日集中医誌. 2007;14:551～554.

心臓移植の術後急性期管理

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要約：2006年末までに20例の心臓移植を経験したので，その術後急性期管理について報告する。原疾患は19例が拡張型心筋症で，18例で左心補助人工心臓が装着されていた。ICU入室直後から9例でイソプロテレノールを投与するとともに，全例で心臓ペーシングを行い心拍数を調節した。全例でドパミンなどのカテコラミンとヒト心房性ナトリウム利尿ペプチドを投与した。肝腎機能に問題のない症例ではシクロスポリン（またはタクロリムス），ミコフェノール酸モフェチル，メチルプレドニゾロンの三者併用免疫抑制療法を行い，肝腎機能障害を呈した症例ではムロモナブ-CD3で免疫抑制を導入した。全例バイオクリーンルームに収容し，カテーテル類の早期抜去に努めた。全例順調に回復し，平均8日でICUを退室した。心臓移植術後の治療は，除神経心に配慮した呼吸・循環管理と腎機能の保護が肝要となる。

Key words: ① heart transplantation, ② denervated heart, ③ atrial natriuretic peptide

Ⅰ．はじめに

本邦では1997年の「臓器の移植に関する法律」施行後，2006年末までに39例の脳死心臓移植が行われ，そのうち当施設は20例を経験した。症例数は少ないものの心臓移植後の生存率は欧米を上回っている[1),2)]。以前，心臓移植術後2例の腎機能の保持と除神経心に対する循環管理の重要性を報告したが[3)]，今回，当施設における心臓移植の術後急性期管理について概説する。

Ⅱ．症例と急性期管理

症例は男性16例，女性4例。平均年齢40歳，原疾患は拡張型心筋症19例（うち2例は心サルコイドーシスによるもの），拡張相肥大型心筋症1例であった（Table 1）。20例中18例で左心補助人工心臓（left ventricular assist system, LVAS）が装着され，LVAS装着期間は707 ± 398日，最長1,444日であった。心臓移植術式は両大静脈吻合法変法[4)]18例，両大静脈吻合法1例，Lower-Shumway法1例であった。

1）循環管理

ICU入室時の循環動態は，心拍数102 ± 10 beat·min^{-1}，平均動脈圧73 ± 9 mmHg，中心静脈圧9 ± 4 mmHg，心係数3.0 ± 1.0 l·min^{-1}·m^{-2}，混合静脈血酸素飽和度68 ± 5 %であった。

ICU入室時，心不全予防あるいは治療目的でドパミン（4.1 ± 1.2 μg·kg^{-1}·min^{-1}）を全例に投与し，またノルエピネフリン（0.14 ± 0.04 μg·kg^{-1}·min^{-1}）を6例，エピネフリン（0.12 ± 0.08 μg·kg^{-1}·min^{-1}）を3例，ドブタミン（4.2 μg·kg^{-1}·min^{-1}）を1例に投与していた。症例5ではドナー管理に大量のカテコラミンを投与していたため，人工心肺離脱時にエピネフリン（0.09 μg·kg^{-1}·min^{-1}）を必要とした。症例12では低血圧に対しノルエピネフリン（0.2 μg·kg^{-1}·min^{-1}）を必要とし，ICU入室後に肺動脈圧（平均）が60/31（43）mmHgまで上昇したが，肺胞虚脱や高炭酸ガス血症が肺血管抵抗を増大させた可能性を考え，PEEP 8 cmH_2Oで軽度の過換気（$PaCO_2$ 33 mmHg）を行ったところ，改善した。症例13ではドナー心の虚血時間が255分と長かったためか，肺高血圧を伴う右心不全を呈した。PEEP調節や過換気が奏効しなかったため，一酸化窒

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受付日 2006年12月 6日
採択日 2007年 3月22日

Table 1 Patients' profiles

Case	Age	BW (kg)	Gender	Diagnosis	Duraion of LVAS support (day)	Ischemic time of donor heart (min)	Duration of CPB (min)	Duration of surgery (min)	Blood loss (ml)	Transfusion volume (ml)	ARF	On the admission to ICU				
												ISP	NE	EPI	MIL	DOB
1	40's	49	M	DCM	39	226	146	559	5,400	5,000		Yes				
2	20's	60	M	DCM	—	215	176	398	800	2,400	Yes	Yes				Yes
3	40's	47	F	DCM	227	209	147	480	2,850	3,450	Yes	Yes				
4	10's	42	M	DCM	319	210	161	566	6,930	5,790	Yes	Yes				
5	50's	46	M	DCM	618	212	211	650	4,102	4,460		Yes		Yes		
6	30's	62	M	DCM	669	188	159	600	2,096	4,340	Yes/ CHDF					
7	20's	45	M	DCM	500	223	134	515	2,076	2,420		Yes				
8	30's	60	M	DCM	—	208	130	290	2,030	2,040	Yes	Yes				
9	30's	64	M	DCM	993	137	152	605	5,580	6,340	Yes					
10	40's	56	M	dHCM	838	229	142	615	2,145	3,720						
11	50's	35	F	DCM	99	206	99	465	1,950	6,680		Yes	Yes			
12	60's	50	M	DCM	1,227	185	127	550	3,000	5,360			Yes			
13	40's	57	M	DCM	1,057	255	190	640	1,700	4,600	Yes			Yes	Yes	
14	40's	63	M	DCM*	1,171	207	123	560	4,660	5,100			Yes			
15	30's	48	M	DCM	964	166	136	475	3,445	3,870						
16	30's	50	M	DCM	597	225	105	485	3,000	4,566		Yes				
17	20's	36	F	DCM	867	210	210	645	6,260	9,680			Yes			
18	50's	67	M	DCM*	1,444	213	113	595	3,800	8,230						
19	50's	57	M	DCM	674	220	193	710	3,185	8,464	Yes		Yes	Yes	Yes	
20	30's	40	F	DCM	417	181	134	620	5,000	8,200			Yes			
Average		52			707	206	149	551	3,500	5,236						

BW, body weight; LVAS, left ventricular assist system; CPB, cardiopulmonary bypass; M, male; F, female; DCM, dilated cardiomyopathy; dHCM, dilated-phase hypertrophic cardiomyopathy; DCM*, DCM secondary to myocardial sarcoidosis; ARF, acute renal failure; CHDF, continuous hemodiafiltration; ISP, isoproterenol; NE, norepinephrine; EPI, epinephrine; MIL, milrinone; DOB, dobutamine.

素吸入療法を開始するとともにエピネフリン(0.21 $\mu g \cdot kg^{-1} \cdot min^{-1}$), ミルリノン (0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) を投与した。症例14ではドナー心のサイズがレシピエントに対して小さく(サイズミスマッチ), 術後1日目に心原性肺水腫に陥ったため, 血管拡張作用を伴う強心薬であるミルリノン (0.66 $\mu g \cdot kg^{-1} \cdot min^{-1}$), ドブタミン (3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) を開始した[5]。

術中から14例で, ICU入室中には全例で心房ペーシング (心拍数80～110 beat·min^{-1}) を行い, 無効例 (3例)で心房心室順次ペーシングあるいは心室ペーシングを行った。加えて, 除神経心の洞性調律・房室伝導を促進するため, イソプロテレノール (0.02 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$) を9例で投与した。

2) 呼吸管理

通常の開心術後と同様, 同期式間欠的強制換気とプレッシャーサポート換気を併用した。術中に大量輸血・輸液を必要としたが人工呼吸離脱は概ね円滑で, 持続的気道内陽圧4 cmH_2O, プレッシャーサポート10 cmH_2O の補助の下, 呼吸・循環動態が落ち着いた段階で離脱した。症例13では右心不全と覚醒遅延のため離脱に77時間を要した。症例14では入室15時間後に一旦離脱できたが, サイズミスマッチおよび創痛による後負荷増大のため心原性肺水腫に陥り再挿管となり, 人工呼吸は延べ102時間となった[5]。症例19でも軽度のサイズミスマッチが認められたため, 呼吸器離脱を緩徐に進め, 45時間を要した。以上3症例を除く人工呼吸期間は12 ± 7時間 (3～28時間) であった。

3) 腎機能の推移

血清クレアチニン値の推移をFig. 1に示す。術前, 血清クレアチニン値が1.5 mg·dl^{-1} を上回る腎機能障害を3例に認めた。また術後血清クレアチニン値が術前値より50%以上上昇した急性腎機能障害を8例に認めたが, いずれも腎機能は改善し, ICU退室時の血清クレアチニン値は0.83 ± 0.27 mg·dl^{-1} に低下した。全例でICU入室時よりヒト心房性ナトリウム利尿ペプチド(human atrial natriuretic peptide, hANP) (0.07 ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$) を併用し, 16例ではICU退室後も投与を継続した。これは, 初期の2例で腎機能障害や尿量低下を認めたとき, hANPが有効であったためである[3]。症例6ではシクロスポリンによる急性腎機能障

