表4　筋病理所見のチェックポイント

1）筋線維は異常か？
　筋線維径は平均よりも小さいか大きいか？（筋線維萎縮・肥大）大小不同か？（筋原性）
　筋線維内の構造異常はないか？
　　染色性の低下した壊死線維は？（筋ジストロフィー・筋炎）
　　マクロファージが侵入していないか？（筋ジストロフィー・筋炎）
　　好塩基性（H&E染色で青い）胞体で大型核か？（再生線維）
　　中心核線維はないか？（再生線維・ミオチュブラーミオパチー）
　　空胞はないか？（内部にグリコーゲン，脂肪蓄積など）
　　封入体はないか？（封入体筋炎）
　　ネマリン小体はないか？（ネマリンミオパチー）
　　ターゲット状に中心が抜けていないか？（セントラルコア病）
　　ミトコンドリアの異常増加はないか？（赤色ぼろ線維，ミトコンドリア病）
2）筋原性か？神経原性か？
　神経原性所見
　　群集萎縮はないか？
　　タイプ1またはタイプ2の筋線維タイプ群集はないか？
　　小角化線維はないか？
　筋原性所見
　　筋線維大小不同は？
　　壊死再生線維は？
　　筋線維内構築異常は？
　　結合織増生は？
　　脂肪置換は？
3）筋線維タイプ分布異常はないか？
　タイプ1線維とタイプ2線維の比率（1：2）が崩れていないか？
　　筋線維タイプ群集はないか？（神経原性）
　　筋線維タイプ萎縮はないか？
　　　タイプ1線維萎縮？（先天性ミオパチー・筋強直性ジストロフィー）
　　　タイプ2線維萎縮？（中枢神経障害，廃用性萎縮などの非特異的萎縮）
　　　タイプ1線維優位はないか？（しばしばタイプ1線維萎縮にともなう）
4）間質変化
　細胞浸潤は？
　結合織増加は？
　血管の変化は？
　筋内神経に異常は？
　ザルコイド結節，アミロイド蓄積は？

XIII．検体または標本を送付する際の注意点

3％グルタルアルデヒドによる電顕用固定は筋生検後可能な限り早い方がよいので，固定後，室温下0.1M カコジル酸緩衝液冷所保存で他施設へ送付する。未固定の新鮮筋肉ブロックの場合は，前述した生食液をしみ込ませたガーゼを保存ラップに包み，氷を入れた保冷箱で送る。筋組織が凍結しないように注意する。1～2時間程度であれば解析結果への影響は少ない。それ以上の時間を要す場合は，前述の凍結保存した後，標本が傷つかないように容器に入れドライアイスを入れた保冷箱で送る。絶対に融解しないように，筋肉ブロックを入れた容器が直接ドライアイスに接触するようにする。季節によっても異なるがドライアイス3～4 kgあれば24時間の行程

は可能である。届けられた直後に送付先での検体処理，保存ができるように送付先に事前に連絡しておくのがよい。冷凍輸送（ドライアイスの減少を少なくすることができる）到着時間指定のできる宅配業者を利用し，搬送時に患者診療情報，インフォームドコンセント書類を添付する。

XIV. 筋生検でわかること

筋生検の結果を解釈するにあたっては症状，病変分布，進行過程，発症時期，理学所見，血液生化学検査，筋電図などの電気生理学的所見，筋 CT・MRI 所見とあわせて病理所見・筋生化学所見をあわせて総合的に解釈する必要がある。

正常筋を H&E 染色で観察すると筋細胞は多角形をし筋線維径は比較的均一である。核は周辺に偏在するが成人では２～３％の筋線維に中心核を認める。筋線維径（横断面の短径）は年齢によって異なり，新生児で15μ，青年期以降で80～90μ程度である。横断面形状は新生児で円形に近く５歳以降多角形となる。乳児では筋紡錘，神経束が標本中に含まれることが多く，筋線維または浸潤細胞と混同することがあるので注意を要する。

ひとつの運動神経単位によって支配される筋線維はタイプ１，タイプ２線維に二大別される。タイプ１筋線維はタイプ２線維に比べより遅く持続する筋収縮に関与し，疲労しにくい。さらに好気的環境下で主に脂肪をエネルギー源としミトコンドリア，酸化的酵素，脂肪に富んでいる。タイプ２線維はより速い筋収縮に関与し疲労しやすく，主に解糖系によってエネルギーが供給される。したがって，グリコーゲン顆粒，解糖系酵素に富んでいる。タイプ２線維はさらに２A，２B，２C 線維に分別される。ATPase 染色によってこれらの筋線維タイプは分別される。タイプ２C 線維は通常５％以下であり未分化あるいは再生途上にある筋線維である。

表４に筋病理標本からどのようなことが読み取れるのかについて示した。

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☆　☆　☆　☆　☆　☆

＝短　　報＝

脳卒中様発作に対しmidazolamが奏効したMELAS（mitochondrial encephalopathy, lactic acidosis and stroke-like episodes）の2例

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武藤順子[1]　鶴見映子[1]　矢崎枝里子[1]
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要　　旨

MELAS（mitochondrial encephalopathy, lactic acidosis and stroke-like episodes）は反復する脳卒中様発作を主症状とし，その治療方法については対症療法以外に確立されていない．今回我々は遺伝子検査でミトコンドリアDNA np A3243G変異を呈し，臨床症状と合わせてMELASと診断された2女児において，頭痛，嘔吐，意識障害等の脳卒中様発作出現時にmidazolam 0.3 mg/kg静注，その後0.2 mg/kg/hrで持続投与を行ったところ，静注後数十秒以内に頭痛消失，意識清明となり，1例では脳波異常も消失した．Midazolamは MELASの脳卒中様発作症状に対し即効的な効果を示した．MELAS脳卒中様発作の病態は未だ解明されていないが，脳卒中発作時の選択薬としてmidazolamは短期の使用が有用と考えられた．

見出し語　midazolam, MELAS, 脳卒中様発作

はじめに

MELAS（mitochondrial encephalopathy, lactic acidosis and stroke-like episodes）は反復する脳卒中様発作を主症状とする進行性のミトコンドリア脳筋症の1型である．脳卒中様発作の代表的な臨床徴候は，頭痛，嘔吐，全身性痙攣，視野視力障害，運動麻痺，意識障害である．これらは，多くは一過性であるが重症の梗塞の場合は長期に持続し後遺症を残す場合がある．その発生機序は未だ不明であるが，近年，虚血性血管障害説や代謝障害説等の仮説が報告されている．発作に対する根本治療は確立されておらず，対症療法が行われるのみである．今回我々は脳卒中様発作を繰り返すMELASの2症例に対し，発作時にmidazolamの静注を行ったところ，即効的な症状回復の効果を示したので報告する．

I　症　　例

症例1　9歳，女児．

家族歴　母親；A3243G変異の保因者，兄；20歳，Down症．

既往歴　3歳までは正常発達．

現病歴　3歳より易疲労感，体重減少，筋力低下が出現．4歳頃から痩せが目立ち，5歳時に歩行困難となり，当科精査入院．遺伝子検査でミトコンドリアDNA（mtDNA）np A3243G変異を呈しMELASと診断された．cytochrome Cを開始し，運動機能の改善を認めたが，6歳1カ月時，発作性の嘔吐，意識障害，頭痛が出現．ジクロロ酢酸療法を開始して，一時的に頭痛発作は改善した．7歳9カ月頃より，頭痛発作頻発．次第に意欲低下，筋力低下，持続性の色覚視覚異常が出現．頭部MRI上多発性梗塞巣を繰り返し，経口摂取不良，皮質盲，寝たきりの状態となった．その後クレアチンを開始し，頭痛発作の頻度，日常生活動作（ADL）は改善した．

入院後経過　9歳5カ月時，夜間入眠中，激しい頭痛嘔吐発作が出現し入院．39度台の発熱，傾眠傾向を認めた．濃グリセリン点滴静注，diazepam坐薬（10 mg）を投与するも症状の改善は認められなかった．Midazolam 0.3 mg/kg静注を施行したところ，直ちに開眼し意識清明，会話可能となり頭痛も消失した．その後0.2 mg/kg/hrで持続投与を施行した．その後数日間かけてmidazolamを徐々に減量した．入院時のMRI画像上，左後頭部広範囲にT_2強調画像で脳回に沿った高信号域が認められ（図1A），midazolam使用後の脳波上，左側頭部領域に律動性の高振幅徐波が認められた．

9歳8カ月時，38度台の発熱の翌日，不機嫌な状態が続いていたところ，突然「怖い！，怖い！」と叫びだし全身を震わせて母親にしがみつき，意識が混濁した．頭痛は認めなかったが発作症状と考え，midazolam 5 mg（0.25 mg/kg）静注を施行したところ，数十秒後に意識清明となり，恐怖感も消失し会話可能となった．頭部MRI上新たに左側頭葉内側領域に新たな梗塞巣を認め（図1B）．これによる側頭葉てんかんの症状と考えられた．発作時脳波は記録されなかった．

