よるものであり，CMV 感染や拒絶も危険因子とされる[5]．膵移植では腹腔内カンジダ症が圧倒的に多く，ドナー年齢，膵液の腸管排液，腹膜灌流歴などが危険因子とされる[4]．小腸移植では深在性真菌症の頻度が特に高く，ほとんどはカンジダ症である．腎移植では尿路の *Candida* colonization が感染源として重要である．

臓器移植患者における抗真菌薬投与の現状

臓器移植領域においても，抗真菌薬の予防あるいは先制攻撃的（preemptive）投与は，その効果・コスト・毒性などを考慮した上で選択的に行われなければならない．高い発生頻度と予後への影響から，カンジダ症の予防は肝・膵移植のみ，アスペルギルス症予防は肝・肺移植のみが適応となるという意見があるが[4]，これらの領域でも他の臓器でもハイリスク症例のみが対象とされるべきである．

肝移植のハイリスク症例におけるカンジダ症予防にはアゾール系薬剤が用いられる．選択的腸管内除菌の一部として用いられる非吸収性抗真菌薬と比べると colonization の減少はみられるが，侵襲性カンジダ症の予防効果については確証が得られていない[6, 7]．気道からの *Aspergillus* 検出は肝移植ではほぼ常に侵襲性病変の存在を意味し，この時点での抗真菌薬投与は“治療”とみなすべきである．Itraconazole（ITCZ）や低容量の amphotericin B（AMPH）のアスペルギルス感染予防効果は証明されておらず，欧米では脂質型 AMPH を予防的に用いる施設も多いが，コストと比較してその効果は充分に証明されていない．

肺移植でもアゾール系薬剤特に ITCZ が気管吻合に由来する気管気管支炎の治療や侵襲性感染の予防に用いられるが，AMPH 吸入では肺内濃度が上昇しやすく，高い効果が期待できるとされている[8]．ハイリスク症例のアスペルギルス感染予防には，気管吻合が癒合するまでの AMPH 吸入の後に ITCZ を 6 か月程度投与することが推奨されている[4]．他の臓器の移植における *Candida* 感染予防には fluconazole（FCZ）の使用が多いが，本邦では広いスペクトラムと低い MIC から miconazole (MCZ) も使用される．特殊な真菌として *Pneumocystis carinii* の予防には ST 合剤の効果が確立されている．

深在性真菌症治療の原則は，臓器移植患者においても他の免疫不全症例と変わらないが，可能な限り免疫抑制剤は減量すべきであり，異物や感染巣の外科的除去を平行して行うことが重要である．Micafungin（MCFG）の登場まで，高用量のアゾール系薬剤と AMPH が治療薬の中心であったが，腎を中心とした副作用が大きな障害であった．特にアゾール系薬剤では免疫抑制剤の代謝に与える影響にも留意すべきである．欧米では脂質型 AMPH も多用されているが，そのコストと比べ治療成績には限界がある．MCFG についてはその役割が期待されているが，移植領域での予防・先制攻撃的使用についてはまだ充分なデータがない．

今後のガイドラインに求められるもの

他の免疫低下症例と同様に，臓器移植患者では深在性真菌症の初期診断が遅れがちで，診断あるいは強く疑ってからでは，免疫不全因子や薬物相互作用・毒性の存在から治療が難しいことが少なくない．そのため，臓器を問わずに一律の抗真菌薬予防投与が行われる場合が依然少なくない．重症化を未然に防ぐ必要のあることはいうまでもないが，経験的に行われている予防あるいは先制攻撃的治療には明確なデータのないものも少なくなく，コストの面ばかりでなく耐性株の増加も着実に認められている．

各臓器別に，移植前因子，手術因子，異物留置因子，全身状態因子，移植臓器機能因子，免疫抑制因子からなる特異的な危険因子を定量化し，症例を階層化した上でハイリスク症例に対する予防あるいは先制攻撃的治療を行い，それぞれのリスク群におけるプロトコールの効果を判定すべきであるが，領域の性格上，施設間の症例の構成や数の差からも，充分な確証の得られている知見はきわめて限られている．ガイドラインには，本来確証に裏付けられた事項のみが記載されるべきであるが，欧米のものがそうであるように，少なくとも「多くの経験則と臨床的裏付けの恩恵が得られ，かつ具体的である」ことを目標に，情報を「信頼度」別に網羅し提供する役目を負っている．特に本邦で汎用されている血清学的診断法の位置づけについては，諸外国のデータの蓄積がなく，菌学的・画像的・臨床的診断指標との間の位置づけが示されていかなければならない．今回編まれたガイドラインは，これらの問題に“手を着けた”ところであり，多くの試案と検証を繰り返して，精力的に改訂されていくべきものであると考える．

おわりに

欧米の臓器移植領域においても，深在性真菌症を論じる際には，“常に疑い（high index of suspicion）”，“貪欲に培養検体を採る（aggressive acquisition of specimens for culture）”といった表現が用いられる[9]．抗菌薬使用のガイドラインがそうであるように，深在性真菌症において，各臓器別の移植領域の特性と多様性に対応し，危険と無駄のない臨床的治療開始あるいは予防基準（抗真菌薬によらないものも含まれる），状況に合わせた抗真菌薬の使用基準が示され，完全なテーラー・メード医療にたどり着くまでは，今後長い過程が必要になるものと思われる．今回の「ガイドライン」がその小さな第一歩となることを願って止まない．

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Invasive Mycosis in Solid Organ Transplantation

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Invasive mycosis in solid organ transplantation is mainly caused by *Candida* and *Aspergillus*, and its risk is higher in small bowel, liver, pancreas, and lung transplantation. Although limited analyses propose not a few risk factors for invasive mycosis in respective transplanted organs, the efficacy of prophylactic use of antifungal agents or preemptive treatments based on the information is not fully supported by prospective randomized controlled clinical data. The final guideline should be helpful for tailor-made evidence-based management based on the stratification of patients by pretransplant, surgical, immunosuppressive and organ specific characteristics. The process of repeated proposals and verification in a large number of patients is necessary.

この論文は，第47回日本医真菌学会総会の“シンポジウム 3：深在性真菌症における
ガイドラインをふまえた今日的臨床”において発表されたものです．

成人生体肝移植

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内容紹介

生体肝移植は，その開始から10数年しか経過していない若い医療である．脳死肝移植が積極的に行われていない本邦においては，生体肝移植が中心で現在までに2600例を超える症例を積み重ねている．生体肝移植の発展には，手術手技の向上・免疫抑制剤を含めた術後管理の改善によるところが大きい．また，当初小児症例が中心であったが，右葉グラフト（移植肝）に伴う術式やドナーの安全性が確立し，成人生体肝移植の増加へとつながった．成人症例では，肝右葉を用いた場合でも，過小グラフトという問題は残るが，術式の工夫などによりそれも緩和されつつある．今回，成人生体肝移植の現況と疾患別適応について概説する．

はじめに

1963年，米国のStarzl[1]が臨床において初めて脳死者からの肝移植を行ったが，当時は実験的医療と考えられていた．しかし，その後臓器保存液や免疫抑制剤の開発，手術手技の進歩などに伴って1980年代には一般的医療として普及し，米国では現在年間約5000人が肝移植を受けている．この肝移植の飛躍とともに待機患者が増加し，臓器の不足から待機中に死亡する患者が欧米において増え，深刻な臓器不足を解決するために生体肝移植が導入されるようになった．生体肝移植は，1988年ブラジルのRaiaら[2]によって初めて行われたがこれは成功に至らず，最初の成功例は1989年オーストラリアのStrongら[3]によって行われた生後6ヶ月の患児に対する日本人の親子間の移植であった．一方，日本においては1989年に島根医科大学で1例目が行われ，その後症例数は年々増え，日本肝移植研究会の報告によると2002年末までの集計では，累積総数2249例の肝移植を積み重ねている．この内23例のみが死体肝移植（脳死肝移植21，心停止肝移植2）であり[4]，欧米，他のアジア諸国とは大きく異なる点である．本邦においては，1998年に法の整備を受け脳死肝移植が開始されたが，現在までに24例を経験したに過ぎず(2004年4月現在)，生体肝移植に頼っているのが現状である．また，本年1月から保険適応基準が以下のように変更され，着実に一般医療として定着の方向にある．