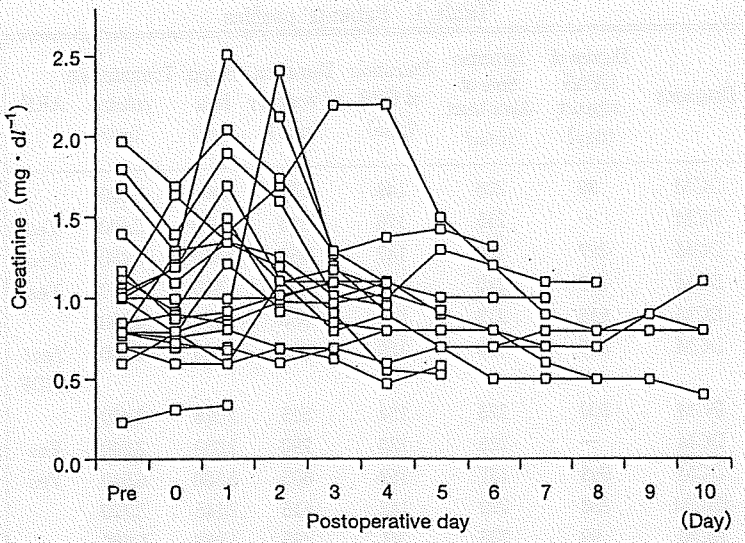

Fig. 1 Time course of serum creatinine before and after heart transplantation

害を呈し12時間の血液濾過透析を要したが，シクロスポリンを中止しhANPを増量することにより，腎機能は回復した。

4) 免疫抑制療法

肝腎機能が正常な場合，免疫抑制療法としてシクロスポリン（あるいはタクロリムス），ミコフェノール酸モフェチル，メチルプレドニゾロンの三者併用療法を行った。術前より肝腎機能障害を呈した5例では，リンパ球特異抗原CD3モノクローナル抗体のムロモナブ-CD3とメチルプレドニゾロンで免疫抑制を導入した。また移植後早期に腎機能障害を起こした1例では，ムロモナブ-CD3とステロイドに切り換えた。6例とも肝腎機能および呼吸・循環動態の推移を見ながら三者併用療法に移行した[6]。

5) 感染対策

ICUではバイオクリーンルームに収容し，接触する医療従事者を医師1名，看護師1名に制限した上，各種カテーテルやドレーンの早期抜去，ならびに抜管後の早期離床とリハビリテーションに努めた。術前LVAS装着例が多いため，多剤耐性ブドウ球菌の感染予防を目的にトラフ値を測定しながらバンコマイシン（あるいはテイコプラニン）を用い，人工呼吸管理中はアズトレオナムを併用した。

全例良好に経過し，急性拒絶を起こすことなく，平均ICU在室期間8±5日で移植病棟へ退室した。

Ⅲ. 考　察

当施設の心臓移植20例の術後急性期管理について報告した。呼吸・循環管理上の注意点は，①除神経心であること，②手術や虚血による洞結節･伝導系障害の可能性，③移植心の一時的な機能低下，④レシピエント側の肺高血圧である[7,8]。①②に対しては，イソプロテレノールの投与あるいは心臓ペーシングを用いることにより心拍数を調節した。③に対しては，心不全の予防目的にドパミンなどのカテコラミンを投与した。ドナー心の機能は基本的に正常であるが，ドナー心摘出前の大量カテコラミン投与，長時間の心筋虚血や臓器保存により，ドナー心機能の低下が起きるため，心不全に対する治療が必要となる。④については，1例で肺高血圧，1例で肺高血圧に伴う右心不全を呈したが，PEEP，過換気，一酸化窒素吸入で対応可能であった。肺血管抵抗や移植心機能の評価のため全例に肺動脈カテーテルを挿入し，経胸壁心エコーを施行した。

呼吸管理については，人工呼吸器関連肺炎予防のため早期抜管を目指した。長時間手術，大量の輸血・輸液にもかかわらず，人工呼吸からの離脱は速やかで，12時間を越えたのは，覚醒遅延，血圧不安定，高乳酸血症，移植心のサイズミスマッチ，腎機能障害などが理由であった。

術前あるいは術後免疫抑制薬使用による腎機能障害に留意し，積極的にhANPを併用した。心臓移植後は容量負荷に対するhANPの反応が鈍く[9,10]，エンドセリンの上昇に対してhANPが相対的に不足している[11]。また心臓移植後の急性腎不全へのhANP投与は，血液透析の頻度や期間を軽減し，シクロスポリンによる腎機能障害を改善すると報告されている[12)~14]。当施設では全例でhANPを投与したため，その腎機能改善効果の判定は困難であるが，2症例でhANP減量と一致して腎機能低下を経験している[3]。

以上，心臓移植の術後急性期管理のポイントを概説した。除神経心である移植心の心機能維持と随伴しやすい腎機能低下を考慮した呼吸・循環管理が肝要である。

本稿の要旨は，第50回日本集中治療医学会近畿地方会（2005年，奈良）において発表した。

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Abstract

Intensive care after heart transplantation

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We present a summary of the intensive care provided to 20 patients who underwent heart transplantation at the National Cardiovascular Center. Nineteen patients suffered from dilated cardiomyopathy, of which 18 had been supported by a left ventricular assist system. In the ICU, cardiac pacing was applied in all patients, with 9 patients requiring isoproterenol infusion in addition, to maintain an appropriate heart rate. All patients received infusions of low-dose of dopamine and atrial natriuretic peptide. The immunosuppression regimen consisted of cyclosporine (or tacrolimus), mycophenolate mofetil, and methylprednisolone in the patients with normal hepatorenal function. Earliest removal of catheters and tubes was always attempted at the ICU. Most of the patients were discharged from the ICU and transferred to the ward on postoperative day 8, without any serious events. In addition to the conventional intensive care provided to patients undergoing open heart surgery, management of the denervated heart and preservation of renal function are important targets of acute care in patients undergoing heart transplantation.

Key words: ① heart transplantation, ② denervated heart, ③ atrial natriuretic peptide

J Jpn Soc Intensive Care Med. 2007;14:551～554.

胸部外科 60：958～962, 2007

特集：心・肺移植後の合併症

心移植術後急性期の合併症と問題点

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「胸部外科」 第60巻 第11号〔2007年10月号〕 別刷

——南　江　堂——

心移植術後急性期の合併症と問題点

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はじめに

本センターでは2006年末までに20例の心移植術を経験した．本稿ではこれらの症例を通じ，術後急性期の合併症，ICU管理の問題点についてまとめる．

20例の内訳は，男性16例，女性4例，平均年齢40歳である（表1）．原疾患は拡張型心筋症19例（うち2例は心サルコイドーシスによるもの），拡張相肥大型心筋症1例であった．20例中18例で左心補助人工心臓（left ventricular assist system：LVAS）が装着され，LVAS装着期間は707±398日であった．心移植術式は第1例でLower-Shumway法，その後の1例で両大

表1．心移植術施行20例の患者背景

症例	年齢・性（歳）	病名	LVAS補助期間（日）	ドナー心の虚血（分）	体外循環時間（分）	手術時間（分）	出血量（ml）	輸血量（ml）	腎不全
1	40's・男	DCM	39	226	146	559	5,400	5,000	
2	20's・男	DCM	—	215	176	398	800	2,400	(+)
3	40's・女	DCM	227	209	147	480	2,850	3,450	(+)
4	10's・男	DCM	319	210	161	566	6,930	5,790	(+)
5	50's・男	DCM	618	212	211	650	4,102	4,460	
6	30's・男	DCM	669	188	159	600	2,096	4,340	(+)/CHDF
7	20's・男	DCM	500	223	134	515	2,076	2,420	
8	30's・男	DCM	—	208	130	290	2,030	2,040	(+)
9	30's・男	DCM	993	137	152	605	5,580	6,340	(+)
10	40's・男	dHCM	838	229	142	615	2,145	3,720	
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12	60's・男	DCM	1,227	185	127	550	3,000	5,360	
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17	20's・女	DCM	867	210	210	645	6,260	9,680	
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19	50's・男	DCM	674	220	193	710	3,185	8,464	(+)
20	30's・女	DCM	417	181	134	620	5,000	8,200	
平均	40		707	206	149	551	3,500	5,236	

LVAS：左心補助人工心臓（left ventricular assist system），DCM：拡張型心筋症（dilated cardiomyopathy），dHCM：拡張相肥大型心筋症（dilated-phase hypertrophic cardiomyopathy），DCM*：心筋サルコイドーシスに続発した拡張型心筋症，CHDF：持続血液濾過透析（continuous hemodiafiltration）

キーワード：心移植，サイズミスマッチ，腎機能障害，ヒト心房性ナトリウム利尿ペプチド

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表2. ICU入室時の血管作動薬

血管作動薬	症例数	使用量
dopamine	20	4.1± 1.2 μg/kg/分
isoproterenol	9	0.02± 0.01 μg/kg/分
norepinephrine	6	0.14± 0.04 μg/kg/分
epinephrine	3	0.12± 0.08 μg/kg/分
hANP	20	0.067±0.028 μg/kg/分
nitroglycerin	15	0.40± 0.11 μg/kg/分
milrinone	2	0.37± 0.10 μg/kg/分

hANP：ヒト心房性ナトリウム利尿ペプチド

静脈吻合法，18例で同変法とした[1]．

Ⅰ．循環面の問題点

心移植術後の問題点として，①除神経心，②移植心の一時的な機能低下，③レシピエント側の肺高血圧，④サイズミスマッチがあげられる．

1．除神経心であること

移植心は除神経心であり，また手術や心筋虚血によっても洞結節・伝導系障害を起す可能性がある．そのため，14例では術中から，全例でICU入室中に心房ペーシング（心拍数80～110拍/分）を試み，無効例（3例）では心房心室順次ペーシングあるいは心室ペーシングを行った．さらに洞調律・房室伝導を促進する目的でisoproterenolを9例で投与した．

2．移植心の一時的な機能低下

ドナー心の機能は基本的に正常であるものの，ドナー心摘出前の大量のカテコラミン投与，長い心筋虚血，臓器保存の問題などでドナー心機能の低下が起るため，カテコラミン投与など心不全に対する治療が必要となる．そのためICU入室時，dopamineを全例に投与し，norepinephrineを6例，epinephrineを3例，dobutamineを1例に投与した（表2）．その結果，ICU入室時の心拍数102±10拍/分，平均動脈圧73±9 mmHg，中心静脈圧9±4 mmHg，心係数3.0±1.0 l/分/m^2，混合静脈血So_2 68±5%と，循環動態はおおむね良好であった．