症例2　10歳，女児．

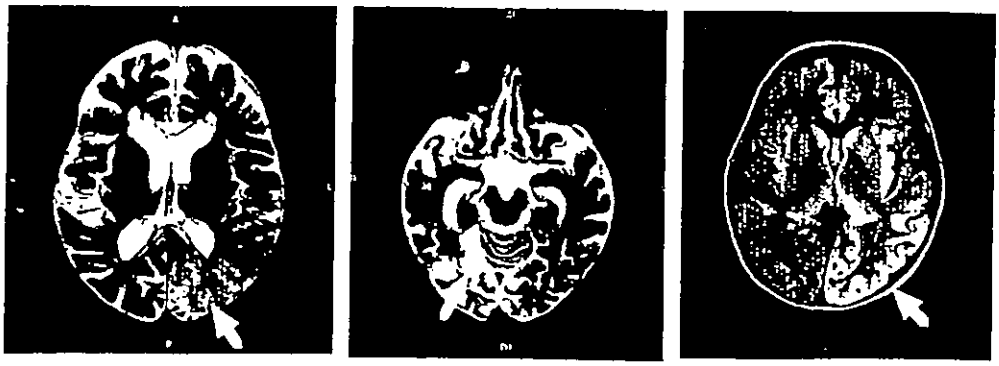
家族歴　特記すべきことなし．

既往歴　6歳までは正常発達．

現病歴　6歳頃から時々頭痛が出現していた．9歳9カ月時，発作性の頭痛，嘔吐に続き発熱，視力障害が出現．9歳10カ月時，脳波異常，血液髄液中の乳酸ピルビン酸の上昇を認め，筋生検でragged red fibers, cytochrome c oxidase活性低下を認め，遺伝子検査でmtDNA np A3243G変異を呈しMELASと診断された．

入院後経過　10歳1カ月時，遠足先で頭痛，嘔吐，視力障害が出現．救急車で当科入院となった．頭痛出現時に，脳波上両側びまん性に持続性の棘徐波複合が出現した（図2）．Xylocaine 2 mg/kg/hr持続静注の開始約15分後に脳波は改善したが，数分で両側後頭部を中心に棘徐波複合が再び出現．その後phenytoin 20 mg/kg静注したが効果を認めず，midazolam 0.3 mg/kg静注を施行後，数十秒で脳波異常，頭痛は消失した．その後0.2 mg/kg/hrで持続静注を施行した．MRI FLAIR画像にて左後頭部の脳回に沿った高信号域が認められた（図1C）．

10歳3カ月時，頭痛，嘔吐，羞明感を訴え入院した．発



A B C

図1 頭部MRI
A. 症例1： 9歳5カ月時
B. 症例1： 9歳8カ月時
C. 症例2：10歳1カ月時

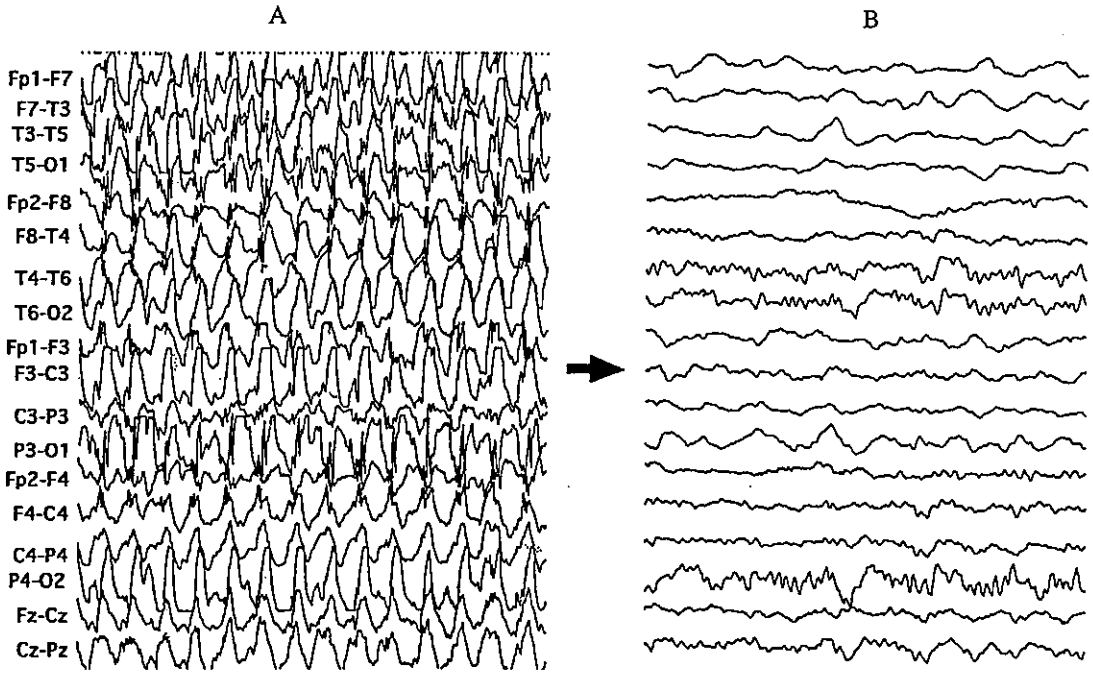


図2 症例2 10歳1カ月時脳卒中様発作時脳波
A. Midazolam使用前
B. Midazolam 0.3 mg/kg静注後0.2 mg/kg/hrで持続静注開始後

作時脳波上後頭部に律動性徐波が出現した．Midazolam 0.3 mg/kg静注後直ぐに症状は消失し，脳波は改善し入眠した．覚醒後再び頭痛を訴えるため0.3 mg/kg/hrで持続静注開始したところ頭痛は消失した．

10歳6カ月時，朝方に頭痛，嘔吐が出現し入院した．Midazolam 0.3 mg/kg/hrで持続静注を開始したところ症状改善した．

2症例ともmidazolam使用中に血圧低下，呼吸障害などの副作用は認めなかった．

II 考 察

MELASは反復する脳卒中様発作を主症状とする進行性のミトコンドリア脳筋症の1型である．Vitamine大量療法，ジクロロ酢酸，クレアチンなどが試みられているが，根治療法は未だない．MELAS脳卒中様発作は，激しい頭痛，嘔吐，意識障害を呈し緊急的な対処が必要である．この脳卒中様発作の病態は不明な点が多いが，二つの仮説が挙げられている．一つは血管内皮細胞のミトコンドリア機能異常に由来する虚血性血管障害説（mitochondrial angiopathy）

である[1,2]．ミトコンドリアが脳内毛細血管内皮細胞に占める割合は他臓器の3～5倍でこれは血液脳関門（BBB）を維持するために必要とされている[3]．MELASではミトコンドリアの異常から，血管内皮細胞内に活性酸素が蓄積し，血管拡張作用のある一酸化窒素を消費してしまうことから脳局所血流の虚血が生じる．しかし頭痛発作時SPECTでは責任病巣の脳局所の血流は増加することが報告されており，これは脳局所の酸化的リン酸化の障害から乳酸値の増加が引き起こされるためと考えられている[4]．また近年MRI拡散強調画像を用いることで，MELASの脳卒中様発作時には一般的な脳梗塞と異なり，血管性浮腫が病態に深く関わっているとの報告もあり[5]，こうした脳循環の自動調節機能の障害が頭痛発作の直接の原因と考えられる．もう一つの仮説は，脳内ニューロンや膠細胞のミトコンドリアの機能異常に基づくエネルギー代謝障害説（mitochondrial cytopathy）[6,7]である．

脳卒中様発作時の脳波所見に関しては，急性期にいわゆるびまん性脳炎，脳症で見られる周期性異常放電(PLEDs)[8,9]や不規則性高振幅徐波を呈する症例[10]，てんかん性異常波を呈する症例[11,12]が報告されており，大脳皮質の過剰興奮性の存在が示唆されている．本症例では症例1では発作時脳波を記録することができなかったが，症例2では頭痛発作時に両側びまん性棘徐波複合が記録され，midazolamの静注後直ちに脳波と臨床症状の改善を認めた．症例1でもmidazolamの静注後直ちに頭痛が消失し，意識の回復を認めた．

MidazolamはGABA作動性ニューロンに作用するベンゾジアゼピン系化合物であり，大脳皮質の興奮性を抑制し抗痙攣作用を有する[13]．症例1，2における急速な症状改善にはmidazolamのこの様な抗痙攣作用が一部に関与し，脳卒中様発作の病態に，ミトコンドリアの異常によるBBBの障害や皮質細胞の代謝障害に起因するてんかん性の大脳皮質の興奮が一部関与するものと考えられる．しかし今回のようにmidazolamにより，MELASの脳卒中様発作の激しい頭痛や意識障害が速やかに改善されたという報告は現在までになされていない．1999年Hayashiらは血管平滑筋細胞から産生され血管収縮作用，自動調節作用を有するendothelin-1（ET-1）とadrenomodullin（AM）に対し，midazolamはその産生を抑制すると報告した[14]．また近年Kogaらは，MELASでは血管内皮機能は例外なく正常の10%以下に低下しており，一酸化窒素の発生を促し血管拡張作用を有するL-アルギニンを静注することで24時間以内に脳卒中様発作の症状改善の効果を認めたと報告した[15]．Midazolamの場合，GABA作動性ニューロンへの作用のほかに，作用機序は異なるがL-アルギニンのような血管拡張作用を有することが，頭痛発作の急速な改善につながったのではないかと考えられる．一方，midazolamは長期使用により薬剤依存性が出現し離脱困難となる場合があることから，使用は短期に留めるほうがよいと考える．

今回の結果から，直接的な作用機序は不明な点が残るが，midazolamはMELASの脳卒中様発作症状を即効的に改善させる効果があることが判明し，発作時の選択薬として有用であると考えられた．今後，さらに症例を重ねてmidazolam使用前後の脳卒中様発作時脳血流SPECTを加えて検討していきたい．