〈変更後の保険適応基準〉

対象疾患は，先天性胆道閉鎖症，進行性肝内胆汁うっ滞症（原発性胆汁性肝硬変と原発性硬

—Key words—
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ドミノ肝移植

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化性胆管炎を含む），アラジール症候群，バッドキアリー症候群，先天性代謝性肝疾患（家族性アミロイドニューロパチーを含む．）多発嚢胞肝，カロリ病，肝硬変（非代償期）及び劇症肝炎（ウイルス性，自己免疫性，薬剤性，成因不明を含む）である．なお，肝硬変に肝細胞癌を合併している場合には，遠隔転移と血管浸襲を認めないもので，肝内に径5cm以下1個，3cm以下3個以内が存在する場合に限る．

I．ドナー側からみた生体肝移植

生体肝移植においてその主役はドナー（臓器提供者）にあると考えられる．臓器の提供は，本人の自発的意志が大前提であり，何ら代償を期待しない善意によって行われるべきことである．当科においては，3度にわたるインフォームドコンセントを行い，社会的圧力や強制がないことを確認し，さらに精神科医が面談することで自発的意思の再確認と術後のドナーの精神的フォローにあたっている．

成人症例においては，肝右葉をグラフトとすることが多く，ドナーに術前に腹部CT検査を行い切除予定の肝区域を計測し，得られる予測グラフト重量を計算している．そして，グラフト重量／レシピエント体重比（graft-to-recipient body weight ratio：GRWR）が1.0%以上を十分な安全域と見なしている[5]．ただし，右葉グラフトの場合，グラフト摘出後の残肝容積がドナーの安全性に重要であり，当科においては残肝容積が35%以上を安全域，30～35%を境界域，30%未満を危険域として，グラフトを選択している．

当院においては，レシピエントとの関係が3親等以内と見なしうる肉親および法的・社会的に認知された配偶者に限定している．

また，血液型については一致あるいは適合移植が望ましいと思われる．生体肝移植では，ドナーの選択に限りがありたびたび血液型不適合の提供希望者に直面する．このような場合，最近では，肝動脈内薬剤注入（プロスタグランディンE1，ステロイド）・門脈内薬剤注入（メシル酸ガベキセート）といった新しい治療[6]が行われ，以前よりは良い成績を上げている．当院においても，術前抗体価8000倍以上といったハイリスク症例を経験した．本症例にも同様の治療を加え，術後血液型不適合に起因する合併症を起こすことなく退院可能であった．しかし，血液型不適合症例においては通常以上の免疫抑制が必要となり，通常以上の感染のリスクがあり敗血症となる症例も少なくない．今後さらなる研究が必要である．

II．成人生体肝移植の現況

当初小児に対し行われた生体肝移植も1993年から成人に対して取り入れられ，以後，ドナーの安全性の確立に伴う術式の変更で成人症例が増え，1999年以降成人症例が小児症例を上回っている．

日本肝移植研究会の集計[4]によると2002年末までの18歳以上の成人症例の原疾患では，胆汁うっ滞性疾患が最多を占め，次いで腫瘍性疾患（そのほとんどが肝細胞癌），肝細胞性肝不全と続く．胆汁うっ滞性疾患は全体の32%で成人ではその半分以上が原発性胆汁性肝硬変である．肝細胞癌は全体の20%，肝細胞癌を合併しないC型肝硬変は8%，B型肝硬変は7%である．

移植後の累積生存率（小児症例を含む）は，1年生存率80.8%，3年生存率78.5%，5年生存率76.7%，10年生存率71.8%であった．

III．成人生体肝移植の疾患別適応と成績

1．原発性胆汁性肝硬変（PBC）／原発性硬化性胆管炎（PSC）

通常，Mayo Clinicの予後予測式や日本肝移植適応研究会モデルが肝移植の適応のタイミングに役立つことが多い．日本肝移植研究会の集計ではPBCの1年生存率が77.4%，3年生存率72.0%，5年生存率72.0%であり，PSCではそれぞれ79.3%，66.4%，66.4%であった．しかし，肝移植のタイミングが遅れ，胆汁うっ滞が進行した症例では生存率が著しく不良となる．その一因として胆汁うっ滞の進行とともに感染率が増え，感染症の存在下での免疫抑制剤の調整が難しいことが挙げられる[7]．

また，PBC[8,9]やPSC[10]においては再発の問題が報告されている．どちらの場合も画像的にも組織学的にも拒絶反応などの他の病変との鑑別が困難である場合があり，再発と診断して治療を進めるには臨床経過を慎重に検討する必要がある．

2．B型肝硬変／C型肝硬変

日本肝移植研究会の集計においてB型肝硬変では1年生存率が74.0%，3年生存率74.0%であった．C型肝硬変ではそれぞれ75.9%，73.9%であった．B型肝硬変の移植においては，移植前にB型肝炎ウイルス（HBV）逆転写酵素阻害剤ラミブジンを投与しHBe抗原とHBV-DNAの陰性化をはかり，術中から抗HBs高力価免疫グロブリン（HBIG）を投与し，術後も適宜HBIGを投与することでHBs抗原とHBV-DNAの陰性化を維持しHBVの再燃予防を行っている．当科でのHBIGの投与目安は，術後1ヶ月まではHBs抗体価を500IU／l以上，1～3ヶ月までは200IU／l以上，3ヶ月以降は100IU／l以上を維持するように投与している．今後はHBVワクチンなどの併用も考慮すべき問題である．一方，C型肝硬変においては術後はほぼ全例でウイルス量が増加し，再発を認める症例が少なくない．HCV関連抗原は移植後半年以内に約90%の肝組織内に観察されるという報告もある[11]．また，組織学的に拒絶反応との鑑別が時に困難であり，安易なステロイド投与はウイルス量の増殖に拍車をかける恐れがあり，慎重投与が必要である．C型肝硬変の移植においてはその再発を予防あるいは治療するためにインターフェロンとリバビリンの併用投与を行う施設が多い．しかし，そのタイミングなどに確立されたプロトコールはなく，移植前投与を試みる施設もある一方，多くは予防投与は行わず，移植後慢性C型肝炎の再発が診断されてからの治療にインターフェロン，リバビリンを使用している．今後，術後のC型肝硬変のウイルス量を抑える工夫が待たれている．

3．肝細胞癌

肝細胞癌に対する肝移植は，肝移植の歴史の中で早期より行われていた．1980年代に，肝機能などで切除不可能な肝細胞癌に対して積極的に肝移植が施行されていた．術前には腹部，胸部，脳CT，骨シンチで肝外転移の有無を確認することが必要である．Mazzaferroら[12]が，5cm以下単発，または3cm以下3個以内の切除不能肝癌48例の肝移植において，4年生存率および4年無再発生存率がそれぞれ76%，83%と良好な成績を報告して以来，近年ではこの基準が，Milan Criteriaとして重要視されている．また，今まで肝切除で好適応と考えられていた症例でも肝移植の方が成績がよいという報告もあり，Figuerasら[13]は肝硬変にMilan Criteria内の肝細胞癌を合併した症例に対する肝移植85例と肝切除35例を比較して生存率を検討している．肝移植例では，1年，3年，5年生存率はそれぞれ84%，74%，60%で，肝切除例ではそれぞれ83%，57%，51%であり有意差はないが，無再発生存率はそれぞれ83%，72%，60%と70%，44%，31%で肝移植の方が優位に好成績を認めている．Milan Criteriaを満たすような早期のものでは肝移植がよい適応となると考えられる．しかし，本邦では欧米と異なり，切除不能癌にPEIT，TAEを繰り返した末の末期の肝細胞癌の最終治療として位置づけられている場合が少なくない．当科では，肝細胞癌に対する適応基準として，明らかな血管浸潤がなく，肝外転移がない症例であれば他に有効な治療のない場合の積極的な選択肢に含めている．

また，Kaiharaら[14]は術後肝細胞癌再発の危険因子として，組織学的分化度，組織学的血管浸潤の有無が優位に影響していると報告している．術後の再発予防に化学療法（ファルモルビシンなど）を施行している施設もあるが未だ確立されたものはない．

4．劇症肝不全（劇症肝炎）

本邦では，脳死肝移植に対し作成された適応基準が生体肝移植でも基本的に用いられている．内科的治療で救命し得るかという正確な判断は難しい．脳CTや脳波検査において不可逆的と考えられる脳障害を来した症例や，ステロイド投与により重症感染症を合併した症例では肝移植は禁忌となる．また，生体肝移植の場合