3．レシピエント側の肺高血圧

長期間の左心不全により，レシピエント側に肺高血圧が進行することがある．そこにドナー心機能低下が合併すれば右心不全が問題となる．実際，2例で肺高血圧およびそれに伴う右心不全を呈した．幸い，呼気終末陽圧（positive end-expiratory pressure：PEEP）増加や，軽度の過換気，一酸化窒素吸入，カテコラミン増量で改善させることができた．

4．サイズミスマッチ

心移植のレシピエント候補を選択するさい，ドナーとレシピエントの体重差は－20%～＋30%が望ましいとされる[2~5]．サイズミスマッチが原因で心原性肺水腫が発症したと考えられる症例を1例経験した（図1）[6]．ドナーの体重はレシピエントの約－30%であったが，1ヵ月前の体重を基準とすれば－20%以内であった．入室後順調に呼吸器を離脱し抜管した．抜管時，血圧115/74 mmHg，平均肺動脈圧17 mmHg，中心静脈圧5 mmHg，心係数1.9 l/分/m^2，体血管抵抗2,250 dynes・秒/cm^5であった．抜管後，創痛の訴えが強く創痛コントロールはむずかしかった．抜管10時間後より収縮期血圧が80 mmHg台に低下し，心係数は1.6～1.8 l/分/m^2へ低下し，体血管抵抗は2,000 dynes・秒/cm^5を超えていた．12時間後には低酸素血症が進行し再挿管となった．胸部X線像で肺水腫像が，経食道心エコーで心機能低下が認められた．そこで，morphine hydrochloride持続投与による創痛コントロール，milrinone，dobutamine，ヒト心房性ナトリウム利尿ペプチド（hANP）追加投与により後負荷の軽減，心収縮力の増加を図ったところ心係数が増加し，体血管抵抗が減少した（図1）．血行動態の安定化を得てから術後5日目に抜管し，その後は順調に経過した．

本例において左心不全の原因は，サイズミスマッチ，搬送を必要とする移植手術に伴う心筋収縮力の低下，創痛による後負荷の増大が過大であったことが考えられる．心室の容量が小さいと，前負荷や後負荷に対する許容範囲が狭くな

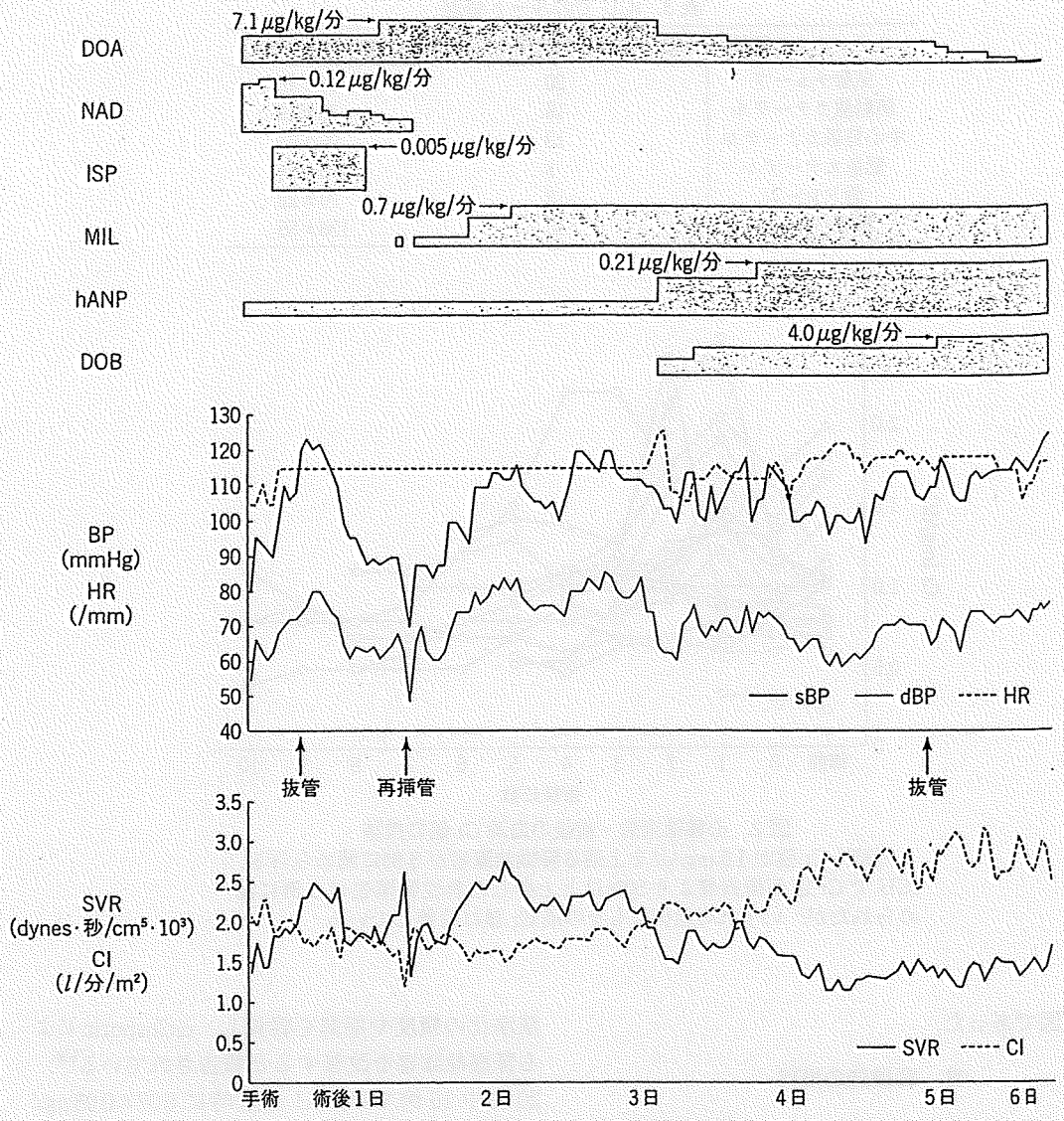

図1. サイズミスマッチ例での血行動態

DOA：dopamine，NAD：noradrenalin，ISP：isoproterenol，MIL：milrinon，hANP：ヒト心房性利尿ペプチド，DOB：dobutamine，BP：血圧，sBP：収縮期血圧，dBP：拡張期血圧 BP，HR：心拍数，SVR：体血管抵抗，CI：心係数

る．前負荷の許容範囲が狭いところへ，血圧維持のために投与されていたnorepinephrineや創痛による交感神経の興奮により後負荷が増大し，心不全に陥ったと考えている．

Ⅱ．呼吸管理

心移植術後では人工呼吸関連肺炎を防ぐために可及的速やかな呼吸器離脱と抜管が必要である．通常の開心術後例と同様，人工呼吸モードとしては同期式間欠的強制換気とプレッシャーサポート換気を併用した．ほとんどの症例では人工呼吸からの離脱は円滑で，循環動態が落ちついた段階で抜管することができた（表3）．ただし，右心不全と覚醒遅延を起した症例では抜管に77時間を要し，上記のサイズミスマッチの症例では延べ102時間の人工呼吸となった．挿管時間が12時間を超えた症例を振り返ると，覚醒遅延，血圧不安定，高乳酸血症，サイズミスマッチ，腎機能障

表3. ICUでのルート管理

カテーテルの種類	ICU在室中に抜去できた症例数	挿入期間(時間)
気管チューブ	20	21±26
肺動脈カテーテル	19	33±19
中心静脈カテーテル	10	95±53
動脈カテーテル	8	175±54
創ドレーン	13	70±22
尿道バルーン	10	136±85

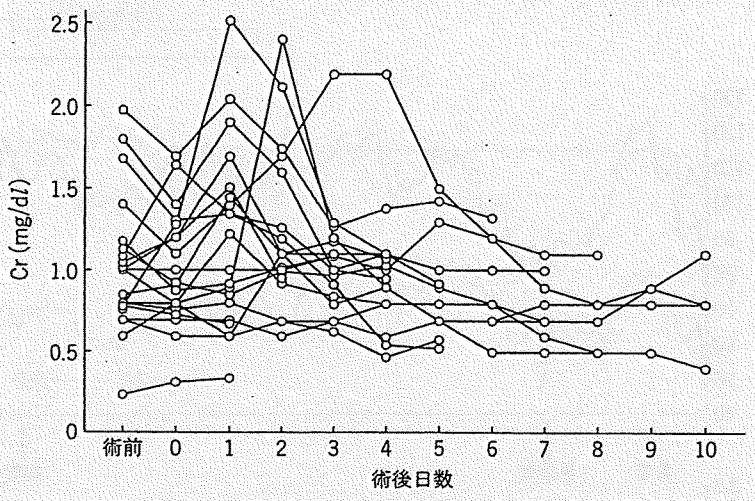

図2. 心移植術前・術後の血清Cr値の推移
術前，Cr値が1.5 mg/dlを上回る腎機能障害が3例に認められる．ICUでCr値が術前値より50%以上上昇した急性腎障害は8例に認められたが，いずれの症例でもその後Cr値は改善している．

害が原因であった．

Ⅲ．腎機能の推移

血清Cr値の推移を図2に示す．術前，Cr値が1.5 mg/dlを上回る腎機能障害が3例に認められた．また，ICU滞在中にCr値が術前値より50%以上上昇した急性腎機能障害は8例に認められたが，その後全例でICU退室までに腎機能は改善した．術前からの腎機能障害や免疫抑制薬による腎機能障害に留意し，積極的にhANPを用いた．これは，初期の2例で一時的な腎機能障害を起したときにhANPが有効であった経験をしたためである[7]．症例6ではciclosporinによる急性腎機能障害を呈し12時間の持続的血液濾過透析を要したが，ciclosporinを中止しhANPを増量することにより回復した．文献上も，心移植後の急性腎不全に対するhANPは血液浄化の頻度や期間を軽減し，ciclosporinによる腎機能障害を改善すると報告されている[8,9]．20例中16例ではICU退室時に0.07±0.03 μg/kg/分の投与を継続した．

Ⅳ．免疫抑制療法と感染対策

肝腎機能が正常な場合，免疫抑制療法としてciclosporin（あるいはtacrolimus），mycophenolate mofetil，methylprednisoloneの三者併用療法を行った．術前より肝腎機能障害を呈した症例ではmuromonab-CD3で免疫抑制を導入した．全例バイオクリーンルームに収容し，早期抜管，カテーテル類の早期抜去に努めた（表3）．

おわりに

1）心移植の術後急性期管理の問題点を概説した．

2) 移植心の心機能維持と随伴しやすい腎機能低下に配慮した呼吸循環管理が必要である.