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研究グループ紹介

第14回多摩小児神経懇話会

期 日 平成14年11月16日
会 場 国立精神・神経センター武蔵病院コスモホール
演 題

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4. 感染を契機に小脳症状，歩行障害を発症した児の1例
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5. 急速に進行した亜急性硬化性全脳炎の1例：周期性同期発射の経時的変化を中心に
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Soluble forms of the selectin family in children with Kawasaki disease: prediction for coronary artery lesions

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Aim: To investigate the relationship between the plasma levels of soluble forms of the selectin family and the incidence of coronary artery lesions (CALs) in patients with Kawasaki disease (KD). *Methods:* Thirty-three patients with KD, including group A patients ($n = 22$) who had no CALs and group B patients ($n = 11$) who had CALs, as well as age-matched febrile ($n = 10$) and afebrile controls ($n = 11$), were studied. *Results:* Peak plasma E-selectin levels (172.0 ± 58.6 ng ml^{-1}) occurred during the acute phase of KD, while peak plasma P-selectin levels (260.3 ± 43.2 ng ml^{-1}) occurred during the subacute phase of the illness ($p < 0.05$). Plasma L-selectin levels (1757.3 ± 244.3 ng ml^{-1}) during the convalescent phase tended to be higher than in either the acute or the subacute phase (not significant). Before intravenous immunoglobulin treatment, the plasma levels of E- (225.1 ± 46.8 ng ml^{-1}) and P-selectin (259.4 ± 76.2 ng ml^{-1}) of patients with CALs ($n = 11$) were significantly higher than those of patients ($n = 22$) with no CALs (E-selectin, 131.6 ± 36.9 ng ml^{-1}; P-selectin, 184.9 ± 84.6 ng ml^{-1}; $p < 0.05$). When a plasma E-selectin value before immunoglobulin treatment of >184.7 ng ml^{-1} was used as the cut-off point, the sensitivity and specificity for the incidence of CALs were 81.8% and 90.9%, respectively. These findings demonstrate the relationship between plasma levels of selectins and disease severity of Kawasaki vasculitis.

Conclusion: Higher plasma levels of E-selectin may have potential as a predictor of the incidence of coronary artery lesions in Kawasaki disease patients.

Key words: *Coronary artery lesions, Kawasaki disease, selectin family, vasculitis*

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Kawasaki disease (KD) is an acute, self-limiting systemic vasculitis syndrome of unknown origin that mainly affects small and medium-sized arteries, particularly the coronary artery, and is found primarily in infants and young children (1, 2). From 3 to 8% of children develop coronary artery lesions (CALs) after intravenous immunoglobulin (IVIG) therapy, and approximately 4% of KD children develop ischemic heart disease with myocardial infarction (3, 4). KD is one of the most common causes of acquired heart disease in children (1–6).

Cell adhesion molecules play important roles in the inflammatory process (7–12). Among these adhesion molecules, the selectin family includes E-selectin, which exists on endothelial cells, P-selectin, on platelets and endothelial cells, and L-selectin, on leukocytes (7–11). These E-, P- and L-selectins mediate the "rolling" of leukocytes (7, 8) on the endothelium (13) and activated platelets (14). Platelets, leukocytes and endothelial cells have been shown to release soluble adhesion molecules in the blood. Accordingly, soluble forms of selectins may be taken as conclusive evidence of those cellular activations (7–12). Histologically, vascular lesions in the acute phase of KD are associated with evidence of activation and damage to endothelial cells (15–17). Therefore, we investigated the relationship between the plasma levels of soluble forms of the selectin family and the incidence of CALs.

Patients and methods

Patients

Approximately 2019 KD patients have been followed Kurume University Hospital since 1974. Before IVIG therapy was introduced, approximately 20% of KD children developed CALs (2–4). At present, about 8% of KD children develop CALs after IVIG therapy in this institution (3). Retrospectively, 33 KD patients (26M, 7F; median age 29.3 mo, range 0.2–7 y), were selected

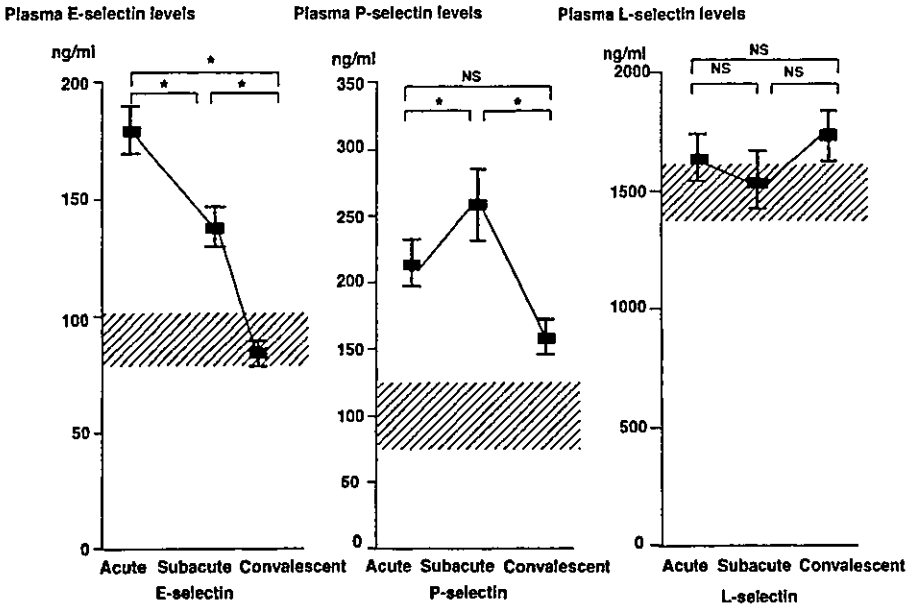

Fig. 1. Kinetics of circulating soluble forms of the selectin family in Kawasaki disease. * Statistical significance ($p < 0.05$). Gray shadows indicate the normal range (mean ± 2 SD) obtained from afebrile control patients.

at random from the cohort. They comprised 22 KD patients with no CALs (group A) and 11 patients with several sizes of coronary aneurysm (group B). The diagnosis of KD was made according to criteria established by the Japanese Kawasaki Disease Research Committee (18). These patients were treated with IVIG (2 g kg^{-1} per day) (19, 20) and with aspirin (30 mg kg^{-1} per day). Serial blood samples were taken from all patients with KD in the acute phase, defined as the phase before the administration of IVIG and aspirin (3–7 d), in the subacute phase, defined as the phase at 48 h after administration of the initial IVIG, and in the afebrile convalescent phase, defined as the phase when the C-reactive protein (CRP) of each patient was less than 0.3 mg ml^{-1} (14–30 d). Full ethical approval of the protocol of this study was given by the Kurume University Ethics Committee. Informed consent was obtained from the both parents of each child at hospitalization, before participation in the study.

Controls

Ten children (5M, 5F; median age 1.8 y, range 0.4–5 y) with fever >38.5°C who had been hospitalized for treatment of severe infection were designated as febrile controls. Their diagnoses were septic meningitis ($n = 5$), bacterial pneumonia ($n = 4$) and group A streptococcal infection ($n = 1$). No medication other than antibiotics and acetaminophen had been administered at the time the initial sample was taken. Eleven age-matched children (6M, 5F; median age 2.0 y, range 0.3–4 y), with congenital heart disease were studied as afebrile controls. They were diagnosed with atrial septal defect ($n = 6$) and small ventricular septal defect ($n = 5$). None of these patients showed any signs of congestive heart failure and none was receiving any medication at the time of sampling. Normal ranges of selectin levels were obtained from afebrile controls.

Assay method

The plasma levels of soluble P-, E- and L-selectin were measured by a sandwich enzyme-linked immunosorbent assay (ELISA) using a commercially available kit from Takara Biomedical for P-selectin, and kits from R&D Systems for E- and L-selectin, respectively (7, 8, 12).

Statistical analysis

Quantitative variables were expressed as mean ± SD. Logistic regression analysis was used as a multivariate model to determine the predictive factors of incidence of CALs. Univariate analysis included nine variables before IVIG treatment, all of which are listed in Table 1. Four variables with $p < 0.4$ in the univariate analyses were entered as covariates in the regression analyses. Variables were entered into the logistic equation in a stepwise manner based on the likelihood ratio test (Table 2) and were selected by a backward procedure with a threshold of $p = 0.05$. The cut-off value to discriminate between patients with CALs and patients with no CALs was calculated with the above parameters by univariate logistic regression analysis, and their sensitivity and specificity were evaluated. Linear

Table 1. Univariate analysis of the prediction of immediate results.