ドナー候補者が医学的に適切かどうか判断するために採血・レントゲンなどの一般検査や腹部CT・エコーなどを行う時間を要し，何よりもドナーの冷静な自発的意志や家族の同意・理解を得る十分な時間をつくる必要がある．そのため，劇症肝炎と診断がついた時点で肝移植という治療の選択肢を念頭に置く必要がある．厚生労働省難治性の肝炎または肝疾患調査研究班による全国集計では，2000～2002年の3年間に劇症肝炎に対する生体肝移植は計80例に行われ，短期的な経過観察期間ではあるが，その生存率は75%という結果が得られている．

IV. 本邦における脳死肝移植

本邦では1999年に初めての脳死ドナーからの肝移植が行われた．2002年末現在までに脳死肝移植21例，心停止肝移植2例が行われ，全肝移植が大半を占めているが外側区域グラフト，右葉系グラフトも用いられている．レシピエントの原疾患は，胆道閉鎖症が最も多く7例，PBC 2例，PSC 2例，B型急性肝不全2例と続く．脳死肝移植はわずかずつ増えてはいるが年間数が最も多い時で2002年の7例である．

V. ドミノ肝移植

ドミノ肝移植とは，肝不全に至らない代謝性疾患をもつ患者が移植を受けた際に，その肝臓を次のレシピエントへ移植する方法である．実際に最も多く行われているドミノ肝移植は，familial amyloidotic polyneuropathy (FAP) 患者の肝臓を用いた他の肝不全患者の移植である．日本肝移植研究会によると，ドミノ移植の一次レシピエント，二次レシピエントの予後は，その後のレシピエントの予後と差がなかったと報告されている．

VI. 生体肝移植の今後に向けて

わが国において肝移植の歴史は浅く，未だ一般内科医にとって急性および末期肝疾患の治療の選択肢のひとつとして常に念頭に置かれるところまでには至っていない．そのため，年間わが国では約2300人の肝移植適応患者がいると推測されているが，移植医療はその10%程度にしか享受されていない．今後，多くの患者を救命できるように一般内科医と移植施設との密な連携の下，移植の適応，タイミング，術前治療，術後治療などを考えていく必要がある．

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一般演題

成人生体肝移植における肝静脈波形の周術期変化

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杉本博行,金子哲也,木内哲也,中尾昭公

肝移植における超音波Doppler法は血管合併症の早期発見に有用とされている．しかし，これまで生体肝移植における肝静脈波形解析の詳細な検討はなく，正常，異常の判断は困難であった．

生体肝移植術後の肝静脈波形異常を検討するためには，正常の肝静脈波形を理解する必要がある．正常者における肝静脈波形とは以下に示す特徴がある（図1）．

1. 心拍動に同期した波形で三相波（A, S, D波）
2. 層流（帯状となりspectral broadeningがない）
3. 適度な流速（30cm/s）

これらの特徴に対し，肝静脈波形の異常は主に肝硬変における変化について報告されている．最も特徴的なのは三相波から定常波に変化する拍動性の低下である．肝硬変患者では肝静脈波形は定常波を示すことが多く，肝の線維化に伴う肝コンプライアンスの低下によるものとされている（ただし肝静脈波形変化はあくまでも心拍出による間接的な所見であることに留意しなければならない）．また，よく観察すると肝静脈波形の拍動性が低下するにつれ，層流からspectral broadeningを伴う，いわゆる乱流に変化

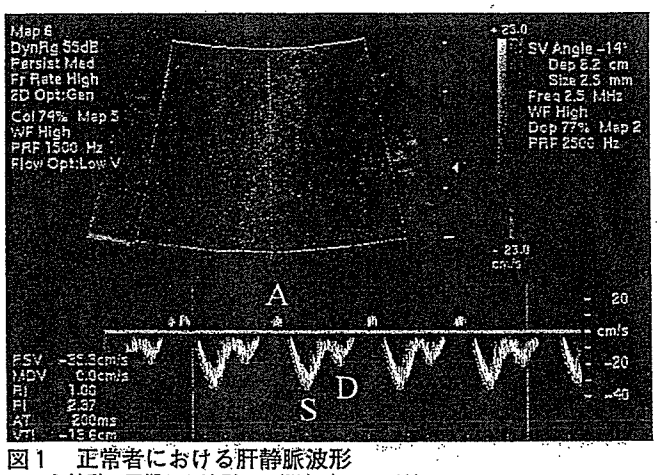

図1　正常者における肝静脈波形
1. 心拍動に同期した波形で三相波（A, S, D波）
2. 層流（帯状となりspectral broadeningがない）
3. 適度な流速（30cm/s）

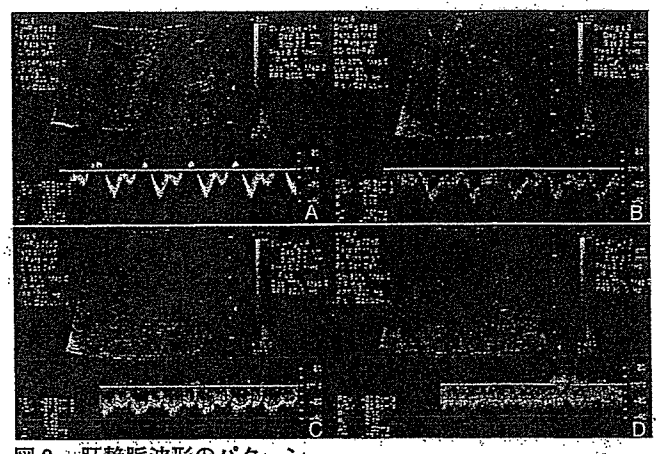

図2　肝静脈波形のパターン
正常では三相波を示す．肝硬変では定常波を示すことが多い．
A. 三相波　　B. 強い二相波
C. 弱い二相波　　D. 定常波

していくことが多いことに気付く．流速に関しては変化はわずかではあるが，やはり拍動性が低下するにつれ減少するものが多いことに気付く（図2）．

では，生体肝移植術後の正常肝静脈波形はどのような特徴を示すかということになるが，前記した“正常肝静脈波形”とは大きく違う可能性がある．問題点を以下に示す．

1. 部分肝である．
2. 術後である．
3. 血管吻合をしている．
4. 他人の臓器である．
5. 術前に肝機能異常が存在する．（特に肝硬変）

これらの問題から生体肝移植術後は生体の適応能力を逸脱する急激な血行動態変化が起こりうると考えられる．

方法

そこで今回，当科で施行した右葉グラフトを用いた成人生体肝移植10例において術後早期の肝静脈波形の変化と肝血行動態につき解析した．解析項目は肝静脈血流速（以下HVV），肝静脈resistance index（以下HVRI）と定性的評価として肝静脈波形を測定し，その周術期変化を検討した．

結果

HVVは4－6病日でやや速くなるが，周術期を通じ40-50cm/sで一定の傾向を示した．HVRIは術後早期に高値を示し，以後は一定であった．定性的評価において肝静脈波形は周術期を通じ三相波を示す症例も存在したが，多くは三相波を維持できず，特に3－6病日では三相波を呈する割合は12.1%にすぎなかった．また層流を呈するものも3－6病日でもっとも少なく30.3%であった．しかし，これらの波形異常はその後回復する傾向があった（表1，図3）．

表1 周術期肝静脈波形変化

術後病日	1–3	4–6	7–10	11–14
HVV (cm/s)	49.4±16.2	53.4±28.9	44.0±14.8	46.2±16.7
HVRI	0.59±0.28*	0.42±0.27	0.41±0.29	0.42±0.31
三相波の割合 (%)	24.2	12.1	20.5	26.3
層流波の割合 (%)	66.7	30.3	35.9	52.6