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SUMMARY

Complications and Problems of Acute Care in Patients Undergoing Heart Transplantation

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We have experienced 20 cases of heart transplantation at the National Cardiovascular Center. We are discussing postoperative complications and intensive care for those cases. Hemodynamic problems may be summarized as the denervated heart, transient cardiac dysfunction, pulmonary hypertension in the recipient's pulmonary circulation, and donor-recipient size mismatch. In a case with donor-recipient size mismatch, cardiogenic pulmonary edema developed immediately after the tracheal extubation, probably due to wound pain and afterload mismatch. In all patients, weaning from mechanical ventilation was smooth. Prolonged mechanical ventilation seemed to result from a delay in awakening, hemodynamic instability, lactic acidosis, and donor-recipient size mismatch. Acute renal insufficiency occurred in 8 patients, while 1 patient needed 12 hours of continuous hemodiafiltration. All of the patients received infusions atrial natriuretic peptide and restored renal insufficiency.

KEY WORDS:
heart transplantation/donor-recipient size mismatch/renal insufficiency/human atrial natriuretic peptide (hANP)

Limited Sampling Strategy for Mycophenolic Acid in Japanese Heart Transplant Recipients

— Comparison of Cyclosporin and Tacrolimus Treatment —

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Background The purpose of the study was to characterize the pharmacokinetics of mycophenolic acid (MPA) in Japanese heart transplant recipients and to find the time point that has the best correlation with the MPA area under the plasma concentration curve (AUC).

Methods and Results Twenty-two Japanese recipients treated with mycophenolate mofetil were evaluated in the study. Approximately 9 months after transplantation, the area under the MPA serum concentration-time curve from 0 to 12 h (AUC_{0-12h}) was evaluated. The MPA AUC_{0-12h} values in the cyclosporine (CsA) and tacrolimus (FK) groups ranged from 13.11 to 50.98 $\mu g \cdot h/ml$ and from 39.19 to 93.18 $\mu g \cdot h/ml$, respectively. Fourteen models were developed and analyzed for their ability to estimate the MPA AUC_{0-12h} based on a limited number of samples in the CsA group. Sixteen models were developed in the FK group. The best model for predicting the full MPA AUC_{0-12h} in the CsA group was a 3-time-point model that included C_{0h}, C_{1h} and C_{2h} (r^2, 0.96; mean prediction error, 0.15±7.85%); a 2-time-point model that included C_{0h}, and C_{2h} (r^2, 0.94; mean prediction error, 0.495±10.35%) was also reliable. In the FK group, a 3-time-point model that included C_{1h}, C_{2h} and C_{4h} (r^2, 0.73; mean prediction error, 2.73±17.09%) was the best model for predicting the full MPA AUC_{0-12h}, but it was not reliable in clinical practice.

Conclusion A 3- (C_{0h}, C_{1h} and C_{2h}) and a 2-time-point model (C_{0h} and C_{2h}) are useful for predicting the full MPA AUC_{0-12h} in Japanese heart transplant recipients treated with CsA but not with FK. (*Circ J* 2007; **71**: 1022–1028)

Key Words: Heart; Mycophenolate mofetil; Pharmacokinetics; Transplantation

Mycophenolate mofetil (MMF) is widely used for the prevention of acute rejection after organ transplantation[1–3] Following oral administration, MMF is rapidly and extensively absorbed and is hydrolyzed to mycophenolic acid (MPA), the active immunosuppressive agent[4–7] Pharmacokinetic studies of MPA in transplant patients showed a large variability in pharmacokinetic parameters including the area under the plasma concentration curve (AUC), time to peak plasma concentration (t_{max}) and maximal plasma concentration (C_{max})[8–11] Several studies showed a significant relationship between the MPA AUC and the occurrence of acute rejection[5–8,12–14] A low AUC in the early post-operative period is associated with a high incidence of rejection during the first 6 months[12] Recent reports suggest that a target of 30–60 $\mu g \cdot h/ml$ might be suitable during both the early post-transplant period and maintenance therapy in heart transplant recipients[7,11,14–16] However, the routine measurement of AUC in clinical practice is very impractical and would be cost prohibitive; therefore, development of an abbreviated sampling strategy for reliable estimation of the MPA AUC is required.

The pharmacokinetics of MPA in Japanese heart transplant recipients has not been previously characterized. The purpose of this study was to characterize the pharmacokinetics of MPA in Japanese heart transplant recipients receiving concomitant cyclosporine (CsA) or tacrolimus (FK), and to find the time point that correlates best with the MPA AUC.

Methods

Patients

Twenty-two Japanese recipients were enrolled in the present study. The individuals underwent heart transplantation at the National Cardiovascular Center (13 recipients), Japan and the overseas hospital, University of California, Los Angeles, CA (9 recipients), USA between May 1999 and November 2006. The participants consisted of 21 recipients with dilated cardiomyopathy and 1 recipient in the dilated phase of hypertrophic cardiomyopathy. They were treated with MMF in addition to corticosteroids and CsA or FK as immunosuppressants. The pharmacokinetics and clinical efficacy of MPA were evaluated approximately 9

(Received November 13, 2006; revised manuscript received March 29, 2007; accepted March 30, 2007)

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Table 1 Characteristics of Study Patients

	Cyclosporine group	Tacrolimus group	p value
Number of patients	11	11	
Gender (M/F)	10/1	6/5	
Age (years)*	39.1±13.1 (15–62)	29.5±13.5 (9–55)	0.10
Weight (kg)*	55.0±6.5 (45.7–67.25)	49.6±8.5 (33.45–63.55)	0.11
Post-transplant time (days)*	273.7±12.1 (249–290)	267±23.9 (227–305)	0.42
Creatinine (mg/dl)*	0.97±0.26 (0.55–1.42)	0.76±0.21 (0.5–1.16)	0.091
Dose of immunosuppressants			
Cyclosporine ($mg \cdot kg^{-1} \cdot day^{-1}$)*	4.34±1.30 (2.60–6.54)		
Tacrolimus ($mg \cdot kg^{-1} \cdot day^{-1}$)*		0.095±0.058 (0.04–0.22)	
Prednisolone (mg)*	8.9±5.2 (2.5–20.0)	6.5±1.6 (5.0–10.0)	0.16

*Mean±SD (range).

months after heart transplantation. There were no recipients with severe gastrointestinal disorders. All research procedures were conducted according to the clinical research guidelines in our institute. All patients gave written informed consent for disclosure of their clinical data.

Medications and Therapeutic Drug Monitoring

The dose of CsA or FK was applied according to the original protocol of National Cardiovascular Center[17] CsA (Neoral, Novartis Pharma K.K., Tokyo, Japan) was initially administered at a dose of 6 $mg \cdot kg^{-1} \cdot day^{-1}$ in 2 divided doses. Thereafter, doses of CsA were adjusted to achieve trough levels of 350 to 450 ng/ml during the first month, 250 to 350 ng/ml at 2–3 months, 200 to 300 ng/ml at 4–12 months and 100 to 250 ng/ml for 13 or more months after transplantation. FK (Prograf, Astellas Pharma K.K., Tokyo, Japan) was initially administered at a dose of 0.05 $mg \cdot kg^{-1} \cdot day^{-1}$ in 2 divided doses. Thereafter, FK was administered to achieve a target trough blood level of 13 to 15 ng/ml during the first 3 months, 10 to 15 ng/ml at 4–5 months and 5 to 10 ng/ml for 6 or more months after transplantation. In addition, the doses of CsA and FK were adjusted based on the AUC during hospital admission for periodic biopsy. Plasma concentrations of both CsA and FK were measured by fluorescence polarization immunoassay (TDx, Abott Japan Co, LTDA).

MMF (Cellcept, Chugai Pharma K.K., Tokyo, Japan) was initially administered at a dose of 1 g in 2 divided doses and then a 2 to 3 g maintenance dose in accordance with the leukocyte count. Subsequent doses of MMF were based on the AUC of MPA and were adjusted during admission for scheduled biopsy.

The areas under the serum concentration time curve from 0 to 12 h (AUC_{0-12h}) of MPA approximately 9 months after transplantation were evaluated. We collected blood samples before dosing and at 1, 2, 4, 6, and 12 h after dosing from recipients taking MMF and CsA concomitantly. In addition, blood samples were obtained before dosing and at 1, 2, 4, 6, 8 and 12 h after dosing from recipients taking MMF and FK concomitantly. Approximately 1 ml of blood was collected each time from an arm vein by a disposable syringe and was transferred to a vacuum blood-collection tube. The samples were centrifuged, and harvested serum was frozen at −30° until analysis.