Variable	Group A CAL (−)	Group B CAL (+)	*p*-Value	OR	95% CI
Gender (M/F)	17/5	9/2	0.7638	1.32	0.21–8.21
Age (mo)	28.9 ± 20.0	32.8 ± 24.4	0.6088	0.99	0.96–1.03
Height (cm)	82.2 ± 19.8	83.7 ± 10.1	0.8067	0.99	0.95–1.04
Weight (kg)	15.7 ± 17.5	11.7 ± 2.7	0.5668	1.05	0.90–1.22
Harada's score	3.73 ± 0.88	5.0 ± 1.9	0.01	0.26	0.10–0.73
P-selectin (ng ml^{-1})	184.9 ± 84.6	259.4 ± 76.2	0.0311	0.99	0.98–1.00
E-selectin (ng ml^{-1})	131.6 ± 36.9	225.1 ± 46.9	0.0129	0.93	0.87–0.98
L-selectin (ng ml^{-1})	1691.0 ± 349.3	1596.9 ± 385.0	0.4743	1	0.99–1.01
Hb (g 100 ml^{-1})	11.2 ± 0.8	11.0 ± 1.0	0.3799	0.97	0.90–1.04
WBC (cells µl^{-1})	14 150.0 ± 4158.2	14 556.4 ± 6047.4	0.8152	1	0.90–1.01
PLT (×10^4 µl^{-1})	34.8 ± 8.4	30.5 ± 11.7	0.226	1.05	0.97–1.15
GOT (U l^{-1})	126.8 ± 277.2	60.0 ± 76.9	0.5097	1	0.99–1.01
GPT (U l^{-1})	79.1 ± 117.7	86.9 ± 73.0	0.8372	1	0.99–1.01
CRP (mg 100 ml^{-1})	10.2 ± 6.2	11.9 ± 5.4	0.4423	0.95	0.83–1.08

CAL: coronary artery lesion; OR: odds ratio; 95% CI: 95% confidence interval; Hb: hemoglobin; WBC: white blood cell; PLT: platelet; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; CRP: C-reactive protein.

regression analyses were used to determine the correlation of plasma E-, P- and L-selectin levels with other laboratory values, including white blood cells (WBC), hemoglobin, platelets, CRP, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase. *p*-Values <0.05 were considered to indicate statistical significance.

Results

Kinetics of soluble forms of the selectin family in Kawasaki disease

As shown in Fig. 1, E-selectin levels of patients with KD in the acute phase were significantly higher than those of patients in the subacute or convalescent phase. Circulating E-selectin values peaked in the acute phase of KD, whereas the peak plasma P-selectin level occurred in the subacute phase of the illness (Fig. 1). Plasma E- and P- selectin levels of patients with KD in both the acute phase (E-selectin 172.0 ± 58.6 ng ml^{-1}, P-selectin 213.3 ± 93.6 ng ml^{-1}) and the subacute phase (E-selectin 138.6 ± 25.7 ng ml^{-1}, P-selectin 260.3 ± 43.2 ng ml^{-1}) were higher than those of the control patients (febrile control: E-selectin 120.3 ± 46.3 ng ml^{-1}, P-selectin 123.7 ± 26.5 ng ml^{-1}; afebrile control E-selectin 90.3 ± 12.5 ng ml^{-1}, P-selectin 102.6 ± 18.9 ng ml^{-1}). Plasma L-selectin levels during the convalescent phase (1757.3 ± 244.3 ng ml^{-1}) of the KD patients tended to be higher than those of patients in the acute phase (1659.7 ± 358.3 ng ml^{-1}) or the subacute phase (1560 ± 265.8 ng ml^{-1}). Nevertheless, no significant differences were found among patients' plasma L-selectin levels (febrile control 1450.8 ± 120.3 ng ml^{-1}, afebrile control 1496.9 ± 197.3 ng ml^{-1}).

Relationship between soluble forms of the selectin family and coronary artery lesions

All 11 patients in group B had CALs: 5 patients had a giant aneurysm and 6 had a small-to-moderate sized aneurysm. As shown in Fig. 2, before IVIG treatment, the plasma levels of E- and P-selectin of patients with CALs were significantly higher than both those of patients with no CALs and those of afebrile and febrile controls. Plasma L-selectin levels in patients with CALs tended to be lower than those in patients with no CALs, but the difference was not statistically significant. At 48 h after the first IVIG treatment, plasma E- and P-selectin levels of patients with CALs were significantly higher than those of patients with no CALs and those of both afebrile and febrile controls (Fig. 3). The plasma L-selectin levels of patients with CALs tended to be higher than those of patients with no CALs, but the difference was not statistically significant (Fig. 3).

Table 2. Multivariate analysis of the prediction of immediate results.

	Parameter estimate	SE	*p*-Value	OR	95% CI
E-selectin (ng ml^{-1})	−0.0846	0.04	0.0342	0.92	0.85–0.99
P-selectin (ng ml^{-1})	−0.0071	0.0082	0.3847	0.99	0.98–1.01
Hb (g 100 ml^{-1})	0.0712	0.0871	0.4136	1.07	0.91–1.27
PLT (×10^4 µl^{-1})	0.6504	0.9593	0.4978	0.92	0.29–12.51

OR: odds ratio; 95% CI: 95% confidence interval; Hb: hemoglobin; PLT: platelet.

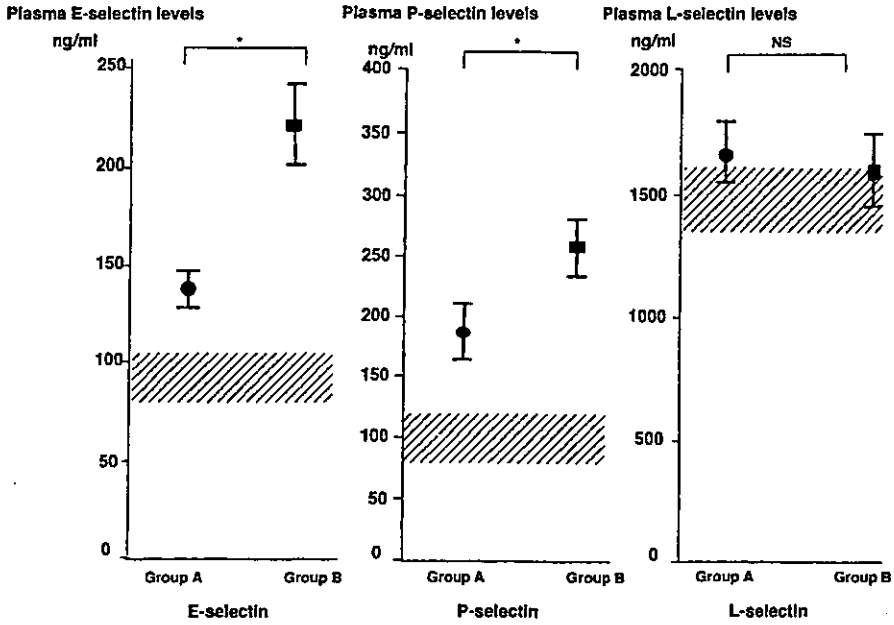

Fig. 2. Plasma E-, P-, and L-selectin levels in patients with coronary artery lesions (CALs) (■) and those in patients with no CALs (●) before intravenous immunoglobulin treatment. Gray shadows indicate the normal range (mean ± 2 SD) obtained from afebrile control patients.

Prediction of the incidence of coronary artery lesions before intravenous immunoglobulin treatment

The univariate analysis of the predictors of the incidence of CALs before IVIG treatment is shown in Table 1. The significant predictors of the incidence of CALs were high values of both plasma E- and P-selectin levels before IVIG treatment. However, the multivariate analysis identified only E-selectin levels as a predictor of the incidence of CALs before IVIG treatment (Table 2). The cut-off value to discriminate between patients with CALs and patients with no CALs was calculated within this parameter ($y = 14.2579 - 0.0771x$). When a plasma E-selectin value before IVIG treatment >184.7 ng ml^{-1} was used as the cut-off point, the sensitivity and specificity for the incidence of CALs were 81.8% and 90.9%, respectively.

Correlation between soluble forms of selectin family and laboratory values

Among patients with KD, a weak positive correlation was found between plasma E-selectin levels and WBC ($r = 0.37$, $p < 0.05$). A significant positive correlation was observed between plasma E-selectin levels and CRP. The values of P-selectin showed no significant correlation with platelet count, nor was any significant correlation found between plasma levels of the selectin family and other laboratory values.

Discussion

Kinetics in plasma levels of the selectin family in Kawasaki disease

The selectin family consists of three proteins, designated E (endothelial), P (platelet and endothelial) and L (leukocyte). These selectins are shed following proteolytic cleavage near the transmembrane domain, or by expression of alternatively spliced messenger RNA lacking a transmembrane domain from the cell surface, following activation with cytokines or other stimuli such as endotoxin (10). It has been suggested that soluble selectins can regulate cell adhesion either by downregulation as competitive inhibitors or by upregulation as co-signaling factors (9). More recent studies have provided evidence that soluble isoforms can be detected in the circulation, and that increased levels may be a key to understanding the prognosis and inflammatory processes of certain diseases (8–12). The physiological roles of soluble selectins in KD are still unknown. E-selectin may represent a marker for endothelial damage or activation in KD vasculitis, because it may play a role as a mediator of the cytokine network, in which immune effector cells are markedly activated in the acute phase (21–23). The soluble form of P-selectin in KD may represent a marker for endothelial damage, because it initially plays the role of mediator of the cellular interaction of endothelial cells or platelets with leukocytes (7, 8). Although the roles of L-selectins are still unclear, it is known that they are shed immediately after activation (7–14). It is

