胸部外科の指針

討論
1. 金子達夫
2. 中野穣太

高リスク例に対するOPCAB

花田智樹　樋上哲哉　金築一摩　清水弘治
今井健介　本多　祐　菊地慶太*

はじめに

冠状動脈疾患例において，高齢化および冠状動脈インターベンションの発展などに伴い，冠状動脈バイパス術（CABG）を要する対象は合併疾患を有する症例が多くを占めるにいたり，いわゆる高リスク例に対する完全冠血行再建の必要性が増大してきている．一方，近年off-pump CABG（OPCAB）の手技の定型化および安全性の向上に伴い，より低侵襲での完全冠血行再建が可能となった．当施設では，単独CABG対象例においては原則としてOPCABを第一選択としている．本研究では，高リスク例に対するOPCABの早期成績からこのような症例におけるOPCABの適応およびグラフト選択を含む手技の安全性・妥当性を評価することを目標とした．

I. 対象および方法

最近2年間に行った単独OPCAB連続110例［小切開CABG（MIDCAB）を除く］を対象とした．平均年齢70.9±8.7（51～90）歳，男性77例，女性33例であった．

対象例のうち脳血管障害（脳梗塞既往，内頸動脈狭窄など），超高齢（80歳以上），腎機能障害（CRE 2.0 mg/dl以上），低左心機能［左室駆出率（EF）40%未満］，糖尿病（インスリン使用），呼吸機能低下（1秒率50%未満），緊急手術（24時間以内），急性心筋梗塞，術前からの大動脈内バルーンパンピング（IABP）あるいは経皮的心肺補助装置（PCPS）の使用を危険因子とし，この有無によって2群に分けて検討した．術前にこれらの危険因子を有する68例を高リスク群（H群），危険因子のない42例を低リスク群（L群）とした．

患者背景を表1に示す．男女比，平均病変枝数

表1. 患者背景

	H群（n=68）	L群（n=42）	p値
平均年齢（歳）	73.0±8.6	67.5±8.0	0.0012
症例数（男/女）	46/22	31/11	NS
平均病変枝数	2.5±0.6	2.4±0.6	NS
Euro score	7.3±3.2	2.9±2.1	<0.0001

表2. H群（n=68）における危険因子

	症例数（%）
脳血管障害	30（44.1）
超高齢（≧80歳）	18（26.5）
糖尿病（インスリン使用）	16（23.5）
腎機能障害（CRE≧2.0 mg/dl）	15（22.1）
低左心機能（EF<40%）	15（22.1）
呼吸機能低下（1秒率<50%）	2（2.9）
緊急手術	12（17.6）
急性心筋梗塞	6（8.8）
術前IABP	14（20.6）
術前PCPS	1（1.5）

キーワード：ハイリスク例，OPCAB

* T. Hanada（講師），T. Higami（教授），K. Kanetsuki，K. Shimizu，K. Imai，T. Honda，K. Kikuchi（講師）：島根大学循環器・消化器総合外科．

表 3. 手術結果

	H 群(n=68)	L 群(n=42)	p 値
平均グラフト枝数	2.9±0.9	2.9±0.9	NS
術中 IABP 使用	0	0	NS
on-pump beating CABG への convert	1	0	
完全血行再建率(%)	85	93	NS
各種グラフト使用率(%)			
LITA	93	100	NS
RITA	82	88	NS
RGEA	50	38	NS
RA	0	2	NS
領域別平均吻合数			
LAD	1.19	1.40	NS
LCx	1.14	0.92	NS
RCA	0.55	0.47	NS
sequential バイパス施行率(%)	48	60	NS

LITA：左内胸動脈，RITA：右内胸動脈，RGEA：右胃大網動脈，RA：橈骨動脈，LAD：左前下行枝，LCx：左回旋枝，RCA：右冠状動脈

表 4. 術後経過

	H 群(n=68)	L 群(n=42)	p 値
グラフト開存率(%)	100.0(n=56)	97.1(n=34)	NS
病院死亡	1 例(1.5%)	0	
術後合併症(例)			
脳梗塞	0	0	
腎不全の悪化(透析)	1(1.5%)*	0	
肺炎	1(1.5%)	0	
呼吸不全(挿管 10 日以上)	1(1.5%)*	0	
周術期心筋梗塞	1(1.5%)	1(2.4%)	
縦隔洞炎	0	2(4.8%)	

* 同一症例

では両群間に有意差はなかったが，H 群は L 群より有意に高齢であり（p=0.0012），また Euro score も H 群が L 群に対して有意な高値を示した（p<0.0001）．

H 群における危険因子の内訳を表 2 に示す．脳血管障害例では脳梗塞の既往 16 例（53%），総頸動脈あるいは内頸動脈の 50% 以上狭窄 5 例（17%），両方とも認めるもの 9 例（30%）であった．また，腎機能低下例のうち 10 例（67%）は慢性透析患者であった．

II. 手術方法

手術では ultrasonic complete skeletonization (UCS) 法により左右の内胸動脈と右胃大網動脈を採取した．一部の症例では橈骨動脈も使用した．体位は右下 Trendelenburg 位とし，原則として 3 針の Lima suture のみにて心臓を脱転した．心臓の脱転位をかえることなくスタビライザーを用いて吻合部の固定が可能であり，すべての吻合を同一心臓位で完了しえた．グラフト吻合時にはシャントチューブを使用し，動脈吻合のすべてを 8-0 ポリプロピレンの連続縫合とした．原則として可及的に *in situ* 動脈グラフトとし，aortic no-touch にて完全血行再建を行った．このさい，多枝バイパスでは sequential バイパスを積極的に用いた．

統計処理は Student t 検定，χ^2 検定を用い，p<0.05 を有意とした．数値は平均値±標準偏差で示した．

III. 結　果

平均グラフト枝数は両群間で有意差を認めなかった．術中に IABP が新たに必要となった症例はなく，H 群の 1 例（術前左心機能は良好）で，吻合中に心電図上 ST が低下したために on-pump beating CABG への convert が必要であった．H 群の 2 例，L 群の 1 例に腹部大動脈瘤に対する人工血管置換術を同時に行った．完全血行再建率は H 群 85%，L 群 93% と，両群間で有意差はなかった．各種グラフト使用率，領域別平均吻合数，sequential バイパス施行率にも両群間で有意差はなかった（表 3）．

術後の冠状動脈造影は H 群 56 例（82%），L 群 34 例（81%）に行い，グラフト開存率は H 群 100%，L 群 97.1% と両群間で有意差はなかった．病院死亡は H 群の 1 例（1.5%）のみで，術後 3 日に不整脈によると思われる突然死にて失った．H 群において，術前にショック状態であった 1 例で腎不全が悪化して慢性透析が必要となり，さらに術後 10 日以上の人工呼吸器管理が必要であった．軽度の周術期心筋梗塞を両群に 1 例ずつ認めたが，CPK や CPK-MB の上昇のみで

血行動態には異常を認めなかった．肺炎をH群で1例，縦隔洞炎をL群で2例認めたが，術後に脳梗塞を生じた症例は両群ともになかった（表4）．以上，なんらかの合併症を発症した症例はH群5例（7.4%），L群3例（7.1%）であった．

IV. 考　　察

近年，社会の高齢化が進展するとともに高齢者に対するCABGの必要性が増大してきている．本研究の対象症例に占める80歳以上の超高齢者の割合は16.4%であり，本邦報告例（2.7～4.1%）[1-3]と比較しても高齢者の比率が高かった．高齢者では動脈硬化がより進行しているため，脳血管障害などの手術危険因子を有している可能性が高く，また急性心筋梗塞など緊急手術が必要となることも多い[2,4]．一方，CABGにおいては近年OPCABの適応が拡大し，成績も安定してきた．Wanら[5]は，人工心肺を使用したconventional CABG（C-CABG）と比較してOPCABではサイトカインの反応や心筋障害が少ないと述べ，Sabikら[6]はOPCABにより完全血行再建率は低下したものの術後の合併症が減少したことを報告した．

以上の経緯を踏まえ，本研究ではH群に対してOPCABを選択する妥当性を明らかにするために，その早期成績を同時期に行ったL群と比較・検討した．

本研究では脳血管障害，超高齢，腎機能障害，低左心機能，糖尿病，呼吸機能低下，緊急手術，急性心筋梗塞，術前からのIABPあるいはPCPSの使用を危険因子とした．手術危険率を予測するEuro score[7]を適用してみると，H群はL群よりも有意に高値であり，2倍以上のscoreであった．このことからも，本研究におけるH群は一般的にもかなりの手術危険率を有するものと考えられる．

人工心肺を使用するC-CABGのもっとも大きな合併症は周術期に発症する脳血管障害であるが，これは上行大動脈の動脈硬化が主な原因とされる[8]．C-CABGと比べOPCABでは送血管の挿入や上行大動脈の遮断が必要ないため，これらの操作により脳塞栓を生ずる危険性はなく，また自己心拍による拍動流によって灌流されるため，低灌流による脳梗塞の発症も回避することができる．このため，C-CABGと比較してOPCABでは術後の脳血管障害が減少する[9]．本研究においてもH群における術前危険因子では脳血管障害がもっとも多く，約半数の症例に認めたにもかかわらず，術後に脳梗塞を新たに発症した症例はなかった．当科では可及的に動脈グラフトのみを用いた*in situ*での血行再建を行っており，人工心肺を使用しないことに加えaortic no-touchにてOPCABを行っていることが，脳塞栓の高リスク例においても脳合併症を回避できた要因と考えられる．

腎機能が低下した症例や慢性透析患者において，人工心肺を使用しないOPCABは術中・術後の水分管理が容易である[10]．橈骨動脈をグラフトとして使用できないことに対しては，UCS法で採取したグラフトは使用できる距離が長いため[11]，sequentialバイパスを積極的に行うことで，両側内胸動脈や右胃大網動脈という*in situ*動脈グラフトのみによる血行再建が可能であった．遠隔期の開存率に問題のある静脈グラフトを使用する必要性は生じなかった．

OPCABでは心臓の脱転やスタビライザーでの圧迫などにより血行動態の悪化を生ずることが懸念される[9,12]が，われわれは冠状動脈吻合時に手術台を傾け，右下Trendelenburg位とし前負荷を増加させることにより，血行動態の変化を最小限に抑えた．また，この体位でLima sutureを3針かけて牽引すると自然に心尖部が挙上するため，スタビライザーで過度に心臓を圧迫することなく良好な視野を確保することが可能であった．吻合中は冠状動脈内シャントチューブを使用し，末梢への血流を維持するように努めた．吻合時に心電図上STが低下した1例でon-pump beating CABGへのconvertが必要であったが，急性心筋梗塞やEF 40%以下の左心機能低下例でもoff-pumpにてCABGを完遂することができた．