Measurement of Plasma MPA Concentration

Serum concentrations of MPA were measured by reverse-phase high performance liquid chromotography with the use of a minor modification of the method of Tsina et al[18] with indomethacin as an internal standard. In brief, in this modified method, an octadecylsilane, C18 column (250×46 mm inside diameter, SHIMADZU, Kyoto, Japan) was used, and the absorbance of the effluent from the column was measured at 254 nm. The mobile phase consisted of a mixture of acetonitrile and 0.05 mol/L phosphate solution (vol/vol, 60:40). With this method, the detectable concentration of MPA was 50 ng/ml, and the inter-day and intra-day coefficients of variation were less than 5%.

Pharmacokinetics Data Analysis

The MPA AUC_{0-12h} values were calculated by trapezoidal approximation. The time to maximum concentration (t_{max}) and maximum concentration (C_{max}) were derived directly from the measured values. Non-compartmental analysis was used to determine the mean residence time (MRT).

Limited Sampling Strategy Development

We searched for predictive models of the MPA AUC_{0-12h} using a multiple regression analysis based on a limited number of samples. These analyses produced equations of the form: $AUC = \alpha_1 C_1 \ldots + \alpha_n C_n + \beta$, where α_n and β are coefficients and n is the number of samples ($n \leq 3$). Data were analyzed with Statcel 2 (Excel, Visual Basic for Applications for Windows). The final limited-sampling strategy models were used to calculate the prediction error (%) in each patient using the following equation: ((estimated AUC−measured AUC)/measured AUC)×100. The variance inflation factor was calculated to check for collinearity of the models.

Results

Patient Characteristics

The characteristics of the study recipients are presented in Table 1. A total of 22 recipients were evaluated (16 male and 6 female; mean age±SD, 39.1±13.1 years (CsA group), 29.5±13.5 years (FK group); mean weight±SD, 55.0±6.5 kg (CsA group), 49.6±8.5 kg (FK group); mean post-transplant time±SD, 273.7±12.1 days (CsA group), 267±23.9 (FK group); mean serum creatinine±SD, 0.97±0.26 mg/dl (CsA group), 0.76±0.21 (FK group)). One patient had high serum creatinine in the CsA group. The mean CsA and FK dose was 4.34±1.30 $mg \cdot kg^{-1} \cdot day^{-1}$ and 0.095±0.058 $mg \cdot kg^{-1} \cdot day^{-1}$, respectively. The mean prednisolone dose in the CsA and FK groups was 8.9±5.2 mg/day and 6.5±1.6 mg/day, respectively.

MPA Pharmacokinetics in CsA- and FK-Treated Heart Transplant Recipients

Serum concentration-time profiles of MPA in the CsA

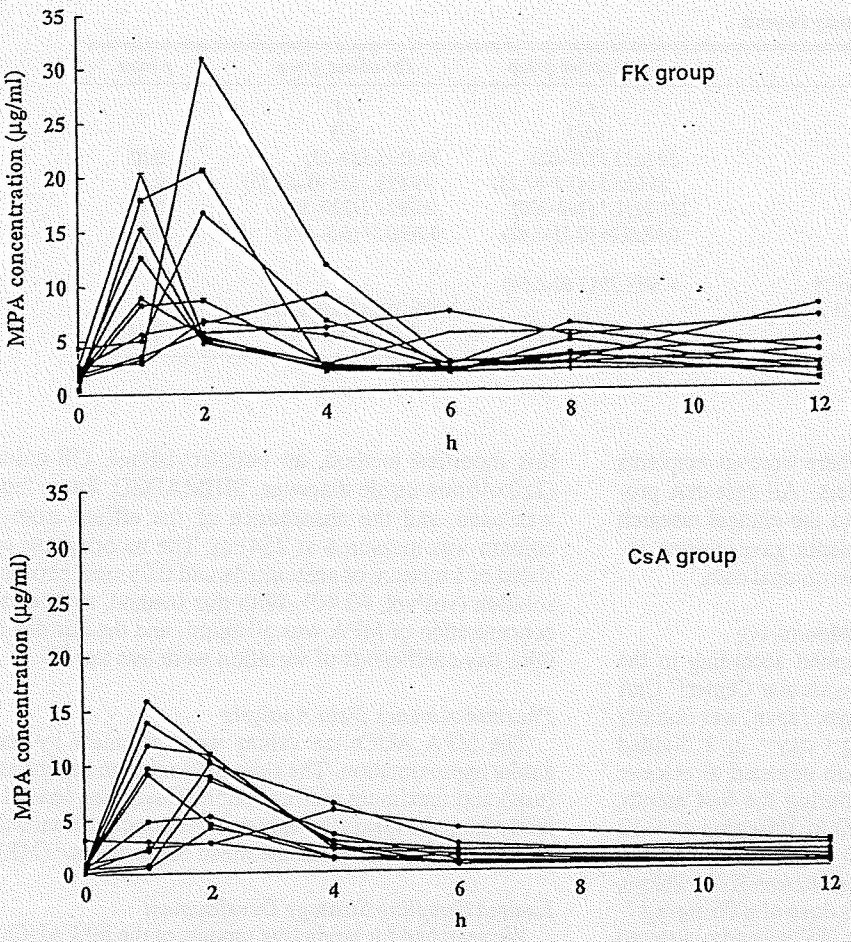

Fig 1. Mycophenolic acid (MPA) plasma concentration-time profile of Japanese heart transplant patients for tacrolimus (FK) group (Top) and cyclosporine (CsA) group (Bottom).

Table 2 MPA Pharmacokinetic Parameters in Heart Transplantation Patients (Cyclosporine Group and Tacrolimus Group)

	Cyclosporine group	*Taclorimus group*	*p value*
MMF dose (mg·kg⁻¹·day⁻¹)	*25.42±14.17 (9.29–58.82)*	*34.01±14.95 (14.95–60.42)*	*0.18*
t_{max} (h)	*1.73±0.90 (1–4)*	*2.18±1.54 (1–6)*	*0.41*
C_{max} (μg/ml)	*8.82±4.10 (2.78–15.90)*	*14.23±7.43 (6.75–30.80)*	*0.04*
MRT(h)	*3.76±0.77 (2.56–5.54)*	*4.75±0.93 (3.57–6.40)*	*0.01*
AUC_{0-12h} (μg·h/ml)	*32.57±13.07 (13.11–50.98)*	*58.55±17.51 (39.19–93.18)*	*<0.01*

Mean±SD (range).
MPA, mycophenolic acid; MMF, mycophenolate mofetil; t_{max}, time to maximum concentration; C_{max}, maximum concentration; MRT, mean residence time; AUC, area under the concentration-time curve.

and FK groups are depicted in Fig 1. The pharmacokinetic profiles of MPA were characterized by an early increase of MPA concentration with the first peak concentration reached at approximately 1 to 2 h after dosing. In the FK group, a secondary plasma peak of MPA occurred 8 h after administration. The pharmacokinetic parameters of MPA in the CsA and FK groups are presented in Table 2. The mean MMF dose in the CsA and FK groups was 25.42±14.17 mg·kg⁻¹·day⁻¹ and 34.01±14.95 mg·kg⁻¹·day⁻¹, respectively. There was no difference in the mean dose of MMF between the CsA and FK groups. The MPA AUC_{0-12h} values in the CsA and FK groups ranged from 13.11 to 50.98 μg·h/ml (mean±SD, 32.57±13.07 μg·h/ml) and from 39.19 to 93.18 μg·h/ml (mean±SD, 58.55±17.51 μg·h/ml), respectively. The mean MPA AUC_{0-12h} in the FK group was significantly higher than in the CsA group ($p<0.01$). The correlations between the dose of MMF per body weight and AUC_{0-12h} are shown in Fig 2. Significant correlations between the dose of MMF per body weight and AUC_{0-12h} of MPA were observed in the both the CsA and FK groups. The mean t_{max} in the CsA and FK groups was 1.73±0.90 h (1–4 h), 2.18±1.54 h (1–6 h), respectively. The coefficient of variation of t_{max} in the CsA and FK groups was 52.4% and 70.5%, respectively. The mean MPA C_{max} in the CsA and FK groups was 8.82±4.10 μg/ml and 14.23±7.43 μg/ml, respectively. The mean MPA MRT in the CsA and FK groups was 3.76±0.77 h and 4.75±0.93 h, respectively. The mean MPA MRT in the FK group was significantly longer than in the CsA group ($p=0.01$). In the CsA group, there were 5 recipients who had an MPA AUC_{0-12h} <30 μg·h/ml, but no recipient experienced International Society for Heart & Lung Transplantation (ISHLT) Grade III rejection. In the FK group, there was no recipient who had an MPA AUC_{0-12h} <30 μg·h/ml and no recipient experienced ISHLT Grade III rejection. In the FK group, there were 5 recipients who had an MP

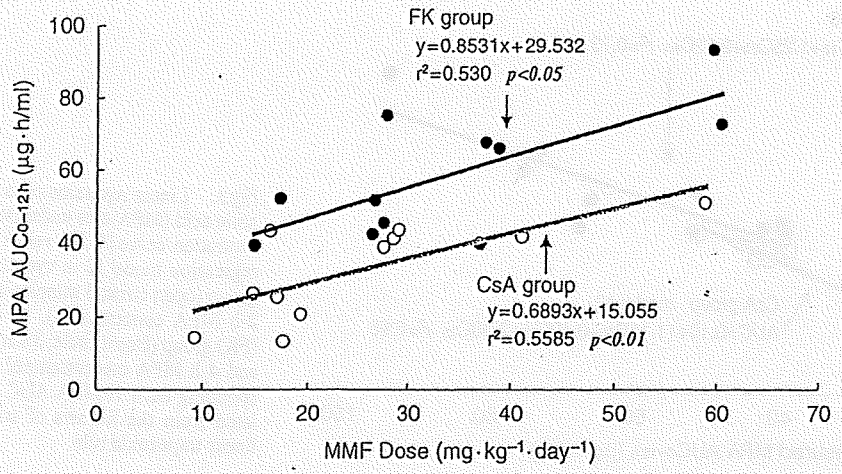

Fig 2. Relationship between mycophenolate mofetil (MMF) dose·kg^{-1}·day^{-1} and mycophenolic acid (MPA) AUC_{0-12h} for tacrolimus (FK) group (closed circle) and cyclosporine (CsA) group (open circle).