*p<0.05

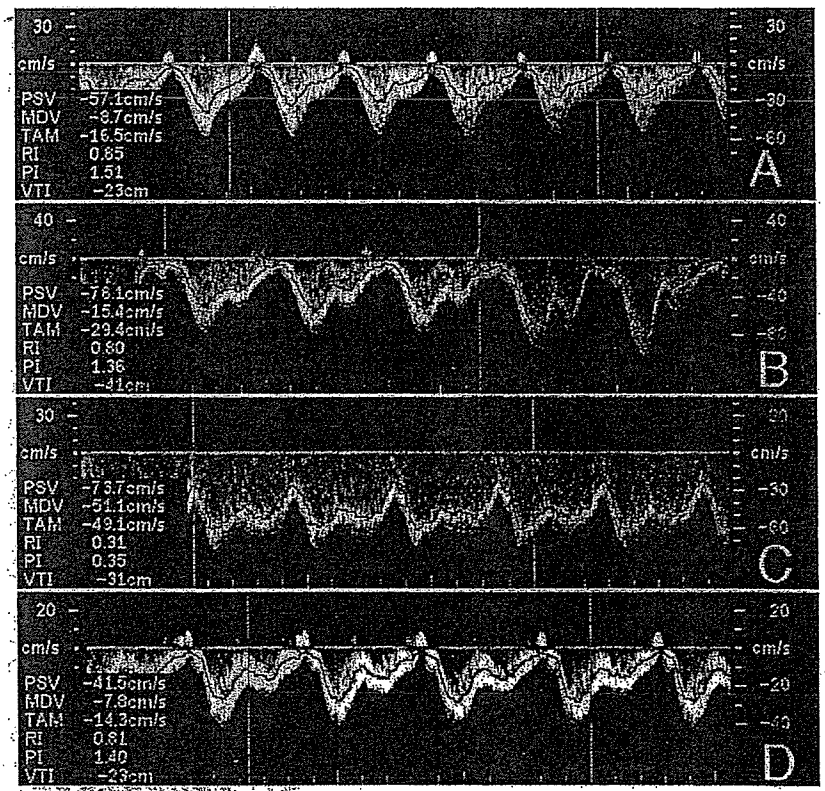

図3 周術期肝静脈波形変化
A. 第1病日 57.1 cm/s, 三相波
B. 第4病日 78.1 cm/s, 強い二相波
C. 第5病日 73.7 cm/s, 弱い二相波，乱流傾向
D. 第10病日 41.5 cm/s, 三相波，層流

考察

生体肝移植術後の肝静脈波形変化を“正常者における肝静脈波形”と比較検討すると，“正常”と同様に

1. 心拍動に同調した波形，三相波（A, S, D波）
2. 層流（帯状となりspectral broadeningがない）
3. 適度な流速（40cm/sぐらいでやや“正常”より速い）

を示す症例，期間があり，この肝静脈波形を“生体肝移植術後正常肝静脈波形”と定義できる（図4）．

逆にこの状態とは正反対の“異常肝静脈波形”として

1. **心拍動に同調しない波形，定常波**
2. **乱流（spectral broadening）**
3. **過度な流速（>80cm/s or <20cm/s）**

を示す症例，期間が存在した（図5）．

このような“生体肝移植術後異常肝静脈波形”を示すものには，例えば急性拒絶があった．また，異常な肝静脈高速血流は肝硬変では見られない，生体肝移植特有の変化で類洞の相対的な狭小化（肝細胞腫大，類洞収縮，過剰流入血など）を示唆するものと考えられた．

しかし，多くの症例，期間は，“生体肝移植術後正常肝静脈波形”でも“生体肝移植術後異常肝静脈波形”でもない波形を示す．この幅広い境界域のどこまでを“生体肝移植術後正常肝静脈波形”に含ませるのかは今後の課題であるが，“正常肝静脈波形”とほぼ等しい“生体肝移植術後正常肝静脈波形”を示す症例が存在するということは，境界域症例はやはり境界域であり，何らかの負荷，障害を来しているものと考えられる．

結語

生体肝移植術後肝静脈波形を詳細に解析した．肝静脈波形解析により肝血行動態を推測し，合併症の発見と治療に役立てたい．

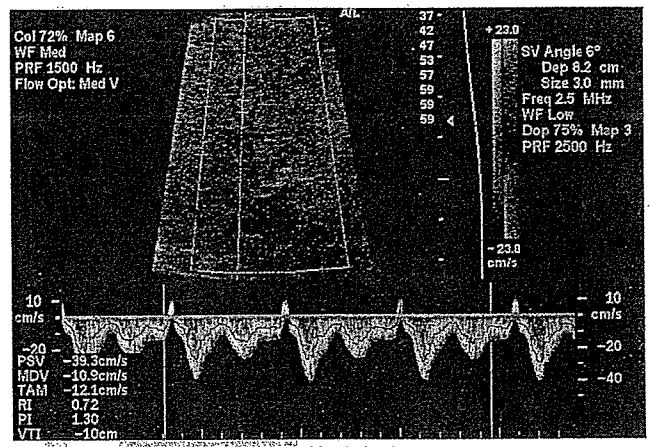

図4　生体肝移植術後正常肝静脈波形
1. 心拍動に同期した波形で三相波（A, S, D波）
2. 層流（帯状となりspectral broadeningがない）
3. 適度な流速（40cm/s）

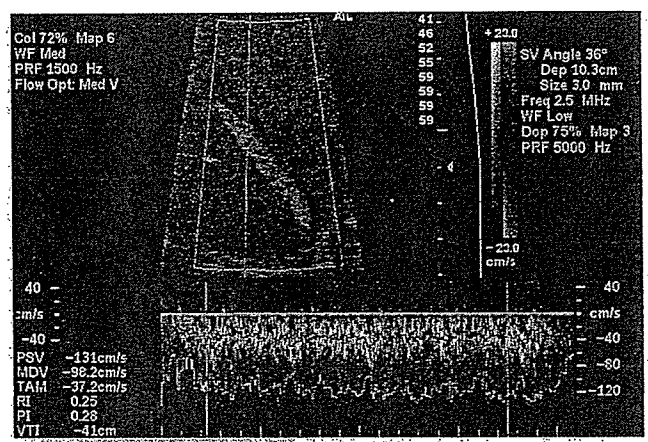

図5　生体肝移植術後異常肝静脈波形
1. 心拍動に同期しない波形で定常波
2. 乱流（spectral broadeningを伴う）
3. 過度な流速（>80cm/s or <20cm/s）

ELSEVIER

Initial Dosage Adjustment for Oral Administration of Tacrolimus Using the Intestinal MDR1 Level in Living-Donor Liver Transplant Recipients

S. Masuda, M. Goto, M. Okuda, Y. Ogura, F. Oike, T. Kiuchi, K. Tanaka, and K. Inui

ABSTRACT

The role of intestinal P-glycoprotein (encoded by the *MDR1/ABCB1* gene) and/or metabolic enzyme CYP3A4 for tacrolimus therapy was examined in recipients of living-donor liver transplantation (LDLT), under the hypothesis that these proteins are factors for pharmacokinetic variability. The intestinal mRNA expression level of MDR1 and CYP3A4 was evaluated by real-time polymerase chain reaction (PCR), using the upper jejunum from a part of the Roux-en-Y limb for biliary reconstruction at LDLT. For 7 days postoperatively, good inverse correlation was found between the tacrolimus concentration/dose (C/D) ratio and the intestinal mRNA level of MDR1 ($r = -0.776$), but not of CYP3A4 ($r = -0.096$), in the 46 cases. After classifying the patients according to median of the intestinal MDR1 mRNA expression, the oral dose of tacrolimus in the high-MDR1 group was approximately twofold higher than in the low-MDR1 group ($P < .001$), whereas its trough level was similar between the two groups. In addition, the correlation between the intestinal MDR1 mRNA level and the tacrolimus C/D ratio was confirmed with a larger population ($r = -0.645$, n = 104). Using the regression line between the intestinal MDR1 mRNA level and tacrolimus C/D ratio, we could prospectively predict the individual C/D ratio of tacrolimus immediately after LDLT. Known genetic variations of the *MDR1* gene had no effect on intestinal MDR1 mRNA level and tacrolimus C/D ratio in LDLT patients. This suggests that the intestinal mRNA level of MDR1 is a useful molecular marker for determination of the personalized oral dose of tacrolimus in recipients of LDLT immediately after surgery.

LIVING-DONOR liver transplantation (LDLT) with the immunosuppressant tacrolimus is a principal life-saving therapy for patients with end-stage liver failure. Because the success of the transplantation depends on a delicate balance between immunosuppression and rejection, the maintenance of adequate levels of blood tacrolimus is critical. Tacrolimus is principally metabolized by cytochrome P450 (CYP) 3A subfamilies in the liver. Recently, the contribution of active secretion by P-glycoprotein (the product of the *MDR1/ABCB1* gene) and the metabolism by CYP3A expressed in enterocytes have been acknowledged as factors influencing the bioavailability of tacrolimus. In the present study, we examined the role of intestinal P-glycoprotein and/or CYP3A4 for tacrolimus therapy in LDLT recipients, under the hypothesis that these proteins are factors in pharmacokinetic variability.

MATERIALS AND METHODS

The upper jejunum was obtained from a part of the Roux-en-Y limb for biliary reconstruction at LDLT.[1] The intestinal mRNA expression level of MDR1 and CYP3A4 was evaluated by real-time

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polymerase chain reaction (PCR). The genomic DNA isolated from the homogenate of a grafted liver biopsy specimen and intestinal mucosa or peripheral blood from recipients was used for genotyping by the PCR restriction enzyme length polymorphism (RFLP) method.[2] This study was conducted in accordance with the Declaration of Helsinki and its amendments, and was approved by the ethics committee of Kyoto University.