本研究ではバイパス本数にH群，L群間で差は認めなかった．また，使用したグラフトの種類や末梢吻合の領域についても両群間で大きな差はなかった．Sequentialバイパス施行率，完全血

行再建率はL群で高い傾向にあったが有意差はなく，また術後早期のグラフト造影ではL群の開存率が97.1%であったのに対し，H群では全例開存していた．これらの結果は，H群においてもL群と同様のクオリティの手術を行いうることを示すものと考えられる．

病院死亡はH群に1例認めた．急性心筋梗塞にて緊急手術を行った症例で術後経過は良好であったが，術後3日に一般病棟にて不整脈が原因と思われる突然死で失った．術後の合併症については症例数が少ないため正確な比較はむずかしいが，L群と比較してH群で合併症が増加することはなかった．諸家の報告でも，Carrierら[13]は無作為試験を行い，高リスク例ではC-CABGと比較しOPCABで術後の合併症が少ないことを示した．またAromら[14]は，とくに高リスク例において死亡率が有意に改善したことを報告した．当施設ではCABGを原則としてすべてOPCABで行っているためC-CABGとの比較はできないが，合併症の頻度がL群とほぼ同等であったことは，H群における術中・術後の合併症を回避するうえでOPCABが非常に有用であることを示唆している．

社会の高齢化は加速しており，高リスク例に対するOPCABの必要性は今後さらに増大していくと思われる．本研究ではすべて*in situ*動脈グラフトを用いることにより，H群に対してもL群と同様のクオリティにて安全に冠血行再建を行いうることが示唆された．今回は術後の早期成績について検討したが，遠隔成績や個々の危険因子についてのさらなる検討が必要である．

おわりに

高リスク例に対するOPCABの成績は良好であり，とくに脳血管障害を有する症例にはきわめて有用と考えられた．高リスク例においても安全に*in situ*動脈グラフトにて血行再建を行うことが可能であった．

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SUMMARY

Off-pump Coronary Artery Bypass in High-risk Patients

Tomoki Hanada et al., Department of Cardiovascular and General Surgery, School of Medicine, Shimane University, Izumo, Japan

In this study, 110 consecutive patients who had undergone off-pump coronary artery bypass (OPCAB) in the past 2 years were evaluated for early results of OPCAB. Patients were classified as a high-risk group (H group : 68 patients consisting of 46 men and 22 women) and a low-risk group (L group : 42 patients consisting of 31 men and 11 women), respectively, and were evaluated for the early operative results. No differences were noted between the H and L groups in the mean number of bypass grafts (2.9±0.9 in the H group, 2.9±0.9 in the L group), the rates of complete revascularization (85% in the H group, 93% in the L group), those of various graft materials bypassed, or those of sequential bypass. In all patients, we were able to undergo coronary revascularization by the aortic no-touch technique using arterial grafts exclusively. In the H group, 1 patient (1.5%) died in hospital, but no patients developed cerebral infarction postoperatively, and the frequency of complications was similar to that in the L group. The results of OPCAB for high-risk patients were good, and it was suggested that OPCAB using *in situ* arterial grafts was very useful particularly in patients with cerebrovascular diseases.

KEY WORDS : high-risk patient/OPCAB

討論1

金子達夫*

2年間の単独off-pump冠状動脈バイパス術(off-pump CABG：OPCAB)例連続110例を対象とした，リスクによる分類での指針論文を拝読した．まず死亡1例，合併症をすべて含めて8例という手術成績に敬意を表するものである．この要因として*in situ*動脈グラフトを使用したOPCABが大きな関与をしていることは否めない．すなわち人工心肺を使用せず，中枢吻合を必要としない手術手技が安全に行われた結果であろう．

この成績を踏まえたうえで，花田らの述べた高リスク例について検討してみたい．まず，80歳以上の症例の占める割合が16.4%と非常に高いのはなぜであろうか．人口構成比やバイパス術の平均年齢からしても多少の違和感を覚える．また，花田らの定義する高リスクには，脳梗塞既往例や50%以上の頸動脈狭窄，腎機能障害がCRE 2.0 mg/dl以上，左室駆出率(EF) 40%未満の低左心機能，インスリン使用の糖尿病，1秒率50%未満など，一般的にはさほど高リスクと考えられない事項が列挙され，その結果として高リスク例が62%(110例中68例)と過半数を超える高値となってしまっていることに注目したい．これらのうちで真に高リスクと考えられるのは，75%以上の頸動脈狭窄，合併症を伴った超高齢者，透析例，緊急手術，急性心筋梗塞，経皮的心肺補助装置(PCPS)以上の左室補助を伴う症例などではないであろうか．日本胸部外科学会の2003年レポートでは，緊急手術と再バイパス術および透析例が高死亡率として報告されている[1]．リスクの階層化にEuro scoreは有用であり，花田らの結果でも高リスク例では術後合併症が高率である．

手術手技については，左右内胸動脈と胃大網動脈をUCS法で採取し，Lima stitchとスタビライザーによるシャントチューブ使用下のOPCABで，大動脈に触れずにバイパス術を行っており，問題となる点は見当たらない．ただ，1例のみ吻合中にST低下がみられ人工心肺を使用したのはなぜであろうか．また，採取グラフトの距離が長いのでsequentialバイパスを多用しているとのことであるが，吻合個所は増えるがTあるいはY型グラフトによるバイパスのほうが技術的に容易な場合もあるかもしれない．しかし，いずれにせよ動脈グラフトによる*in situ*バイパスを主

* T. Kaneko (副院長)：群馬県立心臓血管センター(〒371-0004 前橋市亀泉町甲3-12)．

体としている点は筆者も賛成である．

また完全血行再建について，花田らは高リスク例では必要であると述べている．リスクをもつ患者に対しあえて完全血行再建をめざすのであれば，一般的には手術リスクはさらに増すのではないであろうか．高リスク例ではあえて完全再建にこだわらず，キーベッセルにバイパスをおき他はハイブリッドあるいは内科治療にゆだねる症例もあるのではないかと思われる．もちろん，無理なく完全血行再建ができるのであればそれに越したことはないであろうが．

OPCABに関しては徐々に適応が拡大され，本邦における2003年のCABG例の半数以上がこれによると報告[1]されている．この点について筆者の現在の考えは，まずはじめにOPCABありきではなく，質の高い，すなわち動脈グラフトによる安全なバイパスを行うことが可能であれば行うべきで，最初からOPCABにこだわる必要はないのではないかということである．大動脈硬化でも術中エコーを使用して安全な場所を選択すれば人工心肺が可能な場合が多く，80歳以上の超高齢者でも70歳台のconventional CABG (C-CABG) と比較して安全に施行可能であった[2]．本論文とは関係ないが，OPCABであるがゆえに静脈グラフトとしたり，冠状動脈末梢の遠位部で縫合せざるをえなくなるのは本末転倒ではないであろうか．また，術中にST低下や不整脈の出現，さらには血圧の低下を招いてまで手術を遂行し，その結果大動脈内バルーンパンピング (IABP) やPCPSなどの補助循環が必要になったという話も耳にする．あるいは径1mmの吻合を拍動下で行うのと静止野で行うのでは，おのずと縫合の質に差が生ずるのではないであろうか．本論文ではそれらの点について述べられていないが，この間のon-pump例はいかほどあったのであろうか．たしかにOPCABは低侵襲であることは論をまたない．しかし，手術に求められるのは侵襲に見合った結果である．手術の侵襲度からいえばOPCABといえどもカテーテル治療とは比較にならないはずで，薬剤溶出ステント (DES) の出現以来バイパス数は世界的に減少し，本邦でも2003年にそれまで右肩上がりであった虚血手術ははじめて低下をきたした．考えるべきはまず手術の安全と患者の術後長期QOL向上をめざした手術で，次の手段としてon-pumpかoff-pumpの選択となるのではないかと筆者は考える．

最後に，高リスクの患者にどのようなバイパス術を行うべきかという点について簡単に言及したい．頸動脈狭窄への対策としては，同時手術と待期手術の選択問題がある．高齢者と透析例では個々の症例で石灰化の位置などを把握したうえでグラフト選択を行い，完全血行再建に拘泥せずに対応すべきと考える．急性心筋梗塞と緊急例では手術成績が不良であるため，さらに慎重な適応と術式への配慮が必要となる．しかし，補助循環を行っている症例はon-pump beatingとかわらないので，そのまま心拍動下でも手術可能であろう．

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討論 2

中野穣太　岡林　均*

本論文では，脳血管障害など高リスク患者に対してoff-pump冠状動脈バイパス術（off-pump CABG：OPCAB）を安全に施行しえた結果が示された．ここでは三つの課題について述べたい．

一つは高リスクの定義の問題である．Euro scoreが7.3と高い値となっているため全体として問題ないと考えるが，CREの値や低左心機能の定義などがEuro scoreのものとはずれており，また経皮的心肺補助装置（PCPS）使用下のCABGはOPCABではないのかと考える．実際，今回の定義と併せて考えると，当科で2000～2005年にかけて施行したOPCABの1,500例中，771例（51.4%）と過半数が高リスクとなる．たとえばEuro score何点以上を高リスクとしたという定義のほうが鮮明となるし，他施設との比較も容易になると考える．また，急性心筋梗塞でポンプ失調をきたし，大動脈内バルーンパンピング（IABP）のみならずPCPS使用が必要となる症例はわれわれも経験しているが，これはPCPSというポンプ補助を行っているため，術前状態を含めOPCABとは分けて考える必要がある．

次にグラフト選択についてであるが，ほとんどの症例で両側内胸動脈と右胃大網動脈を用いてバイパスを行っているが，完全血行再建率が高リスク群で85%，低リスク群で93%とやや低値である．CABGはpalliative operationであることを考えるならば完全血行再建をめざすべきとわれわれは考えており，当科では96.4%に完全血行再建を行い，平均末梢吻合箇所は3.7ヵ所であった．また，とくに狭窄の程度の軽い右冠状動脈に対しては，右胃大網動脈ではcompetitionを起すことがあるため，大伏在静脈か橈骨動脈によるACバイパスがよいと考える．