Table 3 Multiple Regression Analysis to Correlate Abbreviated MPA AUC Values With AUC Values Calculated Using the Full Set of 12 Timed MPA Concentrations (CsA Group)

Model	Sampling times (h)	Model equation	r^2	Prediction error (%)				VIF					
				Mean±SD	Within±15%	<–15%	>15%	C_{0h}	C_{1h}	C_{2h}	C_{4h}	C_{6h}	C_{12h}
1	0	$8.73C_{0h}+25.11$	0.29	15.77±48.21	1 (9.1)	5 (45.5)	5 (45.5)						
2	1	$1.40C_{1h}+23.14$	0.36	14.27±44.60	5 (45.5)	2 (18.2)	4 (36.3)						
3	2	$2.67C_{2h}+13.38$	0.46	11.30±35.83	10 (90.9)	0 (0)	1 (9.1)						
4	4	$4.00C_{4h}+21.39$	0.28	31.57±6.97	9 (81.8)	1 (9.1)	1 (9.1)						
5	6	$8.18C_{6h}+20.24$	0.43	12.94±39.31	3 (27.3)	3 (27.3)	5 (45.5)						
6	12	$13.64C_{12h}+18.93$	0.54	11.90±42.13	4 (36.3)	3 (27.3)	4 (36.3)						
7	0,1	$15.34+8.92C_{0h}+1.43C_{1h}$	0.66	7.53±27.91	5 (45.5)	2 (18.1)	4 (36.3)	1.00	1.00				
8	0,2	$-0.51+11.47C_{0h}+3.24C_{2h}$	0.94	0.49±10.35	10 (90.9)	0 (0)	1 (9.1)	1.04		1.04			
9	0,4	$21.31+5.36C_{0h}+2.39C_{4h}$	0.35	14.42±42.57	10 (90.9)	0 (0)	1 (9.1)	1.74			1.74		
10	0,6	$19.27–4.90C_{0h}+11.60C_{6h}$	0.44	12.68±40.79	3 (27.3)	3 (27.3)	5 (45.5)	5.55				5.55	
11	0,12	$18.80–2.38C_{0h}+15.81C_{12h}$	0.55	12.02±43.02	5 (45.5)	3 (27.3)	3 (27.3)	2.78					2.78
12	0,1,2	$0.10+11.15C_{0h}+0.42C_{1h}+2.80C_{2h}$	0.96	0.15±7.85	11 (100)	0 (0)	0 (0)	1.68	1.06	1.61			
13	0,2,4	$-0.23+12.70C_{0h}+3.36C_{2h}–0.80_{4h}$	0.94	0.36±9.80	10 (90.9)	0 (0)	1 (9.1)	1.23		2.04	2.08		
14	1,2,4	$1.28+1.91C_{1h}+0.26C_{2h}+5.91C_{4h}$	0.95	0.77±7.94	10 (90.9)	0 (0)	1 (9.1)		2.21	2.02	1.43		

CsA, cyclosporine; VIF, variance inflation factor. Other abbreviations see in Table 2.

Table 4 Multiple Regression Analysis to Correlate Abbreviated MPA AUC Values With AUC Values Calculated Using the Full Set of 12 Timed MPA Concentrations (FK Group)

Model	Sampling times (h)	Model equation	r^2	Prediction error (%)				VIF						
				Mean±SD	Within±15%	<–15%	>15%	C_{0h}	C_{1h}	C_{2h}	C_{4h}	C_{6h}	C_{8h}	C_{12h}
1	0	$1.53C_{0h}+55.48$	0.01	7.96±30.17	6 (54.5)	3 (27.3)	2 (18.2)							
2	1	$-0.23C_{1h}+60.75$	0.01	8.03±30.64	3 (27.3)	3 (27.3)	5 (45.5)							
3	2	$1.66C_{2h}+41.16$	0.65	3.50±20.06	6 (54.5)	2 (18.2)	3 (27.3)							
4	4	$2.97C_{4h}+44.54$	0.32	5.84±26.97	5 (45.5)	2 (18.2)	4 (36.3)							
5	6	$3.03C_{6h}+49.93$	0.10	7.03±27.03	4 (36.3)	3 (27.3)	4 (36.3)							
6	8	$5.90C_{8h}+36.99$	0.22	5.71±22.48	6 (54.5)	1 (9.1)	4 (36.3)							
7	12	$1.57C_{12h}+53.61$	0.04	7.57±28.68	3 (27.3)	3 (27.3)	5 (45.5)							
8	0,1	$57.83+1.14C_{0h}–0.17C_{1h}$	0.01	7.97±30.42	3 (27.3)	3 (27.3)	5 (45.5)	1.16	1.16					
9	0,2	$34.87+2.95C_{0h}+1.69C_{2h}$	0.68	3.26±19.57	6 (54.5)	2 (18.2)	3 (27.3)	1.01		1.01				
10	0,4	$47.63–2.01C_{0h}+3.17C_{4h}$	0.33	5.80±26.71	4 (36.3)	3 (27.3)	4 (36.3)	1.13			1.13			
11	0,6	$48.52+0.79C_{0h}+2.97C_{6h}$	0.10	7.01±26.99	4 (36.3)	3 (27.3)	4 (36.3)	1.02				1.02		
12	0,8	$39.36–2.93C_{0h}+6.86C_{8h}$	0.24	5.48±21.92	6 (54.5)	1 (9.1)	4 (36.3)	1.27					1.27	
13	0,12	$50.41+1.58C_{0h}+1.581C_{12h}$	0.05	7.49±28.42	3 (27.3)	3 (27.3)	5 (45.5)	1.00						1.00
14	0,1,2	$26.93+4.17C_{0h}+0.49C_{1h}+1.77C_{2h}$	0.70	2.97±18.28	7 (63.6)	1 (9.1)	3 (27.3)	1.08	1.20	1.24				
15	0,2,4	$35.03+2.39C_{0h}+1.59C_{2h}+0.43C_{4h}$	0.68	3.24±19.48	6 (54.5)	2 (18.2)	3 (27.3)	1.688		1.882	1.3			
16	1,2,4	$23.56+1.05C_{1h}+1.25C_{2h}+2.53C_{4h}$	0.73	2.73±17.09	6 (54.5)	1 (9.1)	4 (36.3)		2.21	1.645	3.105			

FK, tacrolimus. Other abbreviations see in Tables 2,3.

AUC_{0-12h} >60 μg·h/ml, and in the CsA group, there was no recipient who had an MPA AUC_{0-12h} >60 μg·h/ml. No recipient had severe side effects in either group.

Limited Sampling Strategy

The correlations between MPA concentrations at various time points and the full MPA AUC_{0-12h} values and prediction errors for the abbreviated AUC_{0-12h} profiles in the CsA and FK groups are summarized in Tables 3 and 4. Fourteen

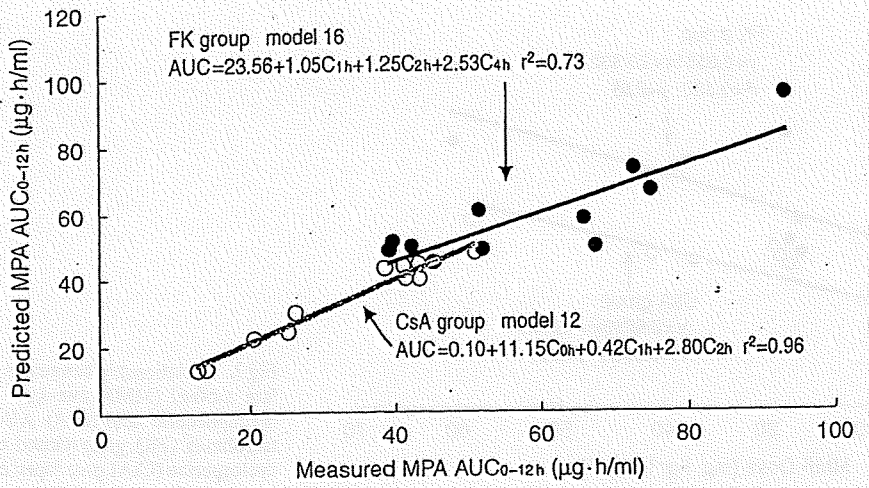

Fig 3. Linear regression plots of mycophenolic acid (MPA) area under the plasma concentration curve (AUC) values predicted by regression model 12 in cyclosporine (CsA) group (open circle; 3 samples is 0-h, 1-h and 2-h MPA concentration), 16 in tacrolimus (FK) group (closed circle; 3 samples; 1-h, 2-h and 4-h MPA concentrations) vs the corresponding each 11 MPA AUC values calculated from the full sets of samples by the linear trapezoidal rule.