Normally distributed values were presented as the mean ± SE. Logarithmic transformation of the mRNA expression levels of MDR1 and CYP3A4 was performed to improve normality before performing statistical analyses. The unpaired Student's t test was used to compare groups with respect to normally distributed variables.

RESULTS AND DISCUSSION

Although the tacrolimus dosage regimen for each recipient was defined as the daily trough level of tacrolimus from day 2 in each recipient, half of the tacrolimus trough levels were below the lower limit of the therapeutic range, which was set at 10 to 20 ng/mL, during 7 postoperative days (90 of 201 measurements, n = 46).

The quantified average expression levels of MDR1 mRNA and CYP3A4 mRNA in all 48 intestinal mucosa obtained was 0.41 ± 1.19 and 1.58 ± 1.25 (micromoles per gram total RNA; mean ± SE), respectively.[3] To clarify whether MDR1 and CYP3A4 play roles as pharmacokinetic factors for tacrolimus therapy after LDLT, we examined the pharmacokinetic significance of these absorptive barriers with the tacrolimus C/D ratio in LDLT recipients. The logarithmically transformed mRNA expression level of MDR1 (r = 0.776), but not CYP3A4 (r = 0.096), was inversely correlated with the C/D ratio of tacrolimus administered orally. Moreover, we categorized recipients by mRNA expression levels of MDR1 and CYP3A4 on the basis of each mean value. The differences in dose, the trough level, and the C/D ratio were examined between the high and low groups for both MDR1 and CYP3A4. The tacrolimus trough level did not differ significantly between the two MDR1 groups (11.5 ± 0.58 in the high-MDR1 group vs 11.0 ± 0.52 ng/mL in the low-MDR1 group, P = .476). However, the oral dose and the C/D ratio of tacrolimus in the high-MDR1 group were approximately twofold higher (0.13 ± 0.01 vs 0.07 ± 0.01 mg/kg per day, $P < .001$) and lower (143.8 ± 18.2 vs 230.1 ± 20.9 ng/mL · mg/kg per day P = .002) than in the low-MDR1 group, respectively. There was no significant difference between the high- and low-CYP3A4 groups in tacrolimus dose or C/D ratio.

Next, we preliminarily predicted the initial oral dosage of tacrolimus based on the mRNA expression level of intestinal MDR1 mRNA at LDLT. Despite the small number of subjects, the period required for the blood level of tacrolimus to reach therapeutic range (10 ng/mL) was faster in the predicted group (n = 27) than in the nonpredicted group (n = 35). In addition, the correlation between the intestinal mRNA level of MDR1, and the tacrolimus C/D ratio during 7 postoperative days was confirmed in the additional cases

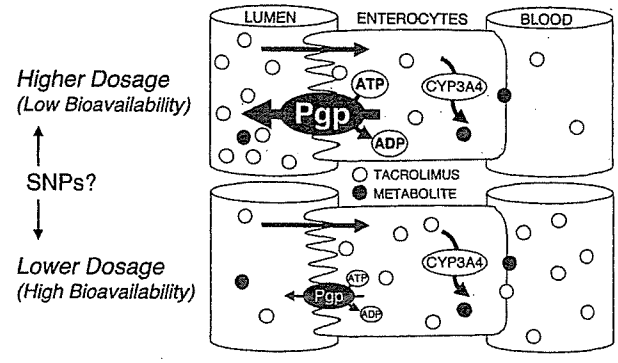

Fig 1. Interindividual variation of tacrolimus absorption. Recipients with a high level of intestinal MDR1 require a higher initial dose of tacrolimus.

(n = 104, r = −0.645). These results suggest that the intestinal expression level of MDR1 was a good molecular marker to define the oral dosage regimen of tacrolimus, at least immediately after LDLT.

Recently, the MDR1 cDNA 3435C/T and 2677G/AT single-nucleotide polymorphisms (SNPs) were reported as factors affecting the intestinal expression and/or functional property of MDR1.[4] However, the frequencies of MDR1 3435C/T and 2677G/AT genotypes were similar to previous reports, but both the tacrolimus C/D ratio during 7 postoperative days and the intestinal mRNA level of MDR1 were not affected by these SNPs.[4,5] Therefore, the intestinal mRNA expression level of MDR1 at LDLT was a potent pharmacokinetic factor without the influence of these two SNPs.

In conclusion, intestinal MDR1 functions as an absorptive barrier for orally administered tacrolimus, and its mRNA level at LDLT could contribute to establishment of an individualized oral dosage regimen of tacrolimus immediately after surgery (Fig 1).

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IMAGES OF INTEREST

Hepatobiliary and pancreatic: The color bar sign after living donor liver transplantation

In living donor liver transplantation, the first reported procedures were carried out with a left liver graft. Subsequently, better results were achieved with a right liver graft, particularly when the recipient was an adult. One technical issue involves the venous drainage of the right graft that normally includes the right hepatic vein and tributaries of the middle hepatic vein. In order to avoid venous congestion of the right anterior section of the graft, remnant tributaries of the middle hepatic vein are often anastomosed to the right hepatic vein. The challenge is to document these anastomoses in the postoperative setting, when it might be difficult to distinguish branches of the portal vein from branches of the middle hepatic vein.

We have used color Doppler ultrasonography to assess different features of the vasculature after living donor liver transplantation. The portal vein accompanies the hepatic artery, although it is often difficult to detect the hepatic artery on the periphery of the liver. Furthermore, blood flow velocity in the portal vein decreases towards the liver periphery, whereas blood flow velocity in the drainage veins (right hepatic vein and tributaries of the middle hepatic vein) increases towards the liver periphery. These features are shown in Fig. 1. The remnant tributary of the middle hepatic vein is shown with solid arrows, whereas open arrows are used for the right hepatic vein. The curved arrow indicates the direction of blood flow. The increasing blood velocity in the remnant tributary of the middle hepatic vein mimics the upper side of a color bar; and hence it is called the color bar sign. Pulsed Doppler ultrasonography can also be used to confirm the drainage vein by analysis of the waveform. The phasic waveform associated with the tributary of the middle hepatic vein is shown in Fig. 2. This new sign might be useful for the diagnosis of functional anastomoses in recipients of a right liver graft.

Contributed by
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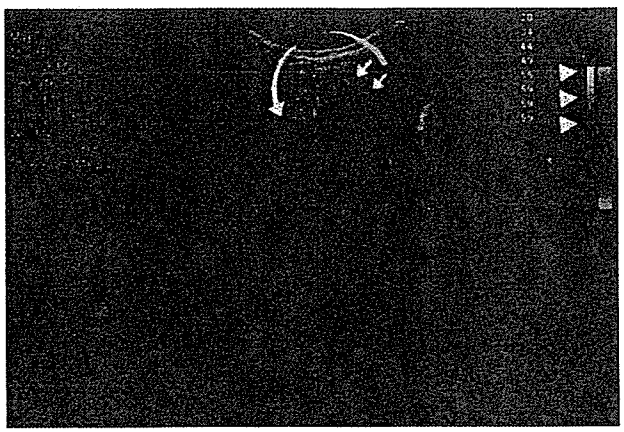

Figure 1

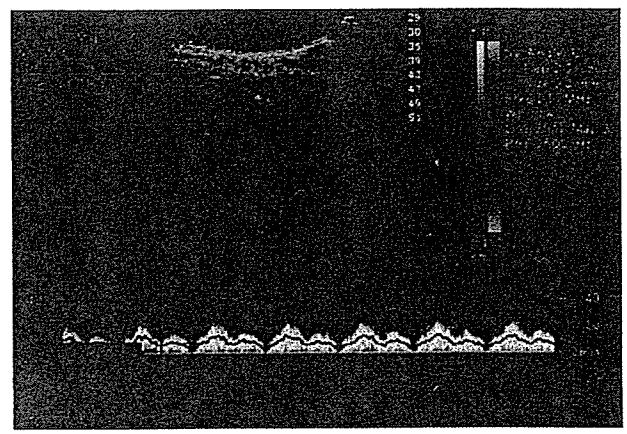

Figure 2

Contributions to the Images of Interest Section are welcomed and should be submitted to Professor IC Roberts-Thomson, Department of Gastroenterology, The Queen Elizabeth Hospital, Woodville South, South Australia 5011, Australia.