最後に周術期合併症であるが，本研究にあるようにOPCABの場合，人工心肺を用いたCABGに比して減少することが明らかとなってきた．とくに脳障害は，Lundらの報告にもあるようにoff-pumpで施行することで減少することが示された[1]．しかし，Likoskyらが指摘するように周術期脳障害は術中の要素と術後の要素とを分けて考える必要があり[2]，当科でも1,500例中21例の周術期脳障害を経験しており，そのうち17例は遅発性脳障害であった．つまり，人工心肺を使用せず，aortic manipulationを行わないことで術中脳障害は回避できるが，術後遅発性脳障害は起りうる．この原因の一つとしては心臓手術後の過凝固が考えられ，当科では現在heparin calciumの予防的投与を行っている．

以上三つの課題を述べてきたが，全体として高リスク例に対してバイパス開存率，合併症，死亡率含め問題ない結果を提示されており，今後も遠隔期を含めた高リスク例に対する報告を行っていただきたい．

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* J. Nakano, H. Okabayashi（副院長）：小倉記念病院心臓血管外科（〒802-8555 北九州市小倉北区貴船町1-1）．

Gas Exchange

Development of an Implantable Oxygenator with Cross-Flow Pump

Yuichi Asakawa,* Akio Funakubo,* Kazuyoshi Fukunaga,† Ichiro Taga,† Tetsuya Higami,‡ Tsuyoshi Kawamura,§ and Yasuhiro Fukui*

Thrombogenicity, a problem with long-term artificial lungs, is caused by blood-biomaterial interactions and is made worse by nonuniform flow, which also causes decreased gas exchange. To overcome these obstacles, we changed the inlet and added a uniform flow pump to our previous oxygenator design. Conventional membrane oxygenators have a ½-inch port for the inlet of blood. These port structures make it difficult for the blood to flow uniformly in the oxygenator. In addition, the complex blood flow patterns that occur in the oxygenator, including turbulence and stagnation, lead to thrombogenicity. A cross-flow pump (CFP) can result in uniform blood flow to the inlet side of an oxygenator. In this study, we evaluated the usefulness of an integrated oxygenator with a fiber bundle porosity of 0.6 and a membrane surface area of 1.3 m^2. The inlet part of the oxygenator is improved and better fits the outlet of the CFP. Each of the three models of the improved oxygenator has a different inlet taper angle. The computational fluid dynamics analysis showed that, compared with the original design, uniform flow of the integrated oxygenator improved by 88.8% at the hollow fiber membrane. With the integrated oxygenator, O_2 transfer increased by an average of 20.8%, and CO_2 transfer increased by an average of 35.5%. The results of our experiments suggest that the CFP, which produces a wide, uniform flow to the oxygenator, is effective in attaining high gas exchange performance. *ASAIO Journal* 2006; 52:291–295.

Lung transplant is the treatment of last resort for patients with respiratory failure. Unfortunately, in many cases, patients have to wait a long time for a lung transplant because of a lack of donor lungs. Thus, an artificial implantable lung is a useful respiratory support device for patients with severe lung failure awaiting lung transplantation. We have developed two types of artificial implantable lungs (AIL). The pumpless AIL was designed using a multiobjective genetic algorithm.[1] However, an AIL with a blood pump is also required for patients who need circulatory support.[2–4] The right ventricle might develop cardiac failure due to the resistance created by the oxygenator if an implantable oxygenator is connected to pulmonary artery-left atrium (PA-LA) and blood is circulated without a pump. Though there are many compact centrifugal and axial blood pumps that are commercially available, it is difficult to achieve uniform inflow at the fiber bundle inlet of the oxygenator given that the inlet port has a small diameter, and there is limited space. A high flow speed from the small diameter port causes complex flow in the inlet part of the AIL.[5] This complex flow is the cause of thrombus formation, because the activated procoagulant molecules easily pool in the stagnation area. To avoid this problem, the blood pump for the AIL should be designed to have a wide and uniform outflow. We developed an integrated implantable pump oxygenator using a cross-flow pump (CFP) that can produce a uniform flow to the oxygenator within a limited space.[6–9] The blood flow pattern in an oxygenator depends on the shape of the inlet part.[1] Uniform flow in a fiber bundle is necessary in order to increase the efficiency of the hollow fiber membrane part. If blood flows out from the oxygenator without fully contacting the hollow fiber membrane, gas exchange performance deteriorates; however, if blood stays and does not flow out from the stagnation area when stagnation occurs in the hollow fiber, gas exchange performance deteriorates. Furthermore, if high blood flow causes channeling, and blood flows through a part of the hollow fiber membrane, the contact time and the contact area for O_2 gas are decreased, and gas exchange performance is reduced. Because the membrane's surface area will be used effectively only if the flow velocity in the hollow fiber is uniform, the highest gas exchange performance in the oxygenator is shown under such conditions. To achieve uniform flow, kinetic energy has to be changed efficiently to pressure energy at the inlet part. The CFP can convert kinetic energy to pressure energy efficiently because it has a wide impeller and outlet. In this study, we evaluated the effects on the performance of the oxygenator by examining the uniformity of blood velocity at the hollow fiber membrane part with the CFP.

Materials and Methods

Cross-Flow Pump

The structure of the CFP is shown in Figure 1. The CFP impeller has an inner diameter of 21 mm, an outer diameter of

*Department of Electronic and Computer Engineering, Tokyo Denki University, Japan.; †Frontier R&D Center, Tokyo Denki University, Japan.; ‡Shimane Medical University, Japan.; §Hyogo Prefecture Health Promotion Association, Japan.

Submitted for consideration June 2005; accepted for publication in revised form February 2006.This study was supported by the Tokyo Denki University Frontier Research and Development Center.

Address correspondence: Yuichi Asakawa, Department of Electronic and Computer Engineering, Tokyo Denki University, Ishizaka, Hatoyama Machi, HikiGun, Saitama 350-0394, Japan., Phone:+81-492-96-2911 Ex.3154 Fax:+81-492-96-6413.

DOI: 10.1097/01.mat.0000216165.21432.ee

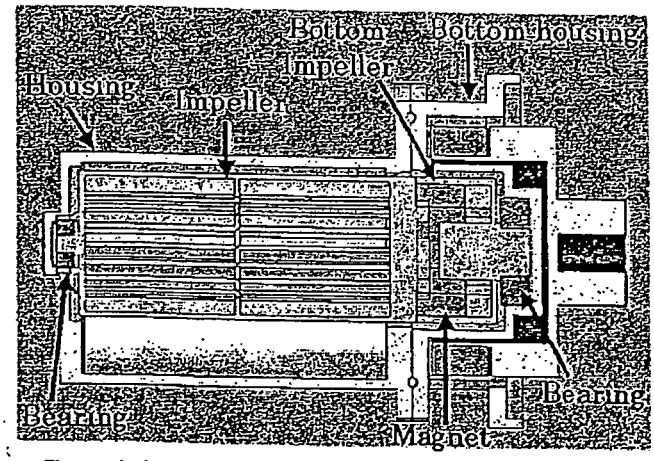

Figure 1. Cross-sectional schematic of the cross-flow pump.

30 mm, and a height of 67.5 mm. The outlet blade angle is set at 30 degrees, and the inlet blade angle is set at 90 degrees. The impeller has 18 vanes.[6-10] The structure of the impeller is shown in Figure 2. The CFP has an outlet of 10 mm × 66 mm. Experimental results show that this impeller design has the highest energy efficiency. The impeller was connected to a DC motor through a magnetic coupling. The performance of the CFP was measured during the *in vitro* experiments. The circuit was filled with glycerin having a viscosity of 3.3 cP. The flow rate and pressure head of the CFP were measured at pump speeds of 1400, 1800, 2200, 2600, and 3000 rpm. At each motor revolution speed, the pressure head, determined as the difference between the inflow and outflow pressures, was varied by partial clamping of the outflow tube, and the pump flow rate was measured. The experimental circuit consisted of the reservoir, the CFP, a flow meter TS410 (Transonic Systems Inc., Ithaca, NY), and a pressure meter RM-6000 (Nihon Kohden CO., Tokyo, Japan).

Oxygenator

Based on our hypothesis, the standard deviation of the flow rate was used as the evaluation index that indicated the variation of flow velocity in the fiber bundle. When blood flows uniformly to the fiber bundle, the standard deviation of the flow rate is smaller. The standard deviation of the flow rate in the fiber bundle was calculated using the following formula:

$$\sigma = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(x_i - \bar{x}\right)^2}$$

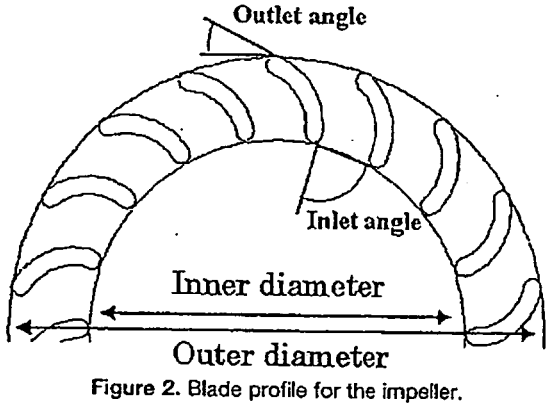

Figure 2. Blade profile for the impeller.

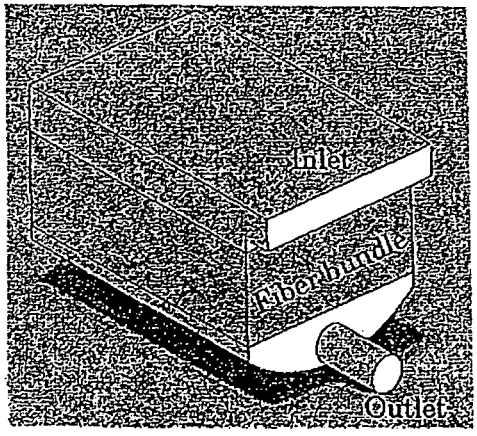

Figure 3. Shown is the standard model that used an improved inlet part of the oxygenator to fit the outlet of the CFP.

where σ is the standard deviation of the flow rate in the fiber bundle, x_i is the flow velocity in each cell, $\bar{x}$ is the average flow velocity of the target cell, and n is the number of cells. The second objective was to minimize the standard deviation of the flow rate in the fiber bundle to obtain better gas exchange performance.[1]

The improved model of αCUBE 6000 (Dainippon Ink & Chemicals Co., Tokyo, Japan) was used as the original design.[1] The oxygenator has a 3/8-inch port. The fiber bundle (DIC membrane) porosity is 0.6, and the membrane surface area is 1.3 m^2. Priming volume is 210 ml. Figure 3 shows the oxygenator model that uses an improved inlet port to fit the outlet of the CFP. The oxygenator has an inlet port of 10 mm × 66 mm. Each of the three models of the improved oxygenator has a different inlet part. The design parameters set up an inlet taper angle α (Figure 4). We selected three representative shapes of the inlet housing that resulted in different α values. Design 1 was the improved standard model. In design 2 α was 10 degrees, while in design 3 α was 40 degrees.