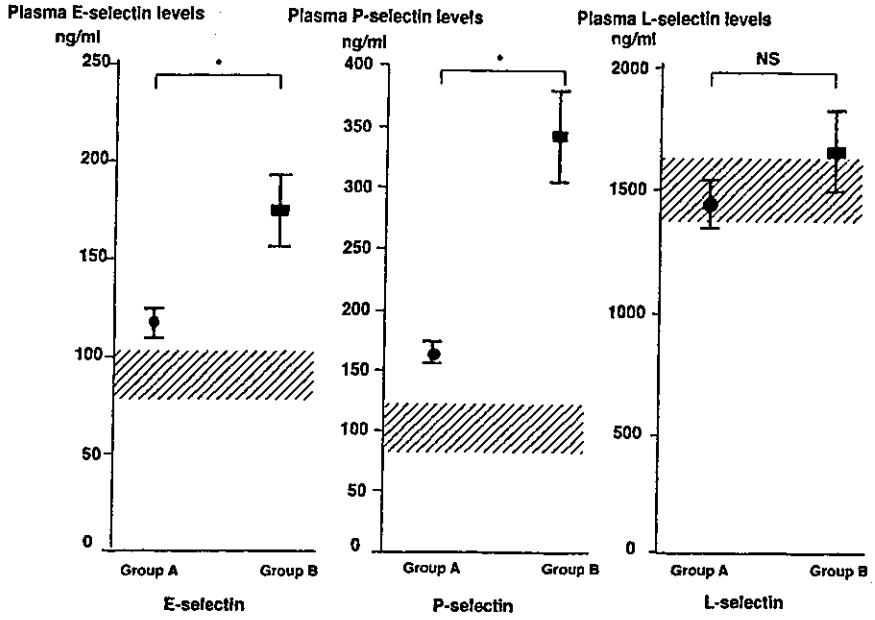

Fig. 3. Plasma E-, P- and L-selectin levels in patients with coronary artery lesions (CALs) (■) and those in patients with no CALs (●) at 48 h after intravenous immunoglobulin treatment. Gray shadows indicate the normal range (mean ± 2 SD) obtained from afebrile control patients.

unclear whether the decreased L-selectin levels contribute to the pathogenesis of vasculitis in KD.

Clinical implications of the selectin family

Previous studies have demonstrated the efficacy of IVIG treatment in the acute phase of KD (19, 20, 24, 25). In KD patients, it is important to achieve early identification of the predictors of the incidence of CALs because early treatment with IVIG is necessary to prevent CALs. Numerous investigators have attempted to correlate clinical features and laboratory findings in patients with CALs. Previously, however, the best predictors of the incidence of CALs have depended on measurements taken in the subacute phase, even when the selectins were identified as predictors (21–23), and these predictors, therefore, have not been helpful in determining the risk of CALs in the acute phase before IVIG administration (26, 27). However, in the present study, the multivariate analysis identified plasma E-selectin levels as the only predictor of the incidence of CALs before IVIG treatment, and when a value of >184.7 ng ml^{-1} was used as the cut-off point both the sensitivity and the specificity for the incidence of CALs were high. These results suggest that E-selectin may reflect disease activity and may represent a marker for endothelial damage or activation in KD vasculitis. Such an evaluation should be based on data on a large number of patients. However, the present study was investigated only a small number of patients with CALs ($n = 11$). Further study should be necessary to validate the cut-off value of E-selectin using a large number of KD patients with CALs. These results are different from those of previous studies which identified no significant difference between plasma E-selectin levels in patients with CALs and those in patients with no CALs (21–23). This discrepancy may be the result of several differences between the present study and previous studies, especially with regard to the subjects (21–23). This study was examined a greater number of patients with CALs compared with previous studies; furthermore, most the patients in the previous studies showed only a mild degree of severity in their CALs, e.g. transient dilatation and small aneurysms. In contrast, the present study, investigated 11 patients with CALs, including 5 who had giant coronary aneurysm and 6 with small to moderate sized coronary aneurysms. In addition, even in previous studies, some patients who had a large-sized aneurysm showed very high E-selectin levels (21, 23).

Several reports have indicated the potential use of the selectin family in new genetic therapies for certain diseases (7, 28, 29). For example, P-selectin antibody has been shown to be useful in animal models of acute coronary syndrome (7) and lung hemorrhage (28), and L-selectin antibody has proven useful in the treatment of baboons (29). In the future, antibodies of the selectin family may be used in genetic therapy for KD patients. The present results demonstrate the merit of further investigation of the alterations in plasma selectin levels

as a source of baseline information for the design of future selectin family-based genetic therapy for KD patients.

Conclusion

Alterations in plasma selectin levels are important clinical molecular markers and, as such, aid in the understanding of the pathophysiology of KD patients. Moreover, E-selectin molecules may have potential as a predictor of the incidence of CALs in patients with KD.

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Pediatric Cardiology

Coronary Artery Aneurysms After Kawasaki Disease in a Patient with a Single Coronary Artery

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Case Report

A 1-year-old boy diagnosed with Kawasaki disease was referred to our hospital and treated with two doses of high-dose intravenous gamma globulin on days 6 and 11 of the illness. Echocardiography on day 10 of the illness showed moderate-sized aneurysms (5 mm) of the left anterior descending coronary artery. It also demonstrated that the right coronary artery arose from the left main coronary trunk, coursing between the aorta and the right ventricular outflow tract (Fig. 1A). There were no other cardiac malformations. Coronary angiography 4 weeks after the onset also revealed two aneurysms at segments 6 and 7 of the left anterior descending coronary artery as well as the abnormal right coronary artery arising from the left main coronary trunk (Fig. 1B).

Discussion

Single coronary artery, found in 0.3–1.3% of all autopsy cases, is one of the most common causes of sudden death in young athletes [1, 2, 4]. During exercise, both the kink at the origin of the left main

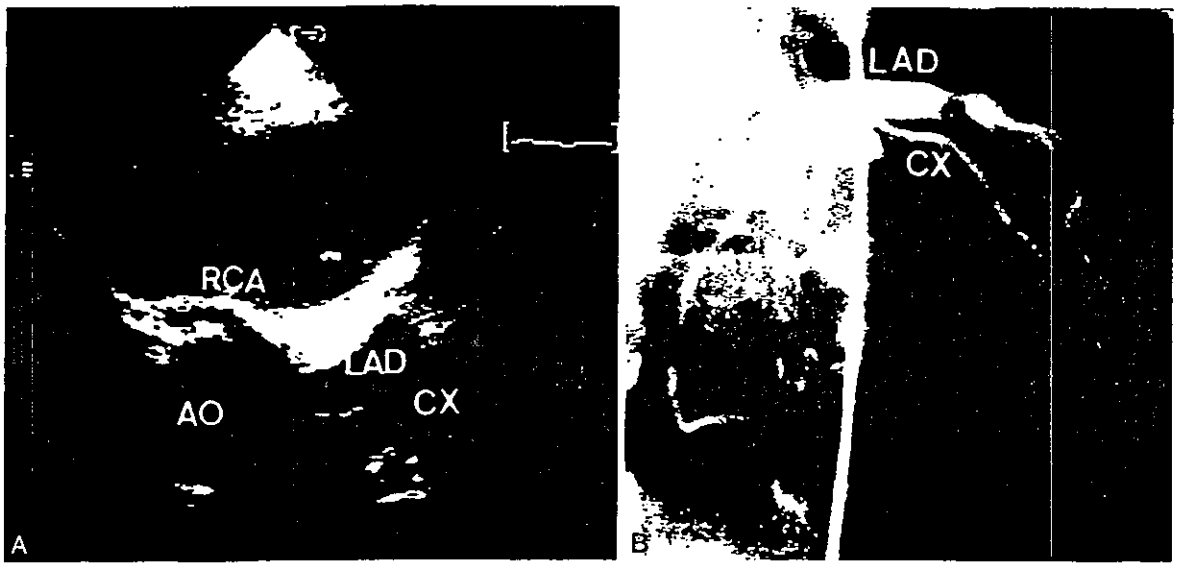

Fig 1. (A) Echocardiograph of the left coronary artery shows a moderate-sized aneurysm (5 mm) of the left anterior descending coronary artery. The right coronary artery arises from the left main trunk and courses between the aorta and the right ventricular outflow tract. (B) Selective left coronary angiography reveals two aneurysms at segments 6 and 7. The right coronary artery arises from the left main trunk. *AO*, aorta; *CX*, left circumflex coronary artery; *LAD*, left anterior descending coronary artery; *RCA*, right coronary artery.

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trunk and the compression of the left coronary artery by the pulmonary artery and the aorta are thought to be causes of sudden death [4]. In the current case, the stiffness of the coronary artery altered by the aneurysms even after regression may possibly increase the risk of sudden death.

In addition, coronary aneurysms after Kawasaki disease have the risk of sudden death by myocardial infarction due to thrombosis formation in the aneurysm [3]. In the current case, the risk may be increased due to the lack of development of collateral vessels from the right coronary artery system.

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Sequential Follow-Up Results of Catheter Intervention for Coronary Artery Lesions After Kawasaki Disease

Quantitative Coronary Artery Angiography and Intravascular Ultrasound Imaging Study

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Background—The purpose of this study was to assess the sequential follow-up results of catheter intervention in Kawasaki disease by use of quantitative coronary angiography (QCA) and intravascular ultrasound imaging.

Methods and Results—Catheter intervention was performed on 23 stenotic lesions in 22 patients (aged 2 to 24 years). Percutaneous balloon angioplasty (PBA) was performed in 4 patients, stent implantation in 7, percutaneous transluminal coronary rotational ablation (PTCRA) in 10, and a combination of PTCRA with stent implantation in 2. A total of 21 lesions (91%) were successfully dilated by catheter intervention without major or minor complications. One patient immediately underwent coronary artery bypass grafting (CABG) surgery because stent implantation failed to resolve his lesion. At 4 to 6 months after catheter intervention, 2 restenotic lesions (9%) were detected by QCA in 2 patients who had undergone PBA, and these patients subsequently underwent CABG surgery. In 6 months to 3 years after catheter intervention, no patients showed evidence of ischemic findings. At 3 to 4 years after catheter intervention, QCA and intravascular ultrasound studies were performed on 15 lesions in 14 patients. Two restenotic lesions (13%) were detected by QCA in 2 patients. One of the 2 had stent implantation and underwent CABG surgery, and the other had undergone PTCRA and underwent re-PTCRA. Thirteen patients demonstrated no ischemic findings at 3 to 8 years after catheter intervention.