Intrahepatic venous anastomosis formation of the right liver in living donor liver transplantation: Evaluations by Doppler ultrasonography and pulse-inversion ultrasonography with Levovist

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Background. *Our aim was to investigate the development of intrahepatic venous anastomoses between the middle hepatic vein (MHV) and the right hepatic vein (RHV) in adult-to-adult, living donor, liver transplantation.*

Methods. *Using Doppler ultrasonography, we studied the formation of venous anastomoses between the MHV tributaries for segments 5 and 8 (V5, V8) and the RHV in the liver remnants of 7 donors of a left liver, including the MHV, and in the liver grafts of 8 recipients of a right liver, without including the MHV. In 1 donor and 5 recipients, we performed pulse-inversion ultrasonography with a microbubble contrast agent to evaluate hepatic parenchymal perfusion in the drainage region of the MHV.*

Results. *We observed 15 MHV tributaries of V5 and 13 of V8 among the 15 adult transplant patients. During the first postoperative week, we detected venous anastomosis between V5 and the RHV in 4 patients and in 10 patients between V8 and the RHV. After the 1st week, we observed the formation of anastomosis between V5 and the RHV in 10 patients, and between V8 and the RHV in 3. In both MHV tributaries, the mean flow velocities increased ($P < .01$). By the end of the 1st week, the formation rate in V8 was higher than in V5 (77% vs 27%, $P < .03$). In the parenchymal phase of the pulse-inversion ultrasonography with the microbubble contrast agent, the V5 drainage region had low intensities, while the V8 drainage territory revealed high intensities in 4 of 6 patients (66.7%).*

Conclusions. *Functional venous anastomoses between either V5 or V8 and the RHV developed in most of the donors of left hepatic lobes and in recipients of right hepatic lobes; however, anastomoses developed earlier in V8 than in V5. Furthermore, perfusion was decreased in the drainage area of V5, compared with V8. (Surgery 2005;138:21-7.)*

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LIVING DONOR liver transplantation has become used widely in the adult patient population.[1,2] The use of a right liver graft without including the middle hepatic vein (MHV) has become a standard option to ensure adequate hepatic graft volumes capable of fulfilling the metabolic demands of recipients.[3-5] The right anterior (segments 5 and 8) of the liver is drained primarily by the MHV.[6] As a result, drainage of the right anterior sector in right liver grafts without the MHV drainage is critically dependent on the integrity of intrahepatic venous anastomoses between the MHV tributaries and the right hepatic vein (RHV).[7]

According to the Kyoto group, graft loss consequent to graft congestion did not occur among their series of more than 200 living donor transplants using the right liver without the MHV.[8] Conversely, Lee et al[9] reported severe congestion of the anterior sector of right liver grafts without the MHV after reperfusion, which resulted in severe graft dysfunction and septic complications. They now reconstruct all the MHV tributaries for the right anterior sector of right liver grafts when the MHV is not included in the graft. It remains

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Table I. Demographic data

Patient total	*n = 15*
Recipient age (y)	43 ± 16 (17-60)
Recipient gender (M/F)	8/7
Donor age (y)	38 ± 12 (21-56)
Donor gender (M/F)	10/5
Diseases	
Hepatitis-induced liver cirrhosis	5
Primary biliary cirrhosis	4
Biliary atresia	2
Familial amyloid polyneuropathy	2
Primary sclerosing cholangitis	1
Fulminant hepatic failure	1
Operative procedures of donor	
Left hepatectomy (segments 2, 3, and 4 with MHV)	7
Right hepatectomy (segments 5, 6, 7, and 8 without MHV)	8

MHV, Middle hepatic vein.

controversial as to whether the MHV tributaries should be reconstructed and whether a single hepatic vein can provide drainage for the entire right liver graft, presumably through the formation of intrahepatic venous anatomoses.[10]

In patients in whom the MHV tributaries are not reconstructed in a right liver graft, the integrity of the intrahepatic venous anastomoses between the MHV and RHV is of considerable importance because there is no other collateral route for blood to exit the liver. Compromise of these anastomoses could lead to venous outflow obstruction, causing graft congestion and potential graft failure. Our aim was to assess the intrahepatic formation of venous anastomoses between the MHV and RHV, utilizing color Doppler ultrasonography (US). Doppler US has been used extensively in the evaluation of liver grafts and hepatic vasculature. The intrahepatic hemodynamics is similar in recipients of a right liver graft without the MHV and in the right liver remnant in donors of a left liver graft with the MHV. As a result, we evaluated formation of venous anastomoses between the MHV tributaries and the RHV in recipients of right liver grafts without the MHV and in donors of left liver grafts with the MHV. We also utilized Pulse-inversion harmonic US with a microbubble contrast agent to assess hepatic parenchymal perfusion as another measure of the development of intrahepatic venous collaterals.[11,12] This technology results in improved spatial and temporal resolution in comparison with conventional Doppler US, as well as in heightened contrast compared with harmonic US.[13]

In this paper, we use the nomenclature specified by the Hepato-Pancreato-Biliary Association regarding the anatomic terminology of the liver.[14]

PATIENTS AND METHODS

Patients. We studied 15, adult-to-adult, living donor liver transplantation procedures. The demographic data of the donors and recipients are listed in Table I. The operative procedures consisted of a left hepatectomy (segments 2, 3, and 4 with the MHV) in 7 patients and a right hepatectomy (segments 5, 6, 7, and 8 without the MHV) in 8 patients. Detailed descriptions of right liver graft recipients, including liver diagnoses and relative sizes of the liver grafts, are shown in Table II. In the right liver grafts, we did not reconstruct the MHV tributaries from the right anterior sector (V5, V8). In the left liver donors, we kept the right livers without the MHV and ligated the MHV tributaries from the right anterior sector. In both groups, the MHV outflow pathway for the right anterior sector was interrupted.

Written informed consent was obtained from all patients in this study.

Intra- and postoperative Doppler US examination of hepatic venous flow. We performed pulse and color Doppler US to measure flow of the MHV tributary from segment 5 (V5) and segment 8 (V8), as well as flow of the portal vein branch to segment 5 (P5) and segment 8 (P8). We performed intraoperative Doppler US examinations and investigated the presence of intrahepatic venous anastomoses between either V5 or V8 and the RHV. All Doppler US exams were performed by transplant surgeons qualified in sonography (T.K., H.S.). Postoperative US examinations were performed by right intercostal scanning during expiration with the use of a commercially available US machine (HDI 5000; Philips, Andover, Mass). The highest-frequency, curved array US transducer that could resolve the Doppler signals was used, namely the C5-2. The sample volume was set at 2.5 mm. So far as was tolerated by the patient, the portal vein flow was investigated fully up to the 3rd-ordered branch. Flow of the ventral branch of P8 was measured. During all intraoperative US exams, a 5 to 8 MHz transducer with a microconvex probe was used; postoperatively, a 2 to 5 MHz transducer with a convex probe was utilized. Among the recipients, we performed Doppler US twice a day postoperatively until postoperative day (POD) 14. Subsequently, Doppler US was performed once a day until POD 28 and then weekly thereafter. Among the donors, we performed Doppler US

Table II. Recipients of right liver grafts

	Liver disease	Age (y)	Gender	GV/SLV × 100 (%)
1	Biliary atresia	16	M	56
2	Primary biliary cirrhosis	59	F	81
3	Familial amyloid polyneuropathy	30	M	45
4	Hepatitis-induced liver cirrhosis	59	M	79
5	Hepatitis-induced liver cirrhosis	58	M	61
6	Hepatitis-induced liver cirrhosis	52	M	52
7	Primary biliary cirrhosis	56	F	56
8	Hepatitis-induced liver cirrhosis	60	M	49
				60 ± 13

GV, Graft volume; *SLV*, standard liver volume.

once a day until POD 14 and then twice a week until POD 28.

The criteria for the presence of a collateral on Doppler US was reversed flow in the ligated MHV tributary toward the periphery that then communicated with the RHV. Reversed flow of the ligated MHV tributary increased toward the intrahepatic anastomoses in a pattern of flow different from the portal vein. This phenomenon has been reported as a "color bar sign," which mimics the color bar at the right side of the color Doppler image.[15]

Pulse-inversion harmonic US with Levovist. We performed a Pulse-inversion harmonic US with Levovist (Schering, Berlin, Germany), a microbubble contrast agent for US between POD 21 and 54 (average, 25 POD) to evaluate hepatic parenchymal perfusion. The Pulse-inversion mode US with Levovist was also performed by transplant surgeons qualified in sonography (T.K., H.S.). We used a commercially available US machine (HDI 5000; Philips) with a Pulse-inversion mode installed on a 2 to 5 MHz transducer with a convex probe. We preset the acoustic power at a mechanical index (MI) of 1.5. We then administered 2.5 g of Levovist as an intravenous bolus (concentration, 300 mg/mL), followed by 10 mL of 154 mmol/L NaCl through an 18-gauge peripheral venous cannula. After 5 minutes, we scanned the entire liver in the Pulse-inversion mode during a breath-hold. The focal zone was set at the shallow one third of the image to evaluate hepatic parenchymal perfusion, particularly in segment 5.