Simulation software, STAR-LT (CD-adapco, Japan), was employed to simulate the flow in the oxygenator. The fluid functioned as a Newtonian fluid. In the current study, the physical properties of blood were assumed to have a viscosity of 3.3×10^{-3} Pa·s and a density of 1060 kg/m^3. The inlet flow rate was 3 l/min. It is difficult to model on a computer the hollow fiber bundle with a complicated structure such as a filter. The hollow fiber bundle part was calculated as a porous medium. The calculation conditions and boundary conditions are shown in Table 1.[1,11,12]

In Vitro Experiment

Gas exchange performance was measured in an *in vitro* experiment and was evaluated using the single path method.

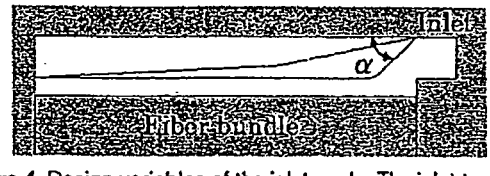

Figure 4. Design variables of the inlet angle. The inlet taper angle α is changed and selected 0 degrees, 10 degrees, 40 degrees.

Figure 5 shows the experimental circuit which consists of an integrated oxygenator with the CFP (n = 4), a reservoir, the TS410 flow meter (Transonic Systems Inc.), and a BF41 water bath (Yamato Scientific CO., Tokyo, Japan). The index artificial lungs used αCUBE 6000 (Dainippon Ink & Chemicals Co.). The oxygenator and the original model were connected to the roller blood pump Mera HAD101 (Senko Medical Instrument Mfg., Tokyo, Japan). The experiment used bovine blood with a hematocrit of 35%. The blood reservoir was placed in a temperature controlled bath at 37°C. Standard bovine venous blood (O_2 saturation, 65 ± 5%; hemoglobin, 12 g/dl; and partial pressure of carbon dioxide, 45 ± 5 mm Hg) was supplied to the inlet to evaluate O_2 and CO_2 transfer rates. Gas exchange performance was evaluated at blood flow rates of 1, 3, and 4 l/min, with blood and gas flow ratios set at 1. O_2 and CO_2 transfer rates were estimated from the blood gas analysis data. O_2 and CO_2 transfer rates were calculated using the following formulas:

$$O_2\text{content} = (Hb \times 1.34 \times SO_2)/100 + PO_2 \times 0.003$$

$$O_2 \text{ transfer rate} = (CaO_2 - CvO_2) \times Q$$

$$\text{Total } CO_2 = HCO_3^- + 0.03 \times PCO_2$$

$$CO_2 \text{ transfer rate} = 22.3 \times (tCO_2v - tCO_2a)$$

where Hb is the hemoglobin, PO_2 is the oxygen partial pressure, CaO_2 is the arterial oxygen content, CvO_2 is the venous oxygen content, Q is the blood flow rate, HCO_3^- is the plasma bicarbonate ion concentration, PCO_2 is the CO_2 partial pressure, tCO_2v is the venous total CO_2, and tCO_2a is the arterial total CO_2. Blood gas samples were analyzed using the gas analyzer Ciba Corning 248 (Bayer Medical Inc., Tokyo, Japan). Values are expressed as mean ± SD.

Results

The relationship between flow rate and pressure head in the CFP at different motor speeds is illustrated in Figure 6. The maximum flow rate of the CFP was 5.38 l/min at 3000 rpm when the pump head was 142 mm Hg.

Computational fluid dynamics (CFD) analysis results are shown in Figure 7, and Table 2 shows a comparison of the uniformity of the blood flow at the hollow fiber membrane part. The standard deviation of the blood flow of the original design at the hollow fiber membrane part was 6.99e-5. The standard deviation of the blood flow for design 1 was 7.80e-6; for design 2, 1.17e-5; and for design 3, 3.42e-5. Compared to the original design as the standard, the uniformity of blood velocity was improved by 88.8% in design 1, by 83.3% in design 2, and by 51.1% in design 3.

The effect of the uniformity of the blood velocity at the hollow fiber membrane part on oxygenator performance was evaluated by gas exchange performance in an *in vitro* experiment. The O_2 and CO_2 transfer rates are shown in Figure 8 and Figure 9. The O_2 and the CO_2 gas transfer performance of the original design were 211 ml/min and 116 ml/min (V/Q = 1), respectively, at a blood flow rate of 4 l/min. With design 1, the O_2 and the CO_2 gas transfer rates were 255 ml/min and 157 ml/min, respectively. The O_2 and CO_2 transfer rates with designs 1, 2, and 3 were higher than in the original design. Overall, when the blood flow rate was 4 l/min, O_2 transfer rates were increased by 20%, and CO_2 transfer rates were increased by 35% in design 1 as compared with the original oxygenator.

At the high flow rate, designs 1, 2, and 3 achieved a higher gas exchange performance than the original oxygenator using a 3/8-inch port. However, no differences in gas exchange performance were found between designs at the low flow rate. The average outlet PO2 of the original design was 531 ± 16 mm Hg at a blood flow rate of 1 l/min. The average outlet PO2 for design 1 was 541 ± 16mmHg; for design 2, 555 ± 19 mm Hg; and for design 3, 555 ± 13mmHg at the same flow rate.

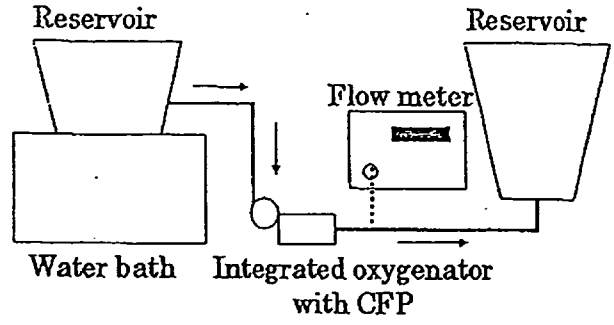

Figure 5. The measurement circuit of gas exchange performance. Gas exchange performance was evaluated using the single path method. The experiment used bovine blood maintained at a temperature of 37°C.

Discussion

The performance requirements of an artificial implantable lung include having a low resistance, achieving adequate gas transfer performance, being nonthrombogenic, and having a

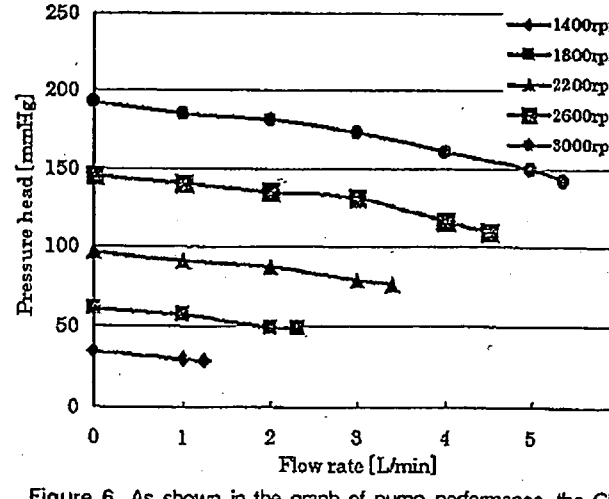

Figure 6. As shown in the graph of pump performance, the CFP generated 5.38 l/min at 3000 rpm when the pump head was 142 mm Hg.

Table 1. Analysis and Boundary Conditions

Porosity of the hollow fiber membrane	0.6
Blood contact surface condition	Nonslip
Outlet flow condition	Free from pressure
Inlet flow rate	3 l/min
Gravitation force	From outlet to inlet
Fluid type	Newtonian
Viscosity of blood	0.0033 Pa-s
Density of blood	1060 kg/m 3

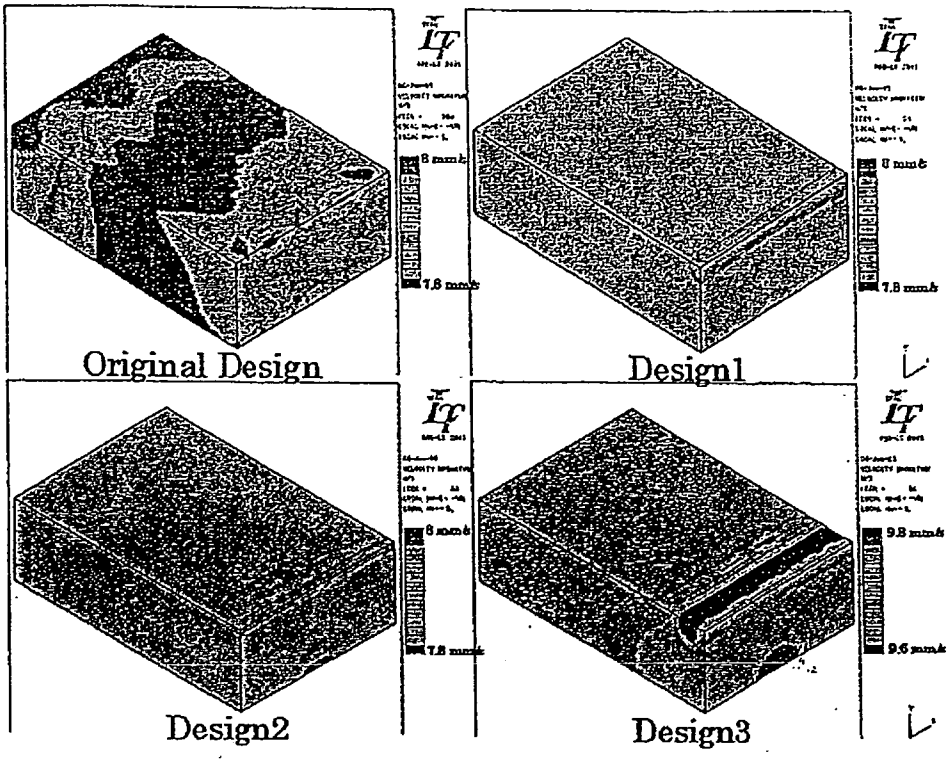

Figure 7. Results of CFD analysis. Shown is the blood velocity at the hollow fiber membrane part.

compact size. Much research has been conducted to improve these performance problems in order to achieve clinical applicability of the artificial implantable lung. Because an integrated oxygenator uses a blood pump, oxygenator resistance that might cause cardiac failure is of no concern. We evaluated the effects of various changes on integrated oxygenator performance by using a combination of CFD analysis and *in vitro* experiments.