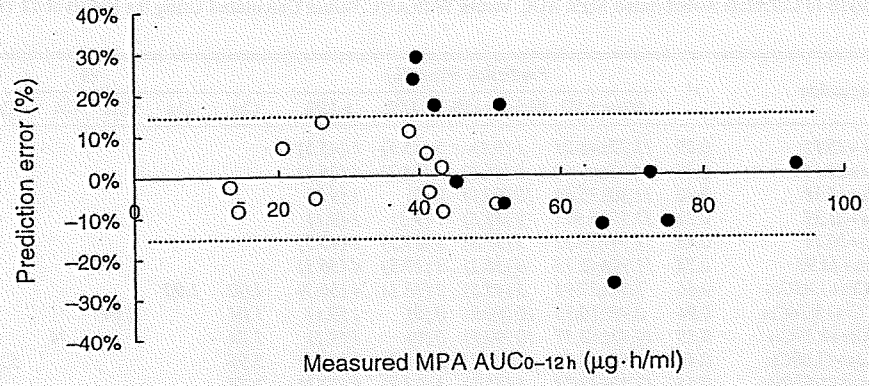

Fig 4. Prediction errors for the abbreviated mycophenolic acid (MPA) area under the plasma concentration curve (AUC) profiles. model 12 in cyclosporine (CsA) group (open circle; 3 samples is 0-h, 1-h and 2-h MPA concentration), 16 in tacrolimus (FK) group (closed circle; 3 samples; 1-h, 2-h and 4-h MPA concentrations) vs the corresponding each 11 MPA AUC values calculated from the full sets of samples by the linear trapezoidal rule.

models were developed and analyzed for their ability to estimate the MPA AUC_{0-12h} based on a limited number of samples in the CsA group. Sixteen models were developed in the FK group. The collinearity check for these models was not violated if the VIF of each model was smaller than 10. Fig 3 shows the MPA AUC values predicted using regression model 12 in the CsA group (model 16 in the FK group) plotted against the corresponding 11 MPA AUC values calculated from the full sets of 12 timed samples by the linear trapezoidal rule. Fig 4 shows prediction errors for the abbreviated MPA AUC profiles (model 12 in the CsA group and 16 in the FK group) plotted against the corresponding 11 MPA AUC values calculated from the full set of 12 timed samples by the linear trapezoidal rule. The best model for predicting the full MPA AUC_{0-12h} in the CsA group was a 3-time-point model (model 12; C_{0h}, C_{1h}, C_{2h}; $r^2=0.96$) with a mean prediction error of 0.15±7.85% (Table 3, Figs 3 and 4). The estimated prediction errors fell within ±15% in 100% of the profiles (11/11) with this model. The 2-sample model that gave the best r^2 value (0.94) was model 8 (C_{0h}, C_{2h}) with a mean prediction error of 0.49±10.35%. At this model, 90.9% of profiles (10/11) had an estimated prediction error within ±15%. The highest coefficient of determination between the MPA AUC_{0-12h} and a single concentration was observed with C_{12h} ($r^2=0.54$). The mean prediction error was 11.90±42.13% and the estimated prediction error fell within ±15% in only 36.3% of the profiles (4/11). The best model for predicting the full MPA AUC_{0-12h} in the FK group was a 3-time-point model (model 16; C_{1h}, C_{2h}, C_{4h}; $r^2=0.73$) with a mean prediction error of 2.73±17.09% (Table 4, Figs 3 and 4). The estimated prediction errors fell within ±15% in 54.5% of the profiles (6/11) with this model. The 2-sample model that gave the best r^2 value (0.68) was model 9 (C_{0h}, C_{2h}) with a mean prediction error of 3.26±19.57%. At this model, 54.5% profiles (6/11) had an estimated prediction error within ±15%. The highest coefficient of determination between the MPA AUC_{0-12h} and a single concentration was observed with C_{2h} ($r^2=0.65$). The mean prediction error was 3.50±20.06% and the estimated prediction error fell within ±15% in 54.5% of the profiles (6/11).

Discussion

The present study showed that the best model for predicting the full MPA AUC_{0-12h} was a 3-time-point model that included C_{0h}, C_{1h} and C_{2h} in the CsA group. The 2-time-point model that included C_{0h} and C_{2h} was also useful for predicting the full MPA AUC_{0-12h}. However, reliable models for a limited sampling strategy could not be obtained in the FK group. The measurement of the MPA AUC using a full set of samples requires considerable personnel time, laboratory resources and large quantities of blood. To support therapeutic drug monitoring of MPA in clinical practice, limited-sampling strategies should be developed for estimation of the MPA AUC. The r^2 values of other 3-time-point models (C_{0h}, C_{2h}, C_{4h}; C_{1h}, C_{2h} C_{4h}) in the CsA group were 0.94 and 0.95, respectively. The mean estimated prediction errors for these models were 0.36±9.8 and 0.77±7.94, respectively. These models could also be used for predicting the full MPA AUC_{0-12h}. In contrast, the r^2 values of 3-time-point models (C_{0h}, C_{1h}, C_{2h}; C_{0h}, C_2

C_{4h}; C_{1h}, C_{2h}, C_{4h}) in the FK group were 0.70, 0.68 and 0.73, respectively. The mean estimated prediction errors for these models were 2.97±18.28, 3.24±19.48 and 2.73±17.09, respectively. Therefore, these models should not be used for predicting the full MPA AUC_{0-12h}. In the 2-sample model (C_{0h}, C_{2h}) with the best r^2 value (0.94) in the CsA group, the estimated prediction errors fell within ±15% in 90.9% of the profiles (10/11). This model is also suitable for predicting the full MPA AUC_{0-12h}. On the contrary, in the 2-sample model (C_{0h}, C_{2h}) with the best r^2 value (0.68) in the FK group, the estimated prediction errors fell within ±15% in 54.5% of the profiles (6/11). Therefore, this model is not suitable for predicting the full MPA AUC_{0-12h}. A single-point method would be useful to support therapeutic drug monitoring of MPA in the clinical management of our recipients; however, a reliable single-point method for predicting the full MPA AUC_{0-12h} was not obtained in either the CsA or FK groups. Moreover, reliable models for a limited-sampling strategy were not obtained in the FK group.

Cho et al reported that MPA concentrations before and at 1 and 8 h after dosing were positively correlated with the AUC in kidney transplant recipients treated with CsA[19] Pawinski et al reported that a 3-sample model with sampling before and at 0.5 and 2 h after dosing was the best model for predicting the full MPA AUC in kidney transplant recipients treated with FK (r^2 value of 0.862 and a prediction error of 6.1±19.0%)[20] In another report, an r^2 value of 0.946 was obtained by a 3-sample model with sampling at 20 min, 1 and 3 h after dosing in kidney transplant recipients treated with CsA[21] The discrepancy among the results of these previous studies might partly be explained by variation of the transplant organ (kidney or heart), concomitant drug therapy and the sampling times used to determine the full MPA AUC. It has been reported that a significant decrease of the MPA AUC and an increase of the oral apparent clearance are observed in renal-impaired recipients[8] The suggested mechanism for these phenomena is a uremia-induced increase of the MPA-free fraction, leading to a temporary increase in the clearance of this restrictively-cleared drug. Thus, the MPA absorption profile might be different between kidney and heart transplant recipients. Cho et al collected blood samples before dosing and at 0.5, 1, 2, 4, 6 and 8 h after dosing[19] Pawinski et al collected blood samples before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 9, 10, 11, and 12 h after dosing[20] Le Guellec et al collected blood samples before dosing and at 20 min, 40 min, 1, 1.5, 2, 3, 4, 6 and 9 h after dosing[21] In our study, blood samples were collected before dosing and at 1, 2, 4, 6, and 12 h after dosing in the CsA group and at 1, 2, 4, 6, 8 and 12 h after dosing in the FK group. Differences in the limited sampling strategies recommended in these studies could be attributable to sampling time differences.

In our study, reliable models for prediction of the MPA AUC were obtained in the CsA group, but not in the FK group. This suggests that concomitant drug therapy might be an important factor for predicting the MPA AUC. The difference in the results between the CsA and FK groups was attributed to distinct MPA pharmacokinetics. It has been reported that a secondary plasma peak of MPA attributed to enterohepatic circulation occurs 6 to 12 h after administration in recipients treated with FK[22] In contrast, CsA might inhibit the transport of 7-O-MPA glucuronide, an inactive metabolite of MPA, into the bile and reduce the enterohepatic recirculation of MPA; therefore, a secondary plasma peak of MPA does not occur when MMF is used concomitantly with CsA[22]

There was no recipient who experienced ISHLT Grade III rejection in the present study. No serious adverse effects were observed in 22 recipients enrolled in the study, including the recipients with an MPA AUC_{0-12h} >60 μg·h/ml. Consequently, the present study could not determine whether the target range of 30–60 μg·h/ml for the MPA AUC is suitable for reducing the risk of acute rejection and adverse effects. Further studies should be conducted on the relationship between the MPA AUC and the risk of rejection and adverse effects in Japanese heart transplant recipients. For this purpose, the development of a limited sampling strategy for estimation of the MPA AUC in Japanese heart transplant recipients is desirable. The 3-time-point model that included C_{0h}, C_{1h} and C_{2h} in the CsA group was useful for predicting the full MPA AUC_{0-12h}. In addition, the 2-time-point model that included C_{0h}, and C_{2h} in the CsA group was also reliable for predicting the full MPA AUC_{0-12h}. Although our study is limited in that a small number of recipients were evaluated, it is the first study to characterize the pharmacokinetic parameters of MPA in Japanese heart transplant recipients. A more detailed study is necessary to verify the assumption that the 2- and 3-time-point models for predicting the MPA AUC are valuable in Japanese heart transplant recipients treated with CsA. Furthermore, limited sampling strategies for predicting the MPA AUC need to be developed in FK-treated transplant recipients.

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Relationship Between Acute Rejection and Cyclosporine or Mycophenolic Acid Levels in Japanese Heart Transplantation

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Circulation Journal
Vol. 71 No. 3 March 2007
(Pages 289–293)

Circ J 2007; 71: 289–293

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Background Cyclosporine (CsA), Mycophenolate mofetil (MMF) and prednisolone (PSL) are widely used for the prevention of acute rejection after heart transplantation. Recently, the serum concentration–time curves (AUC) of CsA and MMF have been demonstrated to be precise predictors of acute rejection.