Pulse-inversion harmonic US is a technique capable of detecting nonlinear echoes. Alternative pulses, 180 out of phase, are transmitted along a given ultrasound line. The signals from the pair are summed and used to form 1 image line. Signals from linear and nonlinear sources can be differentiated in the receiving spectrum because nonlinear signals summate and linear signals cancel.

Statistical analysis. All results were expressed as the mean + SD. Continuous variables were evaluated with repeated measures of analysis of variance (ANOVA), followed by a Bonferroni correction. We used Fisher exact test to compare discrete variables and obtained the correlation coefficient using Spearman rank correlation analysis. Differences with a P value less than .05 were considered statistically significant.

RESULTS

Doppler US examination. We detected formation of intrahepatic venous anastomoses between V5 or V8 and the RHV by color and pulse Doppler US. Color Doppler US demonstrated reversal of venous flow in V5 and V8 into the RHV by development of intrahepatic venous anastomoses. Pulse Doppler US showed mirror image, waveform patterns in V5 and the RHV at the site of the anastomosis (Fig 1).

MHV tributary from segment 5. We evaluated 15 tributaries of V5, identifying 1 tributary in each patient. We found intrahepatic venous anastomoses between V5 and the RHV in 1 patient on POD 1, collateral formation in 3 patients between PODs 2 and 7, in 5 patients between PODs 8 and 14, and in another 5 patients after POD 15. We did not detect any anastomoses in 1 patient. During the first postoperative week, 4 of the 15 patients developed venous anastomoses between V5 and the RHV. After the 1st week, 10 of the 15 patients developed collaterals.

The mean flow velocities of V5 were 1.2 + 4.6 cm/s on POD 1, 4.2 + 7.6 cm/s between PODs 2 and 7, 5.5 + 6.6 cm/s between PODs 8 and 14, and 9.7 + 5.8 cm/s after POD 15. These velocities gradually increased over time ($P < .01$). The mean velocities of PODs 8 through 14 and after POD 15 were greater than those of POD 1 ($P < .05$ and $P < .01$, respectively).

MHV tributary from segment 8. Thirteen tributaries for segment 8 were evaluated. In 2 patients, V8 could not be detected by postoperative Doppler US examination. We were able to detect intrahepatic venous anastomoses between V8 and the RHV in 4 patients on POD 1, in 6 patients between PODs 2 and 7, in 1 patient between PODs 8 and 14, and in 2 patients after POD 15. During the 1st week, 10 of the 13 patients developed

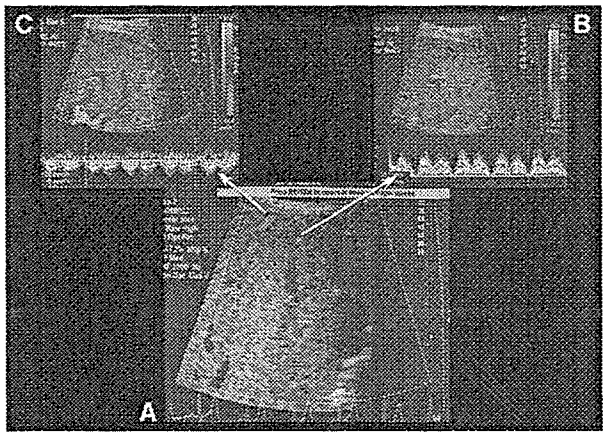

Fig 1. A, Color Doppler US demonstrating intrahepatic venous anastomosis between the MHV tributary (V5) and the RHV. **B,** Pulsed Doppler US at V5 showing reversed flow toward the anastomosis. **C,** Pulsed Doppler US at the RHV showing flow away from the anastomosis.

collaterals, whereas only 23% (3/13) of the patients formed collaterals after the 1st week.

The mean flow velocity of V8 on POD 1 was 3.5 + 5.6 cm/s, 8.4 + 6.2 cm/s between PODs 2 and 7, 10.5 + 6.8 cm/s between PODs 8 and 14, and 14 + 6.0 cm/s after POD 15. These velocities also increased gradually ($P < .01$). The mean velocities of PODs 2 through 7, PODs 8 through 14, and after POD 15 were greater than those of POD 1 ($P < .01$, respectively).

Portal vein branch to segment 5. We examined 15 portal vein branches to segment 5, investigating 1 branch in each patient. Blood flow of the ventral branch of P5 was measured. Hepatofugal flow was observed in 5 patients on POD 1, in 6 patients between PODs 2 and 7, and in 3 patients between POD 8 and 14. We did not observe hepatofugal venous flow in the other patients after POD 15.

The mean flow velocities of P5 on POD 1, POD 2 through 7, POD 8 through 14, and after POD 15 were 0.2 + 7.9 cm/s, 4.3 + 11.1 cm/s, 6.6 + 9.8 cm/s, and 12.1 + 8.1 cm/s, respectively. The mean velocities increased gradually ($P < .05$). The mean velocities after POD 15 were greater than those of POD 1 ($P < .01$).

Portal vein branch to segment 8. We examined 15 portal vein branches to segment 8, evaluating 1 branch per patient. Blood flow of the ventral branch of P8 was measured. Hepatofugal flow was observed in 1 patient between PODs 2 and 7. The mean velocities of P8 on POD 1, PODs 2 through 7, PODs 8 through 14, and after POD 15 were 6.3 + 7.4 cm/s, 7.3 + 7.8 cm/s, 9.4 + 7.6 cm/s, and 12.9 + 6.3 cm/s, respectively. There was no statistical difference in velocity over time.

Comparison of intrahepatic anastomosis formation between V5 and V8. The rate of formation of intrahepatic venous anastomoses during the 1st postoperative week was greater in V8 than in V5 (77% vs 27%, $P < .03$). Subsequently, the rate of formation of anastomoses after the 1st week was greater in V5 than in V8 (68% vs 23%, $P < .03$). These findings indicate that venous collaterals formed earlier in V8 than in V5.

Comparison of mean velocity between V5 and V8 in each POD group. In every postoperative period, the mean velocity of V8 was not statistically different from that in V5.

Correlation between V5 and P5 and between V8 and P8. The gradual increase in mean velocities over time for V5 and P5—and for V8 and P8—was correlated closely ($r = 0.935$, $P < .01$, and $r = 0.955$, $P < .01$, respectively).

Pulse-inversion harmonic US with Levovist. We performed Pulse-inversion harmonic US in 6 patients (1 donor and 5 recipients) at varying postoperative dates. In 4 patients, the drainage region of V5 was visualized at low signal intensity during the hepatic parenchymal phase, whereas the region of V8 showed high signal intensity (Fig 2). These findings suggest that perfusion of hepatic parenchymal was occurring in segment 5 in comparison to segment 8 in these patients. In the remaining 2 patients, the drainage region of V5 was visualized at high signal intensity, concomitant with the high intensity of segment 8.

Clinical outcome. The postoperative courses of the 7 donors of a left liver graft were uneventful; all patients were discharged within 2 weeks. The postoperative courses of 5 of the 8 right liver graft recipients were also uneventful. Three recipients died after transplantation between PODs 12 and 153, secondary to acute rejection, graft-versus-host disease, and exacerbation of hepatitis C virus infection. No sign of acute congestion or acute hepatic dysfunction was present in this study.

DISCUSSION

In hepatic surgery, ligation of the hepatic venous tributaries is not thought to compromise liver function because of the presence of multiple intrahepatic venous communications between adjacent hepatic veins.[16] After ligation of hepatic veins, areas of potential venocongestion can contribute to the dysfunctional volume of a remnant liver. In a right liver graft without the MHV, it remains controversial as to whether adequate venous drainage of the right anterior sector can be provided by a single hepatic vein in concert with the development of

intrahepatic venous anastomoses between the MHV and RHV.[17,18] A consensus does not yet exist regarding the optimal strategy for venous reconstruction of the MHV tributaries.