Overall, the standard deviation of the blood flow at the hollow fiber membrane part was low with the improved oxygenator models; design 1 had the lowest standard deviation, followed by design 2 and then design 3. One can surmise that the membrane surface area would be used effectively, because the low standard deviation value indicates uniform flow at the hollow fiber membrane part. O_2 and CO_2 transfer rates indicated high gas exchange performance, with design 1 having the highest performance, followed by design 2 and then design 3. From these results, it can be deduced that uniform blood flow in the hollow fiber membrane part influences gas exchange performance. Thus, uniform blood flow can be used as a design parameter for the oxygenator. We compared the gas transfer relationship between the port inflow oxygenator and the wide inflow oxygenator. The blood was fully saturated with any inlet design, because the bundle is overdesigned for a low flow rate. Therefore, at low flow, there is very little difference in the gas exchange performance between the port inflow and the wide inflow. However, the difference between the performances of the oxygenators increased at a high flow rate. When the oxygenator with the port inflow was used, a high flow rate caused channeling and decreased the efficiency of the hollow fiber membrane. Therefore, gas exchange performance was reduced. However, use of the wide inflow oxygenator avoided channeling because the CFP produced a wide uniform flow to the oxygenator. Therefore, the oxygenator used the membrane surface area effectively to achieve a high gas exchange performance. Compared with design 1, design 3 had nonuniform flow and low gas exchange performance. The space between the inlet housing and the hollow fiber membrane was small in design 3. Therefore, channeling was

Table 2. Comparison of Results

	Standard Deviation	Improvement Rate (%)
Original design	6.99e-5	—
Design 1	7.80e-6	88.8
Design 2	1.17e-5	83.3
Design 3	3.42e-5	51.1

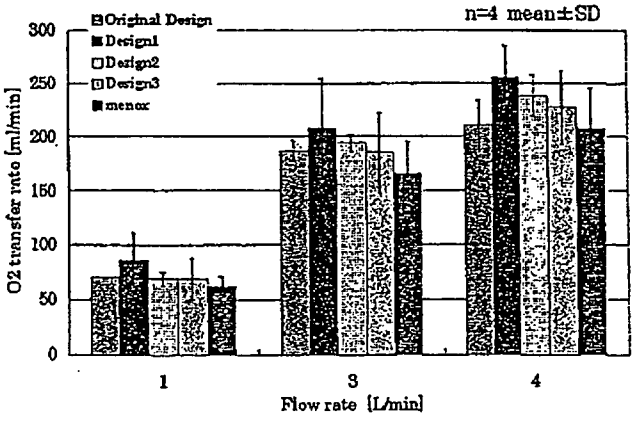

Figure 8. Relationship between O_2 transfer rate and flow rate. O_2 transfer rate of the design 1 was 255 ml/min (V/Q = 1) at a blood flow rate 4 l/min.

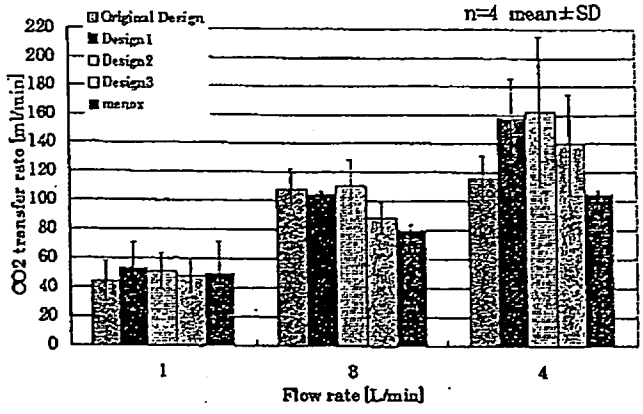

Figure 9. Relationship between CO_2 transfer rate and flow rate. CO_2 transfer rate of the design 1 was 157 ml/min (V/Q = 1) at a blood flow rate 4 l/min.

caused in the hollow fiber membrane part, and gas exchange performance was reduced, because the membrane surface area could not be used effectively. In design 1, kinetic energy was effectively converted to pressure energy, because there is a large space between the inlet housing and the hollow fiber membrane, and the membrane surface area could be used effectively. However, design 1 needed a big priming volume because of the large space. We are planning further studies of integrated oxygenator size, thrombogenicity in the oxygenator, and gas exchange performance.

Conclusion

The result of our experiments suggests that a CFP, which produces a wide uniform flow to the oxygenator, increases the efficiency of the hollow fiber membrane part. We think that this device can be used as an implantable pump oxygenator.

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Clinical and Experimental Pharmacology and Physiology (2006) 33, 381–387

EFFECTS OF ORAL BERAPROST SODIUM, A PROSTAGLANDIN I_2 ANALOGUE, ON ENDOTHELIUM DEPENDENT VASODILATATION IN THE FOREARM OF PATIENTS WITH CORONARY ARTERY DISEASE

Shuzo Ohata,* Yutaka Ishibashi,* Toshio Shimada,* Nobuyuki Takahashi,* Takashi Sugamori,* Takeshi Sakane,* Yoshifumi Hirano,* Nobuyuki Oyake,* Yo Murakami* and Tetsuya Higami†

**Division of Cardiovascular Medicine, Department of Internal Medicine, Shimane University Faculty of Medicine, Izumo City, Shimane, Japan and †Division of Cardiovascular Medicine, Department of Cardiovascular Surgery, Shimane University Faculty of Medicine, Izumo City, Shimane, Japan*

SUMMARY

1. Previous clinical studies with prostaglandin I_2 (PGI_2) analogue beraprost sodium suggested the potential effects on protection of cardiovascular events in patients with peripheral artery disease. Although the mechanism is not well known, experimental studies have shown protective effects of endothelial cells. This study was designed to examine the effects of beraprost sodium on vascular endothelial function in the forearm of patients with coronary artery disease.

2. Beraprost sodium (120 μg/day) was orally administered to 14 coronary artery disease patients for 4 weeks and then stopped for 4 weeks. Eleven control patients did not receive beraprost sodium treatment. Reactive hyperemia was induced in the forearm, endothelium-dependent vasodilatation was assessed by plethysmography, and urinary 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) was measured at baseline, 4 weeks and 8 weeks.

3. Both groups had similar reactive hyperemic responses at baseline. In the control group, reactive hyperemic response and urinary 8-iso-$PGF_{2\alpha}$ remained unchanged for 8 weeks. In the beraprost group, maximum forearm blood flow increased significantly ($P = 0.01$) after 4 weeks of treatment and returned to baseline at 8 weeks. Duration of hyperemia increased significantly ($P = 0.003$) after 4 weeks, and remained greater than baseline at 8 weeks ($P = 0.02$). Urinary 8-iso-$PGF_{2\alpha}$ decreased significantly ($P = 0.03$) after 4 weeks, and tended to be lower at 8 weeks ($P = 0.07$). Changes in reactive hyperemia correlated weakly but significantly with changes in 8-iso-$PGF_{2\alpha}$ ($P < 0.001$).

4. Beraprost sodium decreased oxidative stress and improved forearm endothelium-dependent vasodilatation in coronary artery disease patients. The favorable effects on vascular endothelium could potentially lead to a decrease in vascular events.

Key words: 8-iso-prostaglandin $F_{2\alpha}$, beraprost sodium, prostaglandin I_2, reactive hyperemia.

INTRODUCTION

Prostaglandin I_2 (PGI_2), which is synthesised in vascular endothelial and smooth muscle cells after appropriate stimulation by specific agents, shows antiplatelet action[1] and vasodilating action.[2] In addition, PGI_2 acts in concert with nitric oxide, ectonucleotidase and other endothelial molecules to maintain vascular homeostasis and vasoprotection.[3] Beraprost sodium is a stable and orally active PGI_2 analogue and it has antiplatelet and vasodilating properties. Beraprost sodium has been widely used for treatment of pulmonary hypertension and atherosclerotic peripheral arterial disease. The treatment effects with beraprost sodium have been well known in pulmonary hypertension.[4–6] In contrast, there are conflicting results showing that beraprost sodium as an effective[7] or ineffective[8] treatment to improve symptoms of intermittent claudication in patients with peripheral arterial disease. However, these previous studies suggested the potential benefit in cardiovascular events. If beraprost sodium has a protective effect on cardiovascular events, it may improve vascular endothelial function as one of the mechanisms. The favourable effects of beraprost sodium on vascular endothelial function have been reported in experimental *in vivo* studies.[9,10] However, human study regarding the effects of beraprost sodium on vascular endothelial function has not been fully documented.

The present study investigated the ability of beraprost sodium to improve endothelium-dependent vasodilatation in the forearm vessels of patients with endothelial dysfunction. Furthermore, the present study was also designed to examine the effects of discontinuation of treatment with beraprost sodium, because we have experienced some cases that show improvement of symptoms in patients with peripheral artery disease after cessation of treatment with beraprost sodium.

METHODS

Study population and design

The study was performed prospectively in 30 patients with coronary artery disease. Patients were randomly assigned to either a beraprost group, treated with beraprost sodium, or a control group, treated without beraprost sodium. Beraprost sodium (120 μg/day) was orally administered to 15 patients for 4 weeks, followed by 4 weeks without beraprost sodium. The other 14 age- and gender-matched patients were followed but not treated with beraprost sodium. All other medications were continued throughout the course of the

Correspondence: Dr Yutaka Ishibashi, Division of Cardiovascular Medicine, Department of Internal Medicine, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo City, Shimane 693-8501, Japan.
Email: yuyu@med.shimane-u.ac.jp

Received 3 December 2005; revision 5 September 2005; accepted 4 December 2005.

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study in all the patients and all drugs including beraprost sodium were stopped 12 h before the study. Current smokers and patients with a history of smoking within the past 2 years were excluded from the study. This study was approved by the Human Subjects Research Committee of Shimane University Hospital. Written informed consent was obtained from all participants.

Measurements of forearm blood flow

Forearm blood flow (FBF, mL/min per 100 mL forearm tissue volume) was measured using mercury-filled silicone strain-gauge plethysmography as previously described elsewhere.[11,12] Briefly, a strain-gauge was placed in the widest part of the left forearm and the arm was slightly elevated above the level of the right atrium. The strain-gauge was connected to a Hokanson EC-5R Plethysmograph (Hokanson, WA, USA) that was calibrated to measure percent changes in volume, and this was connected in turn to a chart recorder to record the flow measurements. For each measurement, a cuff placed around the upper arm was inflated to 40 mmHg with a rapid cuff inflator (E-10, Hokanson, WA, USA) to occlude venous outflow from the extremity. A wrist cuff was inflated to suprasystolic pressure 1 min before each measurement to exclude the hand circulation. Flow measurements were recorded for 5 s every 15 s and four readings were obtained for each mean value.

