrow coronary arteries. The frequency of arterial anastomosis is significantly less in the dialysis (73.5%) than the non-dialysis group (95.0%) (p<0.0001). Total arterial revascualrization was also less frequently completed in the dialysis group (60.0%) compared with the non-dialysis group (85.1%) (p=0.003). However, since December 2000, we have accomplished total arterial revascualrization for 6 of 8 dialysis patients (75.0%) by means of bilateral ITA use. No aortic clamping was performed in any dialysis patients.

Early results (Table III). There was no mortality or morbidity in dialysis patients. Perioperative bleeding was similar in both groups, although the incidence of blood transfusion was significantly frequent in dialysis patients. Mechanical ventilation time in the ICU was similar in both groups. No dialysis patients required prolonged ventilation after surgery. ICU stay and hospital stay were similar in both groups. No dialysis patients required hemodialysis from the beginning of the operation to extubation in ICU. They received hemodialysis after extubation in the same protocol as before the operation. Graft patency rate was similarly excellent in both groups.

Discussion

Atherosclerotic vascular disease is the leading cause of morbidity and mortality in patients with end-stage renal failure.[11] Among them, myocardial infarction and other cardiac disorders remain the leading causes of death. Coronary artery bypass surgery can prolong survival

Table II. *Operative technique*

Variables	*Dialysis (n=20)*	*Non-dialysis (n=451)*	*p value*
# of bypass grafts	2.8±1.0	3.2±1.0	0.056
Complete revascularization	11 (55.0%)	333 (73.8%)	0.063
Bilateral ITAs use	9 (45.0%)	152 (33.7%)	0.297
GEA use	3 (15.0%)	15 (3.3%)	0.036
# of arterial/total anastomoses	36/49 (73.5%)	1,337/1,407 (95.0%)	<0.0001
Total arterial revascularization	12 (60.0%)	384 (85.1%)	0.003
Aortic clamping	0	27 (6.0%)	0.620

Plus minus values are mean±SD.
ITA, Internal thoracic artery; *GEA*, gastroepiploic artery.

Table III. *Early results*

Variables	*Dialysis (n=20)*	*Non-dialysis (n=451)*	*p value*
Mortality	0	3 (0.7%)	1.000
Morbidity			
Cerebrovascular accident	0	4 (0.9%)	1.000
Chest infection	0	3 (0.7%)	1.000
Respiratory failure	0	4 (0.9%)	1.000
Operative blood loss	932±493	810±438	0.240
Postoperative blood loss (12 hrs)	655±416	561±316	0.239
Blood transfusion	16 (80.0%)	120 (26.6%)	<0.0001
Mechanical ventilation after the operation (hours)	8.1±3.7 7 (3–14)	9.4±41.0 5 (0–744)	0.904
ICU stay (days)	3.2±1.4 2 (2–5)	3.0±2.7 2 (2–43)	0.805
Hospital stay (days)	21.3±8.1 19 (13–48)	24.4±16.2 21 (9–213)	0.464
Graft patency rate (# of patent/total anastomoses)	43/45 (95.6%)	1,240/1,274 (97.3%)	0.350

Consecutive values are shown by mean±SD or median (range).
ICU, Intensive care unit.

in these patients, however, both early and long-term outcome after revascularization is still poorer compared with patients with normal renal function.[1,12-14] The cause of early high mortality and morbidity in conventional coronary bypass for dialysis patients is mostly associated with the adverse effects of CPB.[12-14] Incomplete revascularization may induce late cardiac events. In our series, complete revascularization was less frequently achieved because of diffuse narrow coronary artery in dialysis patients, although we have tried to anastomose less than 1.5 mm of coronary artery in OPCAB.[15] Graft selection for these patients may also affect both early and long-term results.[12-14,16]

Graft selection. Total arterial revascularization with the aorta no-touch technique minimizes the risk of embolic events caused by aortic manipulation and avoids late vein graft failures. Early and long-term graft patency of saphenous vein graft has been reported to be worse than other arterial grafts.[17] However, selection of bypass grafts is still controversial in patients with chronic renal failure, because the radial artery needs to be preserved.[12-14] Bilateral ITA harvesting has been reported to increase the risk of sternal infection for elderly patients, insulin users, severely obese, and

patients suffering from emphysema or chronic renal failure.[18] GEA sometimes cannot be used because of atherosclerosis or calcification of the artery or chronic gastritis, which is frequently seen in these patients.[19] Furthermore, in patients receiving hemodialysis for a long time, the saphenous vein may have poor endothelial function because of a long-standing inflammatory reaction by the frequent extracorporeal circulation.[20,21]

Y-composite graft using the saphenous vein connected to the side of the ITA seems to be a good option for dialysis patients requiring multivessel bypasses. This method may be more advantageous than an independent graft directly from the ascending aorta, because the saphenous vein is less vulnerable to wall stress and the intraluminally released nitric oxide from the ITA has antiatherosclerotic effects on downstream saphenous vein.[22] In addition, this method does not need any aortic manipulations. However, one of our experiences demonstrated early occlusion of the vein graft 3 months after the operation probably associated with low graft flow velocity from the limited inflow of ITA.[10] Although the other 4 patients have not presented with any cardiac events 2–4 years after the operation, accelerated vein graft disease needs to be remembered in this operation.