Couinaud and Nogueira[19] demonstrated hepatic venous communication in 25 of 30 liver casts by injecting vinyl polychloride into the hepatic veins of autopsied livers. Lasinski and Zientarski[20] found venous anastomosis between the MHV and RHV in half of the examined cases. Nevertheless, these venous anastomoses may not always function immediately after occlusion of the hepatic veins.

In this study, we used color Doppler US to investigate the formation of intrahepatic venous anastomoses between the MHV tributaries and the RHV, as well as the portal venous flow of the right anterior sector. We found that most of the MHV tributaries had developed intrahepatic anastomoses with the RHV after POD 14 during the latter stages of observation (94% in V5 and 100% in V8). Nevertheless, the rate of development of the collaterals differed between the 2 MHV tributaries. During the 1st postoperative week, the intrahepatic venous anastomoses formation rate of V8 was 77% and 27% for V5. In contrast, after the 2nd week, the anastomosis formation rate for V8 was 23%, whereas the rate for V5 was 68%. These results indicate that anastomoses with the RHV develop earlier in V8 than in V5. This finding complements Couinaud's anatomic study of liver casts.[21] He described a prominence of intrahepatic venous anastomoses between the MHV and RHV, especially in segment 8. This finding can be understood from an anatomic standpoint given that the distance between V8 and the RHV in segment 8 is shorter than that between V5 and RHV. The difference in the rate of formation of collaterals between V5 and V8 seems to be therefore a reasonable finding. The mean flow velocity in V8 did not differ from that in V5.

Development of venous anastomoses is influenced invariably by the pattern of venous drainage of the right liver graft. Substantial anatomic variations in the venous drainage of the anterior section have been found. Segment 5 is drained exclusively by the MHV, whereas the dorsal portion of segment 8 is drained reportedly by the RHV in 28% to 35% of patients.[21,22] The grafts in these cases were RHV dominant, and the MHV tributary from the ventral portion of segment 8 was considered to communicate more easily with the RHV.

In this study, hepatofugal venous flow in the portal branch was observed in 6 of 15 livers of P5 during the 1st week after transplantation. In contrast, hepatofugal flow was observed in only 1 of 13 livers of P8 during the 1st postoperative week. The reversal of portal branch venous flow was thought to have impaired the liver regeneration. According to Maema et al,[23] right liver grafts without the MHV had impaired volume regeneration of the right anterior sector when compared with grafts with the MHV preserved. Volume regeneration between segment 5 and segment 8 was not, however, investigated by this group. On the basis of our findings, impaired volume regeneration appears to have been caused primarily by altered venous flow in segment 5. Furthermore, the mean velocity of V5 and V8 correlated closely with the mean velocity of P5 and P8. Consequently, a deficiency of portal venous blood flow in the interrupted venous portion during the postoperative period may be an important factor in compromising the regeneration of the right anterior sector without the MHV.[24] We based this deduction on our long-term postoperative findings.

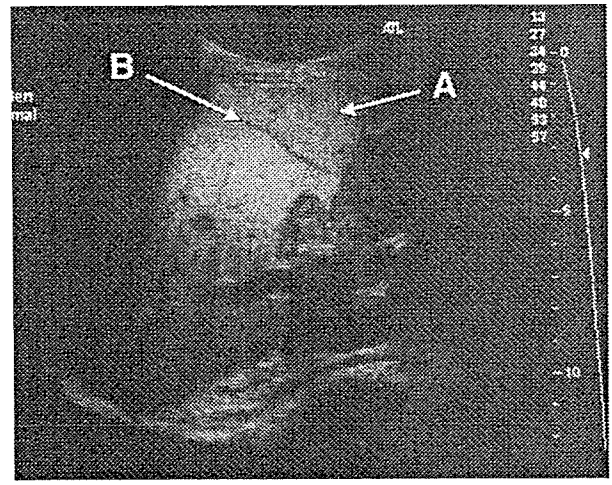

Fig 2. Pulse-inversion harmonic US with Levovist in the liver parenchymal phase of 1 recipient on POD 54. Perfusion in V5 drained area (**A**) was reduced.; V5 (**B**).

In our Doppler US examinations, we investigated the portal venous blood flow up to the 3rd-ordered branch as far as patients could tolerate. In some patients, however, we may have measured proximal portal branch flow that included the well-drained area of segment 8 and the venoocclusive area. Using Doppler US, we found a close correlation between the mean flow velocity of hepatic venous branches and the portal venous branches. Although the points at which these velocities were measured corresponded well between these 2 systems, they were not matched completely with regard to vessel proximity. Nevertheless, the correlation coefficient between mean values was

quite high ($r > 0.9$). This finding warrants further investigation, using a larger number of patients.

The study using pulse-inversion harmonic US revealed decreased hepatic parenchymal perfusion in segment 5 in 4 of 6 of patients, compared with segment 8. This finding suggests that the functional anastomoses between V5 and RHV were less effective than those between V8 and RHV. Even though the number of patients studied was small and the date of the studies varied, we were able to detect a difference in hepatic parenchymal perfusion using a new technique involving Pulse-inversion mode US with Levovist. Furthermore, we consider our findings on hepatic perfusion to be preliminary, given that our initial intention was aimed at compiling data for a large number of patients undergoing pulse-inversion harmonic US studies with Levovist after receiving a living donor liver transplant.

In the acute phase after transplantation, transient congestion of the right anterior sector has been reported.[25] Fortunately, in our small series, we did not notice any patients with severe congestion of the right anterior sector. The degree to which potential congestion of the right anterior sector causes graft dysfunction is difficult to predict. As a result, a large graft size is preferable in patients undergoing living donor liver transplantation for liver cirrhosis. We encountered 2 patients in whom intrahepatic venous anastomoses in both V5 and V8 occurred only after 2 postoperative weeks. These patients carried the diagnosis of primary biliary cirrhosis and liver cirrhosis secondary to hepatitis B virus infection. Neither patient had obvious signs of hepatic failure, presumably because the graft sizes were sufficiently large (average graft volume/standard liver volume $\times$ 100 = 66% [52%-81%]). We also studied 2 patients in whom intrahepatic venous anastomoses in V5 formed after only 2 weeks, yet anastomoses formed in V8 during the 1st week. These 2 patients had biliary atresia and liver cirrhosis secondary to hepatitis C virus infection. Similar to the previous example, no obvious hepatic failure was observed. In the patient with biliary cirrhosis, the graft size was rather small (graft volume/standard liver volume $\times$ 100 = 45%). In this latter patient, we suspect that the metabolic function of segment 8 may have compensated for a presumed lack of adequate function of segment 5 during the acute phase of transplantation. These findings suggest that the gradual formation of intrahepatic venous anastomoses over time may preclude or relieve venous outflow obstruction and congestion of the right anterior section.[26] When graft size is small, areas of graft congestion may translate into greater adverse effects on liver function and potentially unfavorable clinical consequences. Presently, it is difficult to determine whether intrahepatic collateral circulation will be adequate during acute decompression of the right anterior sector.[21] Therefore, it is preferable to reconstruct V5 or V8 when the graft size is small. On the basis of this study's finding, we would choose to reconstruct V5 rather than V8 because intrahepatic venous anastomoses were found to develop later in V5 than in V8.

This study has several limitations. We assumed that the intrahepatic hemodynamics and anatomy of the right liver were essentially the same between recipients of a right liver graft without the MHV and donors of a left liver graft with the MHV. One caveat of this assumption is that the right liver remnant of a donor has preserved venous drainage through the short hepatic veins from the caudate lobe, whereas the right liver graft does not. Nevertheless, the right anterior sector is drained primarily by branches of the MHV, and the significance of short hepatic venous drainage in this sector, or lack thereof, has yet to be established. Another qualification of this study is that preexisting portal hypertension in the recipients of the right lobe graft in comparison with healthy left liver donors may have affected the rate and significance of collateral development. This possibility warrants further investigation.

We also made attempts to eliminate differences caused by variations in graft size of the right liver, knowing that the size of right liver grafts tend to vary widely and may alter the development of collaterals. In this study, the smallest percentage of graft weight compared with standard liver volume was 45%. Small-for-size cases did not exist.

The formation of intrahepatic venous collaterals was also undoubtedly regulated by anatomic and mechanical factors. The hepatic venous system is a low-pressure system. Alterations in hepatic parenchymal consistency likely influence intrahepatic venous flow. It is reasonable to hypothesize that complications after transplantation, such as infection and rejection, could influence the formation of intrahepatic venous anastomoses by changing the hepatic parenchyma. These issues warrants further investigation in the future.

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