Reactive hyperemia and blood sampling

All participants were instructed to abstain from eating food and drinking caffeinated beverages for at least 12 h before the study. The study was performed in the supine position in a room air-conditioned to a temperature of 25–26°C. After measurement of resting FBF, the effect of reactive hyperemia was measured. To induce reactive hyperemia, FBF was occluded by inflating the cuff on the left upper arm to 20–30 mmHg above the systolic blood pressure for 5 min. After the ischaemic cuff occlusion was released, FBF was measured for 5 min. The same procedure was repeated after an interval of 15 min. Forearm blood flow values were obtained by averaging the two measurements. Three parameters were used to assess the intensity of reactive hyperemia: maximum FBF; minimum forearm vascular resistance (FVR) calculated from mean blood pressure and FBF; and duration of reactive hyperemia defined as the interval (seconds) between the release of occlusion and the return to +5% of resting FBF.[13] Blood and urine samples were taken before the study. Serum analysis was performed for chemical factors including total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, glucose, haemoglobin A1c, vitamins C (ascorbic acid) and E, fibrinogen, thrombomodulin (TM), von Willebrand factor (VWF), highly sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6). The urinary concentration of 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) was also measured. Blood pressure was measured with a cuff sphygmomanometer placed on the contralateral arm at rest and every 1 min after release of cuff occlusion. These measurements were repeated at 4 and 8 weeks after enrolment in this study in the same manner.

Calculation of forearm blood flow

Forearm blood flow was calculated by two independent observers with no knowledge of the subjects' profiles, including the drugs used. Intra-observer and interobserver coefficients of variation were 2.1 ± 2.6% and 4.2 ± 3.6%, respectively, in resting FBF, 5.7 ± 4.9% and 7.2 ± 5.6% in maximum FBF, 6.5 ± 4.9% and 8.6 ± 5.9% in minimum FVR and 1.3 ± 3.1% and 2.6 ± 3.6% in duration of reactive hyperemia. In the preliminary study, the mean values in age- and gender-matched apparently healthy subjects (30 male and 18 female) were 2.95 ± 1.02 mL/min per dL in resting FBF, 31.15 ± 9.07 mL/min per dL in maximum FBF, 3.1 ± 1.1 mmHg/mL per min per dL in minimum FVR and 131 ± 27 s in duration of reactive hyperemia.

Laboratory measurements

Fasting blood samples were obtained at baseline and at the end of each 4-week period. Serum and EDTA plasma samples were stored at −80°C and analysed at the end of the study. Total cholesterol and LDL cholesterol were measured by enzymatic procedures. High density lipoprotein cholesterol was quantified after precipitation with phosphotungstic acid magnesium chloride. Frozen serum or plasma was used to measure ascorbic acid by high performance liquid chromatography, TM and VWF by enzyme immunoassay, hs-CRP by latex immunonephelometry and IL-6 by chemiluminescence enzyme immunoassay. Urine for measurement of 8-iso-$PGF_{2\alpha}$ was sampled in tubes containing indomethacin and stored at −80°C until the end of the study. Measurement of 8-iso-$PGF_{2\alpha}$ was performed by enzyme immunoassay (Assay Designs, MI, USA). The mean values in age- and gender-matched apparently healthy subjects ($n = 30$) in our laboratory were 7.5 ± 2.4 mg/dL in vitamin C, 1.5 ± 0.2 mg/dL in vitamin E, 280 ± 100 mg/dL in fibrinogen, 3.2 ± 1.5 FU/mL in TM, 128 ± 66% in VWF, 10 ± 6 × 100 ng/mL in hs-CRP, 1.5 ± 0.5 pg/mL in IL-6 and 142 ± 72 pg/mL in 8-iso-$PGF_{2\alpha}$.

Statistical analysis

At the follow-up for 8 weeks, four patients had dropped out because of infection (1 patient), brain attack (1 patient) and lumbago (1 patient) in the control group and diarrhea (1 patient) in the beraprost group. Statistical analysis was consequently performed for 11 patients in the control group and 14 patients in the beraprost group. Data are expressed as mean±SD unless otherwise indicated. A value of $P < 0.05$ was considered statistically significant. Intergroup differences were analysed with the chi-square test or unpaired *t*-test for baseline characteristics, except for BNP, hs-CRP, IL-6, VWF and 8-iso-$PGF_{2\alpha}$ levels. Either the Mann–Whitney *U*-test or Kruskall-Wallis analysis of variance (ANOVA) followed by Scheffe's post hoc test was used to compare the non-parametric variables BNP, hs-CRP, IL-6, VWF and 8-iso-$PGF_{2\alpha}$. Comparisons of time-course curves of percent changes in FBF during reactive hyperemia were analysed by two-way (group and study point) ANOVA for repeated measures followed by the Bonferroni correction for multiple-paired comparisons. Maximum FBF, minimum FVR and duration of reactive hyperemia were compared with two-way (group and study point) ANOVA followed by the Scheffe's post hoc test.

RESULTS

Baseline characteristics

The baseline clinical characteristics of the beraprost and control groups are shown in Table 1. There were no significant differences between the two groups in age, body mass index, blood pressure, heart rate, lipid data or haemoglobin A_{1c}. Coronary angiographic findings and left ventricular function were comparable, as were the drugs being administered, listed in Tables 2 and 3.

Table 1 The baseline characteristics of the study patients

	Control	Beraprost
n	11	14
Age (years)	72 ± 8	69 ± 6
Sex (M/F)	8/3	10/4
BMI (kg/m^2)	23 ± 3	24 ± 3
Mean BP (mmHg)	83 ± 13	86 ± 9
HR (beats/min)	65 ± 13	59 ± 11
T-cho (mg/dL)	173 ± 31	170 ± 27
LDL-cho (mg/dL)	99 ± 27	104 ± 20
HDL-cho (mg/dL)	39 ± 9	42 ± 12
HbA1c (%)	5.8 ± 0.9	5.4 ± 0.5

Data are mean±SD. BMI, body mass index; BP, blood pressure; HR, heart rate; T-cho, total cholesterol; LDL-cho, low-density lipoprotein cholesterol; HDL-cho, high-density lipoprotein cholesterol.

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Haemodynamics before and after administration of beraprost sodium

Haemodynamics during reactive hyperemia are shown in Table 4. At baseline, blood pressure and heart rate at rest were similar between the beraprost and control groups. Forearm blood flow at rest tended to be higher in the beraprost group than in the control group (3.60 ± 1.31 and 2.98 ± 0.46 mL/min per dL, respectively), but the difference was not statistically significant. During reactive hyperemia, mean blood pressure slightly but significantly decreased immediately after the occlusive cuff was released in both the beraprost group and the control group (86 ± 9 to 84 ± 7 mmHg and 83 ± 13 to 81 ± 10 mmHg, respectively; both $P < 0.05$). Heart rate tended to increase after release of the occlusive cuff, but the difference was not significant (data not shown). Maximum FBF were 22.97 ± 6.63 mL/min per dL in the beraprost group and 22.45 ± 3.03 mL/min per dL in the control group and there was no difference between the two groups.

Oral administration of beraprost sodium did not change blood pressure and heart rate, but significantly increased resting FBF to 4.18 ± 1.43 mL/min per dL ($P = 0.03$) and maximum FBF to 28.27 ± 8.89 mL/min per dL, $P = 0.01$) and returned to baseline 4 weeks after stopping beraprost sodium (22.58 ± 9.09 mL/min per dL). There were no changes in the haemodynamics of the control group. Percent changes in FBF from resting level during reactive hyperemia in the 105-s period after release of the cuff occlusion were significantly greater after 4 weeks of beraprost sodium treatment than at baseline in the beraprost group (Fig. 1). The duration of reactive hyperemia was unchanged over the 8-week course of the study in the control group. In the beraprost group, however, the duration of reactive hyperemia increased significantly from 77 ± 27 to 105 ± 46 s after 4 weeks of treatment with beraprost sodium ($P = 0.003$) and remained longer at 4 weeks after the beraprost sodium treatment was stopped (86 ± 28 s, $P = 0.02$) (Fig. 2).

Table 2 Clinical characteristics in study patients

	Control	Beraprost
Prior myocardial infarction (*n*)	8	9
Prior bypass graft surgery (*n*)	0	1
Prior angioplasty (*n*)	7	7
LVEF (%)	53 ± 9	59 ± 10
BNP (pg/mL)	95.6 ± 134.8	70.2 ± 112.4
NYHA (*n*)		
I	4	6
II	4	7
III	2	1
Coronary angiography (*n*)		
1-Vessel disease	4	11
2-Vessel disease	4	3
3-Vessel disease	2	0

Data are mean±SD. BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association Classification.

Table 3 Background therapies in study patients

	Control (%)	Beraprost (%)
ACE-I	7 (64)	9 (64)
ARB	4 (36)	4 (29)
β-blocker	6 (55)	8 (57)
Ca antagonist	9 (82)	11 (78)
Diuretics	2 (18)	2 (14)
Digitalis	1 (9)	1 (7)
Nitrate	10 (91)	12 (85)
Aspirin	11 (100)	13 (92)
Statin	3 (27)	4 (28)

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Chemical factors before and after administration of beraprost sodium

Table 5 shows changes in chemical factors over the 8-week period for the two groups. At baseline, there were no significant differences in chemical factors between the beraprost group and the control group. In the control group, chemical factors remained unchanged through the follow-up, but in the beraprost group, beraprost sodium treatment significantly reduced urinary 8-iso-$PGF_{2\alpha}$ from 270 ± 221 pg/mL at baseline to 140 ± 53 pg/mL after 4 weeks of treatment ($P = 0.03$) and the value 4 weeks after beraprost sodium treatment was stopped tended to be lower than baseline (189 ± 116 pg/mL, $P = 0.07$). von Willebrand factor, hs-CRP and IL-6 did not change

Table 4 Changes in haemodynamics at rest and during reactive hyperemia

	Rest					Reactive hyperemia		
	HR (b.p.m.)	SBP (mmHg)	DBP (mmHg)	FBF (mL/min per dL)	FVR (mmHg/mL per min per dL)	Max. FBF (mL/min per dL)	Min. FVR (mmHg/mL per min per dL)	Duration (s)
Baseline								
Beraprost	61 ± 11	125 ± 22	71 ± 11	3.60 ± 1.31	28.5 ± 10.9	22.97 ± 6.63	4.3 ± 1.4	77 ± 27
Control	68 ± 13	125 ± 19	69 ± 10	2.98 ± 0.46	28.9 ± 7.5	22.45 ± 3.03	4.8 ± 3.9	75 ± 11
4 weeks								
Beraprost	66 ± 10	125 ± 23	75 ± 14	4.18 ± 1.43*†	26.9 ± 17.6	28.27 ± 8.89*†	3.7 ± 1.0	105 ± 46*†
Control	66 ± 13	125 ± 18	73 ± 14	2.97 ± 0.65	28.9 ± 8.1	23.97 ± 4.46	4.6 ± 0.7	75 ± 21
8 weeks								
Beraprost	59 ± 10	125 ± 21	71 ± 11	3.99 ± 1.21	28.7 ± 6.8	22.58 ± 9.09	4.9 ± 2.5	86 ± 28*†
Control	59 ± 14	123 ± 16	70 ± 13	2.89 ± 0.83	29.8 ± 7.9	25.48 ± 5.10	4.2 ± 0.5	76 ± 12

8 weeks in the beraprost group indicates 4 weeks after stopping beraprost sodium. Data are mean±SD. DBP, diastolic blood pressure; FBF, forearm blood flow; FVR, forearm vascular resistance; HR, heart rate; SBP, systolic blood pressure.