Conclusion—Catheter intervention for Kawasaki disease can be accomplished and can be effective in the short term, but the long-term efficacy should be verified by further study. (***Circulation.*** **2002;105:3004-3010.)**

Key Words: angioplasty ■ balloon ■ pediatrics

Approximately 4% of coronary aneurysms subsequently develop stenotic lesions. Coronary stenosis is a significant cause of sudden death due to myocardial infarction in patients with Kawasaki disease (KD).[1] Catheter intervention for coronary artery lesions is widely performed in adult patients with coronary artery diseases and has provided satisfactory therapeutic results.[2] The coronary artery stenotic lesions in KD commonly involve severe calcification, in contrast with adult coronary artery lesions, which consist primarily of atherosclerosis.[3] Thus, the catheter intervention indicated for adult patients cannot be employed in KD patients.[4–10] Furthermore, indications of catheter intervention for KD patients have not been established, and the long-term prognosis in KD patients after catheter intervention remains unclear.

Recent advancements in intravascular ultrasound (IVUS) imaging have allowed pathological evaluation of the vascular wall structure of coronary stenosis.[11,12] Whenever possible, we used IVUS imaging for this evaluation before catheter intervention and then used these results to select a suitable device for catheter intervention. Furthermore, we used IVUS imaging to confirm therapeutic effects and to observe the vascular wall structure during the follow-up period. Accordingly, we assessed the sequential follow-up results in KD patients treated with catheter intervention by use of quantitative coronary angiography (QCA) and IVUS imaging.

Methods

Study Patients

Twenty-two patients, 18 males and 4 females, who developed coronary stenotic lesions caused by KD, were treated with catheter intervention (23 total treatment sites). At the time of the catheter

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intervention, the subjects ranged in age from 2 to 24 years (median, 15 years), had been monitored for 2 to 22 years (median, 12 years) after the onset of KD, and had no history of myocardial infarction. The follow-up period after catheter intervention ranged from 7 months to 8 years (median, 4 years). Clinical characteristics of the patients are summarized in the Table.

The Kurume University Ethics Committee gave full ethical approval. Informed consent for the participation of the 2-year-old and the 6-year-old was obtained from their parents before the start of catheter intervention. In the case of all patients aged 9 years or older, informed consent was obtained from both the patient and his or her parents. The catheter interventional treatments were performed at Kurume University Hospital and Kokura Memorial Hospital.

Methods of Catheter Intervention

Percutaneous balloon angioplasty (PBA) was performed in 4 patients by use of a high-pressure balloon (Ranger, Boston Scientific Corp). Stent implantation was performed in 7 patients by use of several types of stent (Table). Percutaneous transluminal coronary rotational ablation (PTCRA) was performed in 10 patients by use of a rotational ablation device (Rota Link PLUS, Boston Scientific Corp), and a combination of PTCRA with stent implantation was performed in 2 patients. One patient (patient 10) was treated twice (PTCRA and stent implantation). For each procedure, interventional success was defined as a stenotic lesion having been reduced to <50% stenosis, as determined by QCA. All procedures were performed with local anesthesia. Any patient with multiple-vessel lesions, ostial lesion, or long segmental lesion was excluded.[13] All catheter interventions were performed without major complications, including blood loss requiring transfusion, malignant arrhythmias, or arterial complications.

QCA Study

The QCA of the left and right coronary arteries was performed by manual injection of iohexol through a 4F Judkins-Ishii pediatric coronary angiography catheter (Filmecc Inc). The minimal lumen diameter (MLD) was measured before and after the catheter intervention and on follow-up studies with the use of the image analyzing system (CARDIO 500, Kontron Elektronic Corp), according to our previous studies.[12,14]

IVUS Study

The IVUS examination was performed before and after catheter intervention and at follow-up period, as previously reported.[11,12] The IVUS examination was performed by use of 30-MHz catheters (3.5F, Boston Scientific Corp). We then measured the thickness of the intima-media complex and calculated the calcification index by use of the following formula: Calcification index (%)=(calcification area/area of intima-media complex)×100.

Follow-Up Study Protocol

The acute phase was defined as the period immediately after catheter intervention. The short-term follow-up period was defined as the first 6 months after catheter intervention. Noninvasive follow-up examinations, which included a physical examination, electrocardiography (ECG), and echocardiography, were performed every month. The QCA and IVUS studies were performed at 4 to 6 months after catheter intervention. When coronary stenosis of ≥50% was observed by QCA, it was defined as restenosis. The medium-term follow-up period was defined as the period from 6 months to 3 years after catheter intervention. Noninvasive examinations were carried out every 3 months. Pharmacological stress ^{99m}Tc-tetrofosmin scintigraphy dipyridamole infusion (0.56 mg/kg), and treadmill exercise-stress ECG (according to the Bruce protocol) were performed every year. The long-term follow-up period was defined as the period of 3 years after catheter intervention and beyond. The QCA and IVUS studies were performed at 3 to 4 years after catheter intervention. Noninvasive examinations were performed every 4 months, and the stress tests were performed every 2 years during the long-term follow-up period.

Statistical Analysis

Quantitative variables were expressed as the mean±SD. Logistic univariate and multivariate regression analyses were used to determine the effects of five variables, including age at onset of KD, age at intervention, term from onset of KD, calcification index, and MLD, on the outcome of catheter intervention. Two independent observers, each of whom individually selected the frames to measure MLD and calcification index, and had no knowledge of the results obtained by the other observer, analyzed 10 randomly selected patients at different times. Differences were considered significant at $P<0.05$.

Results

Acute Phase

Twenty-one of 23 stenotic lesions (91%) in 22 patients were successfully dilated by catheter intervention without major or minor complications (Figure 1). The MLD ranged from 0 to 1.7 mm (1.2±0.4 mm) before intervention (Table). The calcification index ranged from 14% to 100% (59±27%) before intervention. The PBA resolved 4 stenotic lesions in all 4 patients (100%) (Figure 2A, 2B). The stent implantation resolved 6 stenotic lesions with mild to moderate degrees of calcification detected by IVUS imaging (calcification index: <75%) in 6 of the 7 patients (86%) (Figure 3A, 3B). The stent implantation failed to resolve the stenotic lesion in one patient (patient 15) in whom severe calcification was observed by IVUS imaging (calcification index: 100%, Figure 4A, 4B). This patient immediately underwent coronary artery bypass grafting (CABG) surgery. The PTCRA resolved 9 stenotic lesions in 9 of the 10 patients (90%) (Figure 5A, 5B). The PTCRA resolved stenotic lesions with severe calcification (calcification index: ≥75%). The PTCRA failed to resolve the stenotic lesion in one patient (patient 6), whose body size was too small to allow the use of an appropriately sized burr. The patient still had 50% stenosis after PTCRA, but his ischemic findings, defined by pharmacological stress scintigraphy, improved. The combination of PTCRA with stent implantation was performed in 2 stenotic lesions in 2 patients with severe calcification (calcification index: ≥75%). First, PTCRA was performed before the stent implantation to reduce the calcification index; immediately thereafter, the stent implantation successfully enlarged the stenotic lesions (success rate: 100%) (Figure 6A, 6B, and 6C). The univariate and multivariate logistic regression analysis identified no significant relationship between 5 variables and the outcome of catheter intervention ($P=0.16$ to 0.99).

Short-Term Examination

The QCA and IVUS studies were performed in 22 lesions on 21 patients at 4 to 6 months after catheter intervention in the entire cohort, except for the 1 patient (patient 15) who underwent CABG surgery immediately after stent implantation. Two restenotic lesions (9%) were detected by QCA in 2 patients undergoing PBA (Figure 1). In 1 patient (patient 20) who underwent PBA, ischemic symptoms were manifested during the short-term follow-up period, and complete occlusion was observed by QCA at 4 months after the PBA (Figure 2C). This patient immediately underwent CABG surgery. In another patient (patient 19) who underwent PBA, a complete occlusion was observed by QCA at 6 months after PBA, and

Clinical Characteristics of the Study Patients

	Patient										
	1	2	3	4	5	6	7	8	9	10	10
Sex	Male	Male	Male	Female	Female	Male	Male	Male	Male	Male	Male
Age at onset of KD, y	6	2	4	0.5	1	1	2	1	0.8	0.8	0.8
Ischemic symptoms	No	No	No	No	No	No	No	No	No	No	No
Ischemic findings detected by stress tests	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No
Age at catheter intervention, y	12	12	16	13	15	9	24	16	18	13	16
Calcification index, %	60	70	90	76	60	84	100	78	88	100	52
Type of procedure	PTCRA	PTCRA	PTCRA	PTCRA	PTCRA	PTCRA	PTCRA	PTCRA	PTCRA	PTCRA	Stent
Target vessel	Seg 2	Seg 6	Seg 6	Seg 6	Seg 2	Seg 2	Seg 6	Seg 6	Seg 2	Seg 2	Seg 2
MLD, mm	1.34	1.7	1.23	0.48	1.1	1.12	1.01	1.2	0.83	1.21	1.38
Acute phase results	Success	Success	Success	Success	Success	Failure	Success	Success	Success	Success	Success
Stenosis before/after procedure, %	75/25	90/25	90/25	90/25	90/25	90/50	90/25	90/25	90/25	90/25	90/25
Balloon pressure, atm	15	4	4	10	4	4	5	4	6	15	11
Burr size, mm	2.25	2.15	2.5	2	2.25	1.75	2.5	2.38	2.38	2.25	
Type of stent											Palmazschatz
Neo-aneurysm, mm	5	No	No	No	No	No	No	No	No	No	No
Follow-up period after procedure, y	6	4	4	7	3	4	5	3	0.6	8	8

Seg indicates segment.