Methods and Results Fourteen heart transplant patients were treated concomitantly with CsA, MMF, and PSL between May 1999 and November 2005 at the National Cardiovascular Center and of them 3 had acute rejection episodes [International Society for Heart & Lung Transplantation grade 3a]. Two patients (man in his 30s; woman in her 40s) had acute rejection with a mycophenolic acid (MPA) AUC_{0-12h} <30 $\mu g \cdot h \cdot ml^{-1}$ and low CsA AUC (AUC_{0-4h}; 2,408 $ng \cdot h \cdot ml^{-1}$, 1,735 $ng \cdot h \cdot ml^{-1}$). However, 1 patient (man in his 30s) with a high CsA AUC_{0-4h} (4,019 $ng \cdot h \cdot ml^{-1}$) did not develop cardiac allograft rejection even if the MMF was temporarily stopped. These 3 patients were investigated to evaluate the relationship between acute rejection and pharmacokinetic parameters, including the CsA C_0, C_2, AUC_{0-4h} and MPA AUC_{0-12h}.

Conclusions The findings suggest that a high CsA AUC_{0-4h} may prevent rejection of a cardiac allograft, even if MMF is stopped or drastically reduced. (*Circ J* 2007; **71:** 289–293)

Key Words: Cyclosporine; Japanese heart transplantation; Mycophenolate mofetil; Serum concentration–time curve

A 3-drug combination therapy consisting of cyclosporine (CsA) or tacrolimus (FK) plus mycophenolate mofetil (MMF) and prednisolone (PSL) is commonly used for basic immunotherapy in heart transplant patients. At the National Cardiovascular Center (NCVC), approximately 30 heart transplant patients, including several from overseas, have received the 3-drug combination therapy, and its usefulness has been recognized[1,2] However, despite this treatment, some patients develop acute rejection. It is well known that, in order to obtain good clinical effects and to prevent acute rejection, it is important to monitor the blood levels of immunosuppressive agents. Generally, the trough level (C_0) has been used in such monitoring; however, in recent times, analysis of the full area under the curve (AUC) of CsA was demonstrated to be a precise predictor of acute rejection and graft survival[3] In addition, it was reported that in renal transplant patients, the AUC during the absorption phase (AUC_{0-4h}) was highly correlated with the full AUC and was a better marker for rejection and nephrotoxicity than the blood trough level[4] It has therefore come to be recognized that absorption profiling is needed in order to monitor the CsA microemulsion (Neoral) more effectively[4–11]

After oral administration, MMF is rapidly and extensively absorbed and hydrolyzed to mycophenolic acid (MPA), the active immunosuppressive agent. Several studies have demonstrated a significant relationship between the MPA AUC and acute rejection[12–19] A low AUC in the first 6 months is associated with a high incidence of rejection[13] and recent reports suggest that a target of 30–60 $ng \cdot h \cdot ml^{-1}$ may be suitable during both the early post transplant period and later for maintenance therapy in heart transplant patients[13,14,18,19]

We present 3 Japanese heart transplant recipients who showed a correlation between the development of acute rejection and the relevant pharmacokinetic parameters, including the CsA AUC_{0-4h}, the 2h post-dose concentration (C_2) and the MPA AUC_{0-12h}.

Methods

Of 14 patients who had received the 3-drug combination therapy between May 1999 and November 2005, 3 had acute rejection episodes (International Society for Heart & Lung Transplantation (ISHLT) grade 3a). In 2 of them, blood levels of CsA and MMF were measured before and after the acute rejection episode. Among the remaining 11 patients who did not have acute rejection episodes, 1 patient stopped the MMF for a long period and only received a 2-drug therapy (CsA and PSL). The 2 patients who had acute rejection episodes and the 1 who did not have an acute rejection episode during withdrawal of MMF were enrolled.

(Received October 11, 2006; revised manuscript received November 28, 2006; accepted December 11, 2006)

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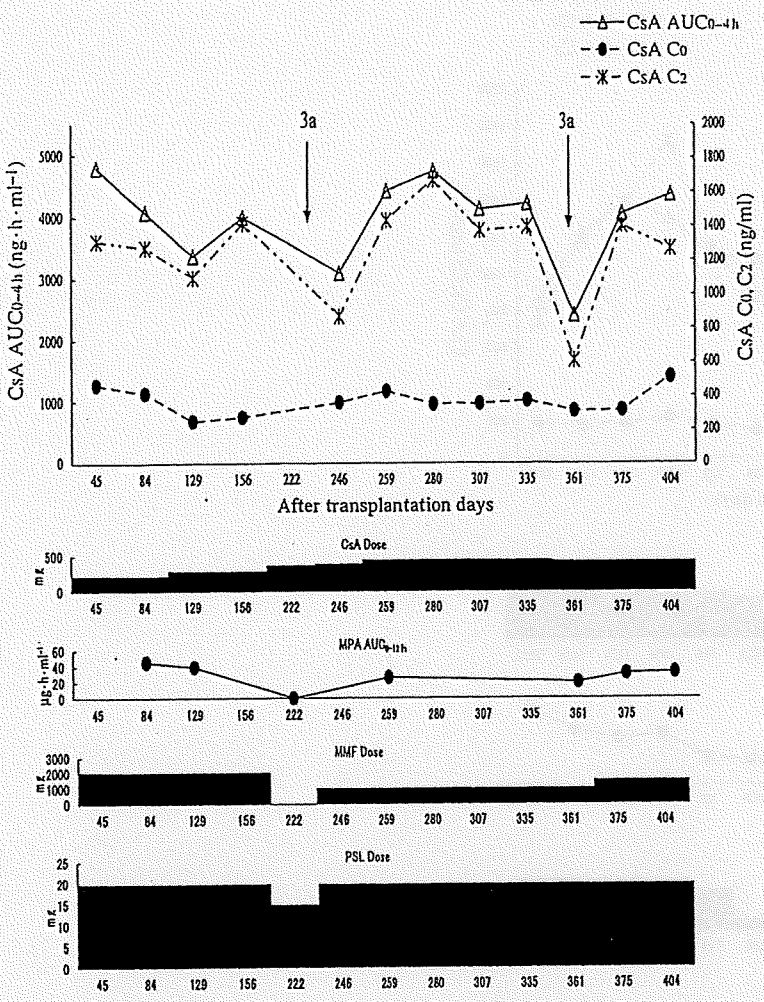

Fig 1. The blood concentration profiles of CsA and MPA, and the doses of CsA, MMF and PSL in patient 1. CsA, cyclosporine; AUC_{0-4}, area under the curve during the absorption phase; C_0, measurement of whole blood trough levels; C_2, 2 h post-dose concentration; MPA, mycophenolic acid; MMF, mycophenolate mofetil; PSL, prednisolone.

Blood for calculating the AUC of CsA and MPA was sampled at 6 time points: before dosing and at 1, 2, 4, 6, and 12 h after dosing. Blood levels of CsA and MPA were measured by fluorescent polarization immunoassay (TDx, Abbott Japan Co, Ltd) and reverse-phase high-perfomance liquid chromatography[20] respectively. AUC was calculated using the trapezoidal method. The AUC_{0-4h} was calculated as:

$$AUC_{0-4h}=1/2\times\{(C_0+C_1)\times1\}+1/2\times\{(C_1+C_2)\times1\}+1/2\times\{(C_2+C_4)\times2\}$$

where C_1 is the 1 h post-dose concentration and C_4 is the 4 h post-dose concentration. All research procedures were conducted according to the institutional clinical research guidelines and all patients gave written informed consent concerning the disclosure of their clinical data.

Results

Patient 1 (Acute Rejection)

A man in his 30 s man with dilated cardiomyopathy (DCM) as the underlying disease received a heart transplant under catecholamine treatment. At the time of transplantation, Human Leukocyte Antigen (HLA) (A, B, DR) compatibility was 0/6; cytomegalovirus (CMV) was (+) for the donor and (−) for the recipient. Initial immunosuppressive therapy was CsA, but the serum creatinine increased to 2.2 mg/dl, so CsA was discontinued from day 3 post-transplant and replaced with orthoclone-OKT3. After renal function improved, CsA was re-administrated with the addition of MMF and PSL.

The blood concentration profiles of CsA and MPA, and the doses of CsA, MMF and PSL are showed in Fig 1. The patient took oral ganciclovir (1,500 mg/day) to prevent CMV infection; however, on day 169 post-transplant, the CMV-polymerase chain reaction test showed a copy number of 1,900 and the antigenemia assay was positive. The patient was therefore hospitalized and ganciclovir injection therapy (10 $mg\cdot kg^{-1}\cdot day^{-1}$) was started.

The patient's leukocyte count decreased to 1,900/μl, which was an adverse reaction caused by ganciclovir and MMF. Therefore, both the ganciclovir injection and MMF (2 g/day) were stopped. The dose of CsA was increased from 300 to 360 mg. After that, on day 222 post-transplant, ISHLT grade 3a acute rejection was confirmed by myocardial biopsy. The CsA dose was 360 mg/day, MMF administration had ceased, and the dose of PSL was 15 mg/day. At this time, blood levels of CsA and MMF were not measured. Three-day pulse therapy with methyl prednisolone (MP, 1 g/day) was instituted, followed by an increase in the doses of CsA and PSL to 380 and 20 mg/day, respectively. MMF treatment was reinstated at 1 g/day. After 2 weeks, a myocardial biopsy showed improvement in the acute rejection, which was ISHLT grade 2. The target Co value of CsA was set at approximately 300 ng/ml.

On day 361 post-transplant, myocardial biopsy again revealed acute rejection of ISHLT grade 3a. The dose of CsA