*$P < 0.05$ versus corresponding value at baseline. †$P < 0.05$ versus corresponding control value.

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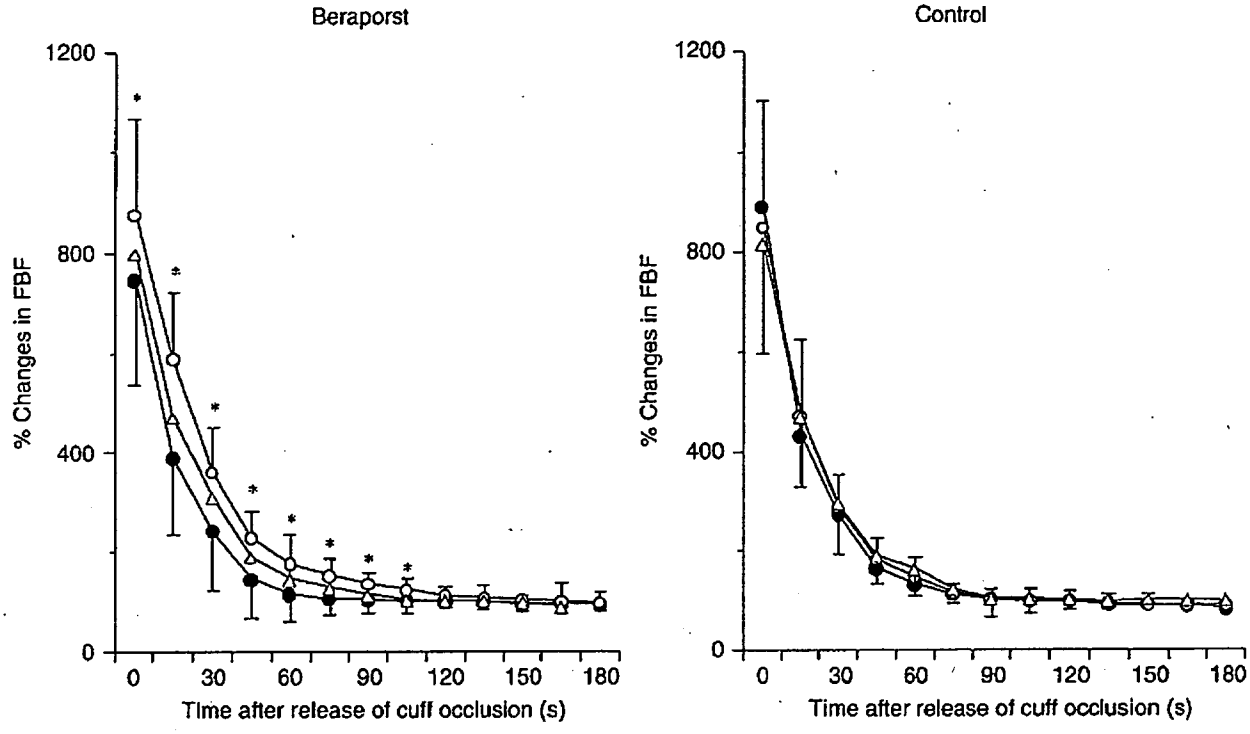

Fig. 1 Left panel: Percent changes in forearm blood flow from rest at baseline, after 4 weeks of treatment with beraprost sodium (4 weeks) and 4 weeks after treatment with beraprost sodium was stopped (8 weeks). Right panel: Percent changes in forearm blood flow from rest at baseline, after 4 weeks and 8 weeks without beraprost sodium treatment.

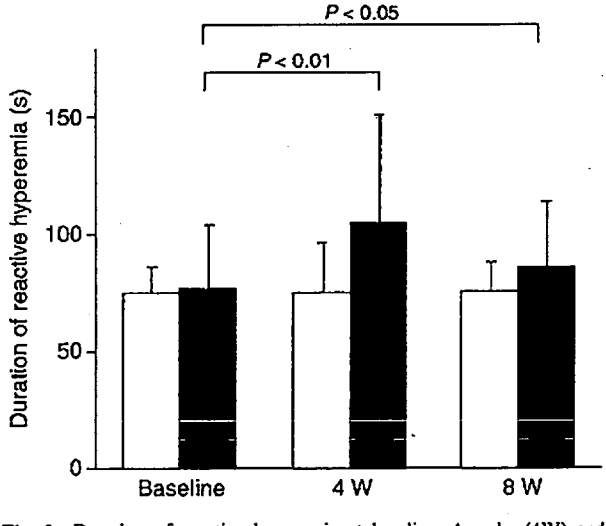

Fig. 2 Duration of reactive hyperemia at baseline, 4 weeks (4W) and 8 weeks (8W) in the control and beraprost groups. Data are expressed as mean±SD.

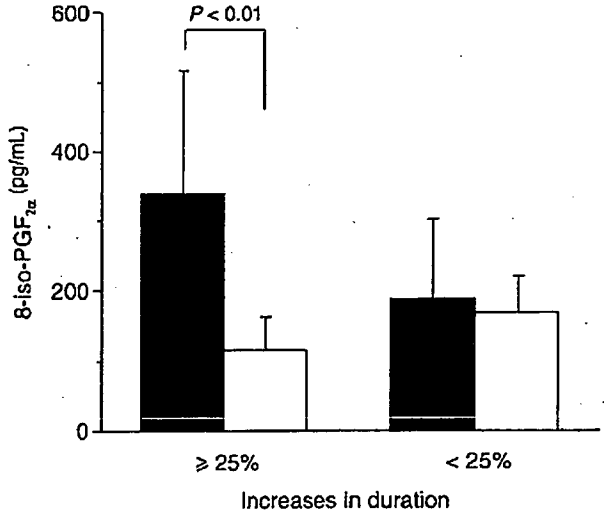

Fig. 3 Urinary concentration of 8-iso-$PGF_{2\alpha}$ at baseline and 4 weeks (4W) in patients in the beraprost group. Patients were classified into two patient groups based on the percent of increase, ≥ 25% and < 25%, in the duration of reactive hyperemia from baseline after 4 weeks treatment with beraprost sodium. Data are expressed as mean±SD.

significantly after 4 weeks of treatment in the beraprost group, but decreased significantly 4 weeks after treatment was stopped.

Relationship between duration of reactive hyperemia and 8-iso-$PGF_{2\alpha}$

The percent changes in duration of reactive hyperemia weakly but significantly correlated with the percent changes in 8-iso-$PGF_{2\alpha}$ ($r = 0.34$, $P < 0.001$). 8-iso-$PGF_{2\alpha}$ significantly decreased from 340 ± 275 to 117 ± 46 pg/mL ($P = 0.02$) after 4 weeks in those patients showing an increase in duration of reactive hyperemia ≥ 25% of baseline after beraprost sodium treatment, while it did not change in those patients without an increase in duration of hyperemia (from 190 ± 112 to 168 ± 52 pg/mL, $P = 0.69$; Fig. 3).

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Table 5 Changes in venous and urinary concentrations of chemical factors

	Control			Beraprost		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Vitamin C (mg/dL)	7.2 ± 4.6	6.3 ± 2.6	6.8 ± 1.5	6.4 ± 2.7	6.4 ± 3.6	5.0 ± 1.5
Vitamin E (mg/dL)	1.00 ± 0.25	1.12 ± 0.38	0.86 ± 0.31	1.13 ± 0.25	1.12 ± 0.31	0.97 ± 0.28
Fibrinogen (mg/dL)	338 ± 101	282 ± 57	269 ± 66	298 ± 115	272 ± 45	200 ± 23
TM (FU/mL)	3.3 ± 1.2	3.4 ± 1.1	3.2 ± 1.5	3.5 ± 1.6	3.5 ± 1.5	3.9 ± 1.9
VWF (%)	198 ± 89	182 ± 69	179 ± 66	180 ± 48	151 ± 41	125 ± 39*†
hs-CRP (× 100 ng/mL)	30 ± 33	25 ± 33	28 ± 38	29 ± 31	19 ± 17	13 ± 15*†
IL-6 (pg/mL)	3.1 ± 1.9	3.7 ± 2.7	3.4 ± 1.6	2.6 ± 1.5	2.8 ± 0.8	1.8 ± 0.7*†
8-iso-$PGF_{2\alpha}$ (pg/mL)	238 ± 183	220 ± 257	218 ± 86	270 ± 221	140 ± 53*†	189 ± 116*

8 weeks in the beraprost group indicates 4 weeks after stopping beraprost sodium. Data are mean±SD. hs-CRP, highly sensitive C-reactive protein; IL-6, interleukin 6, 8-iso-$PGF_{2\alpha}$; 8-iso-prostaglandin $F_{2\alpha}$; TM, thrombomodulin; VWF, von Willebrand factor.

*$P < 0.01$ versus corresponding value at baseline. †$P < 0.05$ versus corresponding control value.

DISCUSSION

The salient finding of this study is that oral administration of beraprost sodium, a long-acting and orally active stable analogue of PGI_2, resulted in an increase in reactive hyperemia as an index of endothelium-dependent vasodilatation in patients with coronary artery disease. In addition, urinary 8-iso-$PGF_{2\alpha}$, a marker of oxidative stress was reduced significantly by treatment with beraprost sodium. These findings suggest that the beneficial effects of beraprost sodium on the vascular endothelium in patients with coronary artery disease is associated with a reduction in oxidant stress. Furthermore, the forearm vasoreactivity enhanced by treatment with beraprost sodium was still observed even 4 weeks after the treatment was stopped.