CABG surgery was subsequently performed. In the other 20 lesions of 19 patients, no significant development of restenosis was observed by QCA at 4 to 6 months after catheter intervention (Figure 1). Neither neointimal hyperplasia nor a progression of calcification was observed by IVUS imaging. A neo-aneurysm developed in 4 of the 22 lesions (18%) during the short-term follow-up period. The 4 neo-aneurysms consisted of 2 lesions in the 2 patients undergoing PBA, 1 lesion from the 1 patient undergoing stent implantation, and 1 lesion from the 1 patient undergoing PTCRA. In 3 of the 4 cases with a neo-aneurysm, the expanded balloon pressure was 12 atm or higher (Table).

Medium-Term Follow-Up Examination

The medium-term follow-up examination was performed in 19 patients. The entire cohort, except 1 patient, underwent CABG surgery at acute phase, and 2 underwent CABG surgery during the short-term follow-up period. The follow-up periods ranged from 7 months to 3 years. No patient had any ischemic symptoms, such as chest pain, or any evidence of ischemic findings detected by stress test (Figure 1).

Long-Term Follow-Up Examination

Fourteen patients were followed up beyond 3 years after catheter intervention, ranging from 3 to 8 years (median 5 years). The 15 lesions on these 14 patients were examined by use of QCA and IVUS imaging at 3 to 4 years after catheter intervention. Two restenotic lesions (13%) were observed by QCA in 2 patients. The CABG was performed in 1 patient (patient 13) previously treated by stent implantation. The re-PTCRA was performed in 1 patient (patient 4) previously treated with PTCRA. One patient (patient 10) was treated twice (PTCRA and stent implantation) because another stenotic lesion had developed during the 3 years after PTCRA. In patient 14, a 19-year-old-girl, no significant restenosis was observed by QCA at 3 years after stent implantation (Figure 3C); however, a mild degree of neointimal hyperplasia was confirmed by IVUS imaging in stent (Figure 3D). In the other 11 patients, no significant restenotic lesions were observed by QCA (Figure 5C), and no neointimal hyperplasia or development of calcification was detected by IVUS imaging (Figure 5D) at 3 to 4 years after catheter intervention. We continued to follow up these 13 patients for 3 to 8 years (median, 5 years) after catheter intervention, with the exception of 1 patient who underwent CABG surgery, and none of the patients showed any ischemic symptoms or findings by stress tests.

Reproducibility of Measurements

An excellent correlation was found between the MLD of QCA measurements made by the 2 independent observers (r=0.95, P<0.001, mean difference 0.21±0.03 mm). Significant correlation and agreement were found between the IVUS calcification index measurements of the 2 observers (r=0.94, P<0.001, mean difference 2.5±1.8%).

Discussion

Comparison With Previous Studies

Catheter intervention for stenotic lesions in KD is currently performed in only a limited number of cases. Previous studies have demonstrated that PBA is effective for patients within 6 years of the onset of KD, but at >6 years after onset, it is less effective.[5,8,15] In the present study, PBA successfully resolved stenotic lesions in 3 patients for whom the time since onset of KD had been <4 years. There have been a few reports in which stent implantation, a technique of coronary intervention commonly performed in adult patients, was applied to KD patients.[6,9,16,17] In the present study, we performed stent

Continued

11	12	13	14	15	16	17	18	19	20	21	22
Male	Male	Male	Female	Male	Female	Male	Male	Male	Male	Male	Male
3	4	9	4	0.8	14	0.8	0.2	4	5	0.6	4
No	No	Yes	No	No	No	No	No	Yes	Yes	No	No
Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
14	16	20	16	16	20	13	2	6	9	15	20
45	75	18	46	100	34	29	—	14	22	80	85
Stent	Stent	Stent	Stent	Stent	Stent	PBA	PBA	PBA	PBA	PTCRA Stent	PTCRA Stent
Seg 2	Seg 6	Seg 2	Seg 6	Seg 3	Seg 6	Seg 2	Seg 2	Seg 2	Seg 6	Seg 6	Seg 7
0.75	1.09	1.38	1.14	1.28	0.42	0.9	0.42	total	0.42	0.41	0.89
Success	Success	Success	Success	Failure	Success	Success	Success	Success	Success	Success	Success
90/25	90/25	99/25	75/25	90/90 Failure	90/25	90/25	90/25	100/25	90/25	99/25	90/25
16	14	13	13	20	11	12	6	6	6	8	11
										2.38	2.38
Palmazschatz	Palmazschatz	Wiktor	Multi-Link	Palmazschatz	Multi-Link					Palmazschatz	Palmazschatz
5.6	No	No	No	No	No	6.2	4.2	No	No	No	No
5	5	6	5	6	1	7	1	4	1	1.5	1

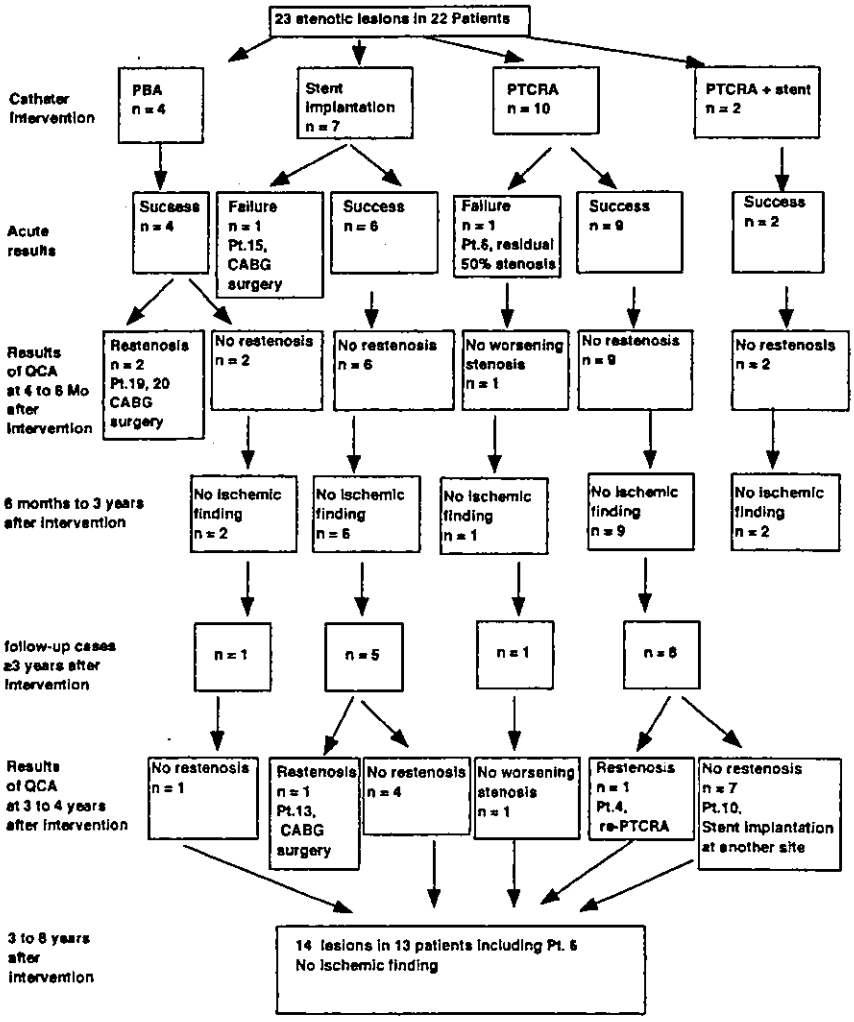

Figure 1. Sequential evaluation of catheter intervention outcomes. n indicates the number of lesions. Patient 10 was treated twice (PTCRA and stent implantation) because another stenotic lesion had developed during the 3 years after PTCRA. Although there might not have been a worsening of stenosis after intervention in patient 6, the primary intervention was unsuccessful.