In-situ bilateral ITA grafting is an attractive operation for these patients, although sternal wound healing is a concern. In this method, not enough length of ITA may be harvested to anastomose the circumflex or right coronary branches, because dialysis patients frequently have poor left ventricular function and left ventricular dilatation. When GEA cannot be used because of calcification or gastritis, a Y-composite graft using bilateral ITA is another good option, although it is still unclear whether a single ITA has enough flow reserve for systematic revascularization.[23-26] Calafiore et al.[24] showed the incidence of hypoperfusion syndrome was 2.4% after this type of operation using CPB. However, Speziale et al.[25] described a single ITA having enough flow reserve for revacularizing the anterior and lateral wall of left ventricle by flow measurement study. Our previous report[26] showed the adaptability of a single ITA for increasing blood flow in an angiographic study, and we had no experience of hypoperfusion syndrome after this operation in the off-pump technique. Flow competition between a composite graft and a native coronary artery is another concern in the Y-composite graft operation.[27,28] Although the fate of arterial grafts that showed competition or string sign is still controversial, we have preferred to graft in a side-to-side fashion to a coronary artery with mild stenosis, with the termination of this conduit being to the coronary artery with severe stenosis.

No sternal infection, no hypoperfusion syndrome, and no flow competition was seen in our dialysis patients, however, strict monitoring for these problems is necessary as long as we select OPCAB using bilateral *in-situ* or composite ITA grafting for dialysis patients.

Early results. CPB causes large fluid shifts in different body compartments.[20,29] Impaired handling of such fluid shifts in dialysis patients may cause prolonged mechanical ventilation or continuous hemodialysis. Dialysis patients are at increased risk of postoperative bleeding, partly as a result of platelet dysfunction and coagulation defects. They are also more susceptible to infection.[29] CPB may promote bleeding or infection in dialysis patients, and OPCAB can avoid these adverse effects caused by CPB.[29] Previous reports described OPCAB as more beneficial than conventional coronary bypass using CPB in terms of less hematocrit drop and blood product use, a lower catabolic rate, and fewer dialysis requirements after surgery.[6,7] The aortic atherosclerotic changes, which are frequently seen in dialysis patients, may be scattered into systemic circulation as atherosclerotic emboli by the aortic cannulation or clamping.[30] These atherosclerotic embolisms can be avoided by the aorta no-touch technique. In our results, dialysis patients receiving OPCAB demonstrated excellent early results. No mortality or morbidity occured in dialysis patients. They did not require special perioperative management such as prolonged ventilation or continuous hemodialysis systems.

Conclusion

The rationale for OPCAB for dialysis patients has been established. Total arterial revascularization with the aorta no-touch technique is applicable for dialysis patients who require multivessel bypass grafts by means of bilateral ITA use. This method minimizes operative risks and simplifies perioperative care in these patients.

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CASE STUDY

Mitral Valve Repair and Cryo-Maze Procedure in Ehlers-Danlos Syndrome

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ABSTRACT

A 48-year-old man presented with typical features of Ehlers-Danlos syndrome, such as soft and hyperextensible skin, subcutaneous nodules, clubbed feet, and a mild degree of pigeon chest. In addition, his past history revealed congenital dislocation of the hip joint, retinal detachment, and repeated episodes of congestive heart failure due to severe mitral regurgitation and atrial fibrillation. We subjected the patient to surgical repair of the mitral valve combined with the maze procedure, which proved successful.

(Asian Cardiovasc Thorac Ann 2005;13:181–3)

INTRODUCTION

The Maze procedure for atrial fibrillation has been applied successfully in patients with various structural heart diseases. Ehlers-Danlos syndrome (EDS) is a connective tissue disorder characterized by hyperextensibility of the skin, fragility of large and small vessels, hypermobility of joints and poor wound healing with atrophic scarring.[1] A successfully performed Maze procedure and avoidance of mechanical valves allows patients to lead an active life without the need for anticoagulation therapy. This is especially true for patients with EDS because such patients have an aortic lesion and tend to bleed easily due to the vulnerability of the vessels.[2]

We herein report the case of a patient with EDS in whom we successfully performed a surgical repair of the mitral valve in combination with the Maze procedure.

CASE REPORT

A 48-year-old man with EDS was referred to our institution for treatment of mitral regurgitation and atrial fibrillation. He had been diagnosed with EDS, presenting with hyperextensible skin, subcutaneous nodules, clubbed feet, and a mild degree of pigeon chest. His past history revealed an episode of congenital dislocation of the hip joint and detachment of the retina without obvious family history.

Atrial fibrillation had been experienced for 10 months and was managed with digoxin. A chest radiography obtained on admission showed a cardiothoracic ratio of 0.65. Echocardiography demonstrated grade 4 mitral regurgitation due to posterior leaflet prolapse (Figure 1). The left atrial dimension increased to 68 mm in systole. Cardiac catheterization revealed that left ventricular end-diastolic volume index and ejection fraction were 149 $mL \cdot m^{-2}$ and 48%, respectively.

At surgery, we approached the mitral valve via a right-sided left atriotomy. We performed cryo-Maze procedure including cryo-ablation for pulmonary venous isolation from the left atrium. The mitral valve was inspected. The findings included a remarkably dilated annulus and a torn chorda of the middle scallop of the posterior leaflet with dysplasia of the posteromedial commissural scallop (Figure 2). The valve was repaired with quadrangular resection of the posterior leaflet and annuloplasty using a 27 mm Duran ring (Medtronic, Minneapolis, MN, USA). Pathological examination revealed that the fibrous tissue of the posterior mitral leaflet had partially vanished and diminished, and that there was severe myxomatous degeneration of the posterior mitral leaflet with deposit of proteoglycans.

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