Effects of beraprost sodium on vascular endothelial function

Numerous previous studies have demonstrated the beneficial effects of acute and chronic therapeutic interventions such as lipid-lowering,[14–16] angiotensin-converting enzyme inhibition,[17,18] physical activity, L-arginine,[19] and anti-oxidant therapy[20] on endothelial function in the forearm and have shown that some of these resulted in lowering the cardiovascular event rate. However, there have been only a few reports on the effect of beraprost sodium on the endothelium. Since Sakai *et al.*[10] first demonstrated the cytoprotective effect of beraprost sodium against chemical injury in cultured human vascular endothelial cells, experimental studies have reported the beneficial effects of this agent on impaired endothelial cells. Matsumoto *et al.*[9] showed that impairment of the vasodilator response of the abdominal aorta to acetylcholine was restored by treatment with beraprost sodium for 28 days in the diabetic rat. In a clinical setting, Nishimura *et al.*[21] measured TM and plasma tissue-type plasminogen activator before and after treatment of patients with diabetes by oral administration of beraprost sodium for 1 month and demonstrated its favourable effect on endothelial function. Recently, Tomiyama *et al.*[22] demonstrated that single administration of beraprost sodium increased reactive hyperemia in the forearm associated with a decrease in plasma TM level in patients with coronary artery disease, suggesting acute effects of beraprost sodium on vascular endothelial function. In the present study, despite beraprost sodium not being administered on the study day, vasoreactivity in the forearm was significantly increased by treatment for 4 weeks. These previous and present results indicate a beneficial effect of beraprost sodium on impaired endothelial function. The favourable effects might lead to a decrease in cardiovascular events, though the efficacy of treatment with beraprost sodium for symptoms in patients with peripheral arterial disease has been conflicting among previous reports.[7,8] Long-term studies should be performed in the future to confirm the beneficial effects of beraprost sodium on the endothelial function and the prevention of cardiovascular events.

Mechanisms of beneficial effects of beraprost sodium on the endothelium

It is well known that PGI_2 is an unstable eicosanoid secreted by the vascular endothelial cells that produces strong vasodilatation[2,23] and suppresses platelet aggregation,[1,24,25] thus supporting blood circulation. Beraprost sodium has been developed as a long-acting and orally active stable analogue to PGI_2[26] that mimics the biological properties of PGI_2, such as activation of adenylate cyclase and elevation of intracellular cAMP levels, through activation of the PGI2 receptor.[27,28] Elevated cAMP activates protein kinase A, which inhibits cytokines, the transmembrane receptor tissue factor, E-selectin and vascular cell adhesion molecule-1 in human monocytic and endothelial cells, leading to a cytoprotective effect on the endothelium.[29,30] Previous studies have furthermore demonstrated many favourable effects on endothelial cells, such as an anti-inflammatory effect,[31] inhibition of superoxide,[32–34] and up-regulation of hepatocyte growth factor[9] and TM expression from the endothelial cells.[28]

In the present study, beraprost sodium augmented the reactivity of the forearm vessels in patients with coronary artery disease and the degree of augmentation of hyperemia correlated with the reduction of urinary 8-iso-$PGF_{2\alpha}$, suggesting that this drug has an antioxidative effect in patients with high oxidative stress, leading to improvement of impaired endothelial function. This possibility is supported by previous experimental studies demonstrating inhibition of superoxide production from human[33] and rat[34] neutrophils. As another mechanism, the increased resting FBF after treatment with beraprost sodium might also contribute to the enhanced reactivity of the forearm vessels, since endothelial cell function might be enhanced by elevated shear stress in a flow-dependent manner. However, it is difficult to ascertain a precise mechanism for this phenomenon from our results. It is interesting that although IL-6 and

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hs-CRP were not affected by beraprost sodium after 4 weeks, they were significantly lower than at baseline 4 weeks after the treatment was stopped. This was accompanied by a decrease in VWF after 8 weeks, suggesting a reduction in endothelial cell damage. The duration of reactive hyperemia was also still greater than at baseline 4 weeks after the treatment was stopped. These findings might suggest that beraprost sodium increases the vasoreactivity via the antioxidative effects in the early stage of treatment and that the effects might link to suppression of inflammation and cytokine production, leading to an increase in vasoreactivity even after treatment is stopped. However, our results do not allow us to draw any conclusions as to whether the beneficial effects of beraprost sodium arise from a direct or indirect effect on the endothelial cells. Furthermore, it is difficult to explain the prolonged anti-inflammatory effects after the cessation of treatment. Niwano *et al.*[35] recently reported that beraprost sodium increased the steady-state levels of endothelial nitric oxide synthase (eNOS) mRNA and protein in cultured human aortic endothelial cells, indicating NO-mediated protective effects on the vascular endothelium, whereas PGI_2 had little effect on eNOS gene expression. Their study might suggest the possibility that beraprost sodium directly evoke eNOS gene expression in the endothelial cells, leading to prolonged anti-inflammatory effects via increased NO production. However, PGI_2 receptor has not been identified on the endothelial cells. To clarify this issue, additional studies will be needed in future.

Study limitations

The present study has several limitations. First, there is methodological limitations in measurement of blood flow by plethysmography. Although blood flow values obtained by plethysmography correlate with actual flow, they may under- or over-estimate the actual flow in some patients.[36] However, this limitation may be obviated by the fact that the present study focused on changes in blood flow in individual patients rather than absolute blood flow values. Second, is the effect of background therapies on endothelial function. In the present study, treatment with angiotensin converting enzyme inhibitor, angiotensin receptor blocker and statins, which have been reported to improve endothelial dysfunction,[17,37–39] were continued throughout the study. Although these agents were unchanged throughout the study, we cannot exclude the possibility that these drugs influenced the present results. Third, is a difference in severity of coronary artery disease between the two groups. The control group included two patients with 3-vessel disease, whereas the beraprost group did not. However, we did not find any effect on reactive hyperemia even in four patients with 1-vessel disease in the control group. Finally, the small number of subjects and the lack of placebo control limit the statistical power of the data and may perhaps mask differences between the two groups.

CONCLUSIONS

The present study demonstrated that beraprost sodium, a stable analogue of PGI_2, caused an augmentation of reactive hyperemia in the forearm of patients with coronary artery disease accompanied by a reduction in urinary 8-iso-$PGF_{2\alpha}$ levels. These findings indicate a cytoprotective effect on vascular endothelial cells for beraprost sodium. These phenomena might contribute to the protective effects of beraprost sodium on cardiovascular events, which have been suggested in previous studies.[7,8] Further studies are needed in a larger sample size and in a placebo control study to confirm our findings.

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● 症 例 ●

Cisplatin肝動注療法とTS-1経口投与が奏効した膵腺房細胞癌肝転移の1例

片岡 佳樹 仁尾 義則 矢野 誠司 小池 誠 橋本 幸直
板倉 正幸 板垣 友子 西 健 遠藤真一郎 樋上 哲哉*

(*Jpn J Cancer Chemother* 33(4): 525-528, *April*, 2006)

Pancreatic Acinar Cell Carcinoma Successfully Treated with Combination of Oral TS-1 and Intra-Arterial Cisplatin: Yoshiki Kataoka, Yoshinori Nio, Seiji Yano, Makoto Koike, Koji Hashimoto, Masayuki Itakura, Tomoko Itagaki, Takeshi Nishi, Shinichiro Endo and Tetsuya Higami (*Dept. of Cardiovascular and Digestive Surgery, Shimane University School of Medicine*)

Summary

Pancreatic acinar cell carcinomas are rare, and little is reported on their chemotherapy. We report a 49-year-old male patient with pancreatic acinar cell carcinoma and multiple liver metastases, which responded to oral TS-1 and hepatic arterial infusion of cisplatin. The patient underwent a partial hepatectomy, MCT abrasions and excision of the pancreatic tumor. Postoperative pathological studies revealed metastases of acinar cell carcinoma to the liver and lymph nodes; the primary lesion was undetermined. After surgery, the patient was treated with hepatic arterial infusion of cisplatin and oral TS-1. Metastatic tumors completely disappeared, and serum lipase decreased to normal levels. Abdominal CT one year after surgery revealed a pancreatic body tumor, which was surgically removed. Pathological studies showed primary pancreatic acinar cell carcinoma, while previous metastases remained under control. To summarize, TS-1 and cisplatin can be effective treatments for pancreatic acinar cell carcinomas. Key words: Acinar cell carcinoma, TS-1, Hepatic arterial infusion (*Received Sep. 5, 2005/ Accepted Nov. 9, 2005*)

要旨 膵腺房細胞癌はまれで，その化学療法に関する報告は少ない。今回，TS-1経口投与とcisplatin肝動注療法が奏効した膵腺房細胞癌肝転移の1例を経験した。症例は49歳，男性。糖尿病の経過中に膵体部腫瘤と多発性肝腫瘍を発見された。術前にTS-1を経口投与後，膵体部腫瘍摘出および肝外側区域切除とMCT焼灼術を行った。病理診断は腺房細胞癌で，膵体部腫瘍は転移リンパ節と診断され，原発巣の所在は不明であった。術後TS-1経口投与およびcisplatin肝動注を行い，肝転移は消失した。しかし約1年後の腹部CTで膵体部腫瘤を認め，再手術を行った。肝転移はコントロールされており膵腫瘍を摘出した。病理診断は原発性膵腺房細胞癌であった。一般に予後不良とされる膵腺房細胞癌に対してTS-1とcisplatinの併用療法が有効である可能性が示唆された。

はじめに

膵腺房細胞癌（acinar cell carcinoma: ACC）はまれで，その化学療法に関する報告は極めて少ない。今回，TS-1経口投与とcisplatin（CDDP）肝動注療法が奏効したACCの1例を経験したので報告する。

I. 症 例

患者: 49歳，男性。

主訴: 全身倦怠感。

既往歴: 20年前，十二指腸潰瘍穿孔で幽門側胃切除術。5年前よりアルコール依存症，糖尿病。

家族歴: 兄が膵癌で死亡。

現病歴: 2002年9月，上記主訴で近医受診。CA19-9の上昇と腹部超音波検査で3 cm大の膵体部腫瘤と4〜5 cm大の多発性肝腫瘤を認め当科紹介となった。

入院時現症: 身長155 cm，体重47 kg。貧血（−），黄疸（−）。右季肋部に腫大した肝を触知し，圧痛を認めた。

連絡先: 〒693-8501 出雲市塩冶町89-1 * 島根大学医学部・循環器・消化器総合外科
片岡 佳樹

0385-0684/06/¥500/論文/JCLS

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