Figure 2. A 9-year-old boy (patient 20) with localized, severe stenosis (99%) at the left anterior descending coronary artery (LAD) (A), in whom PBA was subsequently performed. The stenotic lesion was successfully dilated by a balloon with pressure as low as 6 atm (B). Coronary angiography demonstrated the complete occlusion of LAD (C) at 4 months after PBA.

implantation in 7 patients, with the results demonstrating that the incidence of neo-aneurysm after stent implantation was less than that after PBA alone, despite the use of a high balloon pressure. In the present study, PTCRA was performed in 10 patients and was demonstrated to be especially effective for stenotic lesions with severe calcification, as shown in our previous report.[7]

Outcome of Catheter Intervention in KD Patients

The safety and long-term efficacy of catheter intervention for KD remains unclear. Although mortality was nil in the present study, 1 patient acutely and 2 in the short term required "immediate" CABG surgery. Additionally, 4 patients developed neo-aneurysm after catheter intervention. Further study may be necessary to clarify the safety of catheter intervention in large numbers of KD patients. The ratio of restenosis evaluated by QCA in the present study was 9% in the short-term and 13% in the long-term follow-up. These ratios of restenosis are much lower than that of catheter intervention for arteriosclerotic lesions in adults.[18] In addition, hyperplasias of abnormal endothelium were not observed with IVUS imaging during the follow-up period in almost all cases (Figure 5D). The normal neo-endothelium may derive from media that preserves normal function and structure, as previous pathological studies have indicated.[3,19]

Selection of an Appropriate Device for Catheter Intervention in KD

In the present study, catheter interventions were performed with the use of PBA, stent implantation, or PTCRA. There are currently no established criteria for selecting these devices. Our proposed criteria for device selection are summarized here on the basis of the results from present and previous studies.[5–9,15–17] It is well known that PBA alone is less effective for long-term lesions with severe calcification.[5–9] Half of all coronary artery stenotic lesions, however, occur within 2 years of KD onset.[1] In these cases, the stenotic

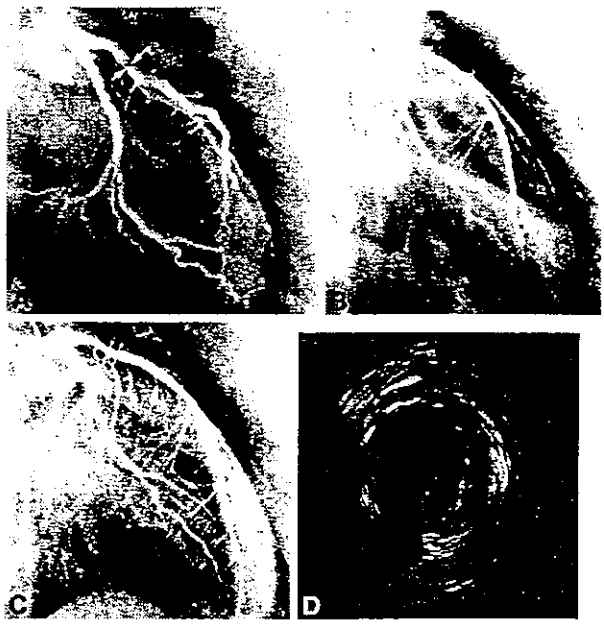

Figure 3. Left coronary angiogram of a 16-year-old girl (patient 14) with 75% stenosis on proximal LAD (arrows) (A). The stenosis improved from 75% to 25% after stent implantation (B). No significant development of restenosis was observed with QCA at 3 years after the stent implantation (C); a mild degree of neointimal hyperplasia was confirmed with IVUS imaging (D).

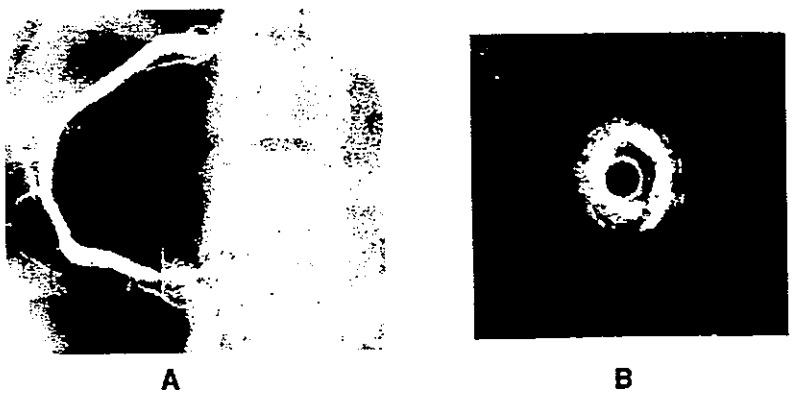

Figure 4. Right coronary angiogram of a 16-year-old boy (patient 15) (A). In this case, the coronary artery stenosis did not improve after stent implantation. IVUS imaging at the site of the coronary artery showed a circumferential, thick, ring-shaped severe calcification (calcification index: 100%) (B).

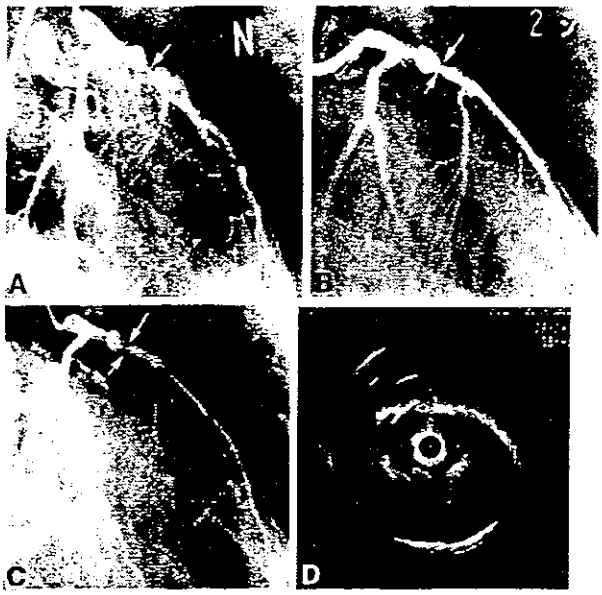

Figure 5. Left coronary artery angiogram of a 16-year-old boy (patient 3) (A). Severe stenosis (90%) was improved by the PTCRA to 25% by use of a 2.5-mm burr (B). No significant development of restenosis was observed by QCA (C), and no development of the neointimal hyperplasia was observed by IVUS imaging 4 years after PTCRA (D).

lesions are caused primarily by intimal hypertrophy without calcification. In such cases, PBA is considered to be the first choice. We performed either the stent implantation or PTCRA in long-term cases. We decided on a therapeutic procedure after pathological observation of the stenosis with IVUS imaging. The stent implantation was performed in cases with comparatively mild calcification, <50% on the calcification index, whereas PTCRA was selected in cases with more severe calcification. When insufficient expansion occurred with PTCRA alone, a stent implantation was also performed, provided that the calcification index was <50% by IVUS imaging. Some institutions utilize PTCRA for all KD patients, as it is effective for stenotic lesions with severe calcification. However, PTCRA produces a higher risk of fatal complications, such as coronary artery perforation and cardiac tamponade, as compared with either PBA or stent implantation.[20] Our institution, therefore, uses IVUS observation to select a suitable device that will present a lower risk to the patient.

In one patient (patient 14), the development of significant stenotic lesions was not detected by QCA, but a mild degree of intimal hyperplasia inside the stent was observed with IVUS imaging at 3 years after stent implantation (Figure 3C and 3D). This patient, like the others, had no risk factors for arteriosclerosis. The clinical significance of this finding is unclear. The long-term follow-up IVUS study is essential to evaluate the vascular wall morphology after intervention to determine the long-term effects of catheter intervention.

Indication of Catheter Intervention for Coronary Artery Stenotic Lesions in KD

American College of Cardiology/American Heart Association guidelines indicate that catheter intervention may be performed in adult patients with ischemia.[21] In the present study, catheter intervention was performed in patients with stenotic lesions of ≥75%, even if no evidence of ischemia was detected by any stress tests. The guidelines for catheter intervention in KD, published by the research committee of the Japanese Ministry of Health, Labor, and Welfare, indicate that patients with severe stenotic lesions in the left anterior descending coronary artery can be considered candidates for catheter intervention because this condition runs a risk of sudden death due to myocardial infarction.[13]

Study Limitations

The present study was not a multicenter study like those commonly performed to investigate catheter intervention in adult patients with coronary artery disease. In the present study, the catheter interventions were performed at 2 institutions, both leading hospitals in Japan, by 4 catheter-intervention specialists (T.U., H.T., H.Y., and M.N.). The present study, therefore, may not fully represent variations in technical expertise among institutions in the manner of multicenter studies. Accordingly, a prospective, multicenter study may be necessary to clarify the long-term prognosis of catheter intervention in KD. In the long term, 13 patients had no ischemic symptoms or findings by several stress tests; however, these findings may not fully represent long-term success, inasmuch as stress tests on patients with KD with severe stenosis often show no ischemic symptoms or findings.

Conclusions

Catheter intervention for coronary artery stenotic lesions in KD demonstrated significant therapeutic effects in the short term. The long-term efficacy of catheter intervention for KD

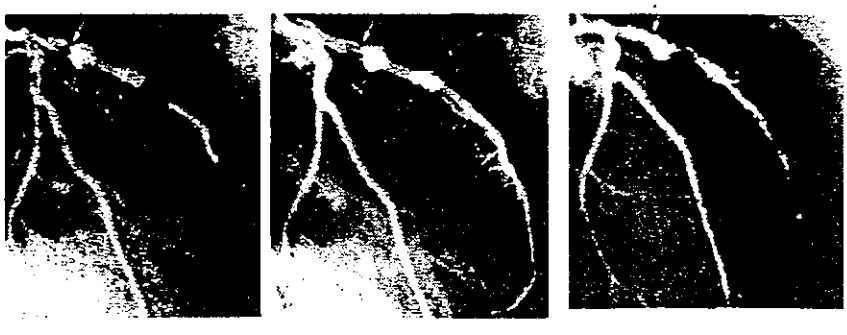

Figure 6. Left coronary artery angiogram of a 15-year-old boy (patient 21) treated with a combination of PTCRA with stent implantation (A). Left coronary stenosis improved from 90% to 50% after PTCRA (B). Left coronary stenosis improved from 50% to <25% after stent implantation followed by PTCRA (C).