メリットは大きく，今後の発展が期待される。

一方，虚血性心疾患に対する細胞治療に関しても，骨髄細胞の冠動脈内注入やNOGAシステムを用いた心筋内移植など，さまざまな臨床試験が進行中である。急性心筋梗塞患者の冠動脈内に骨髄単核球細胞を投与した初期の臨床試験では，梗塞サイズの減少や左室機能の改善，心筋バイアビリティーの改善が報告されているが，その治療効果については否定的な報告も少なくない。また，左室機能改善などの治療効果が血管新生によって得られたものなのか，あるいは心筋細胞の再生によるものなのか，その機序についても不明な点は多い。虚血下肢に対する細胞移植ほど確立された治療にはまだ至っていないというのが現状である。

おわりに

血管新生療法は血管増殖因子を用いた遺伝子治療として幕を開けた。しかしながら，遺伝子のパテント問題や倫理的ハードルの高さから，現在では細胞移植による血管新生療法が主流となりつつある。

虚血下肢に対する細胞移植の治療成績は良好であるが，臨床症状の改善にもかかわらず血管造影での改善を認めないことも少なくない。果たして細胞移植により血管新生が本当に促進されたのか？　単に潰瘍の創傷治癒機転が促進されただけではないのか？　その治療機序に関してはいまだ不明な点が少なくはなく，今後の研究成果が期待される。

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Case Reports

Late Distortion of the Original Palmaz Stent Implanted in Postoperative Lesions Associated With Congenital Heart Disease

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The objective of this study was to report late distortion of a Palmaz stent. Late distortion of an original Palmaz stent, implanted in an extracardiac lesion, is rare. We completed a 1-year follow-up of 54 patients who had been implanted with 80 Palmaz stents in extracardiac lesions. Distortion of two stents was detected in two patients. For case 1, we implanted a P188 stent for supravalvar pulmonary stenosis complicating an arterial switch operation in a 14-year-old girl. Seven months later, we found compression of the stent. Although we implanted two P308 stents anterior to the distorted stent, distortion of both stents developed after 1 month. Two more P308 stents placed inside each stent were gradually recompressed. A CAT scan showed compression of the stent by a dilated sinus of valsalva. For case 2, we implanted a P308 stent for stenosis of the superior vena cava after Williams operation in an 11-year-old boy. A chest X-ray documented longitudinal compression of the stent 27 months after implantation and a CAT scan showed the ascending aorta was in contact with the stent. A Palmaz stent may be distorted when implanted in a lesion adjacent to a pulsating aorta.

Key words: congenital heart defects; heart catheterization; complications; child

INTRODUCTION

Late distortion of an original Palmaz stent, implanted in an intracardiac lesion, has been occasionally reported [1,2]. While compression of a stent with less radial strength in an extracardiac lesion has been reported [3–5], late distortion of an original Palmaz stent in the pulmonary artery or superior vena cava is rare [6,7], as its radial strength is sufficient to support an extracardiac lesion. We describe late fracture and distortion of Palmaz stents implanted in the pulmonary artery and superior vena cava.

CASE REPORTS

We completed a 1-year follow-up of 54 patients who had been implanted with 80 Palmaz stents (Cordis, Johnson and Johnson, Miami, FL) in extracardiac lesions specifically: pulmonary artery, 52 stents in 33 patients; aorta, 15 stents in 9 cases; superior vena cava, 9 stents in 9 patients; and pulmonary vein, 4 stents in 3 patients. Among 33 patients with pulmonary artery stenosis, 3 had undergone a previous arterial switch operation with the Lecompte maneuver. Late distortion of two stents was detected in two patients by chest X-ray or follow-up angiography.

Case 1

A 14-year-old girl who underwent pulmonary artery banding at 1 month and an arterial switch operation at 1 year and 10 months developed supravalvar pulmonary artery

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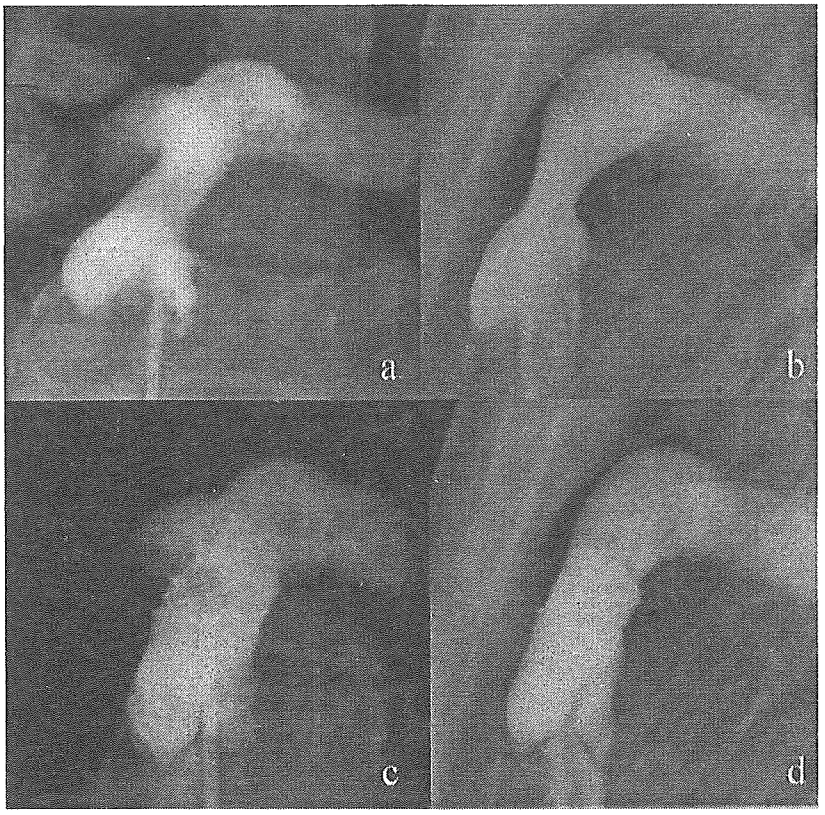

Fig. 1. Pulmonary angiogram before and after stent implantation in case 1. Anteroposterior (a) and lateral projection (b) before stent implantation. c and d: Same projection after implantation of a P188 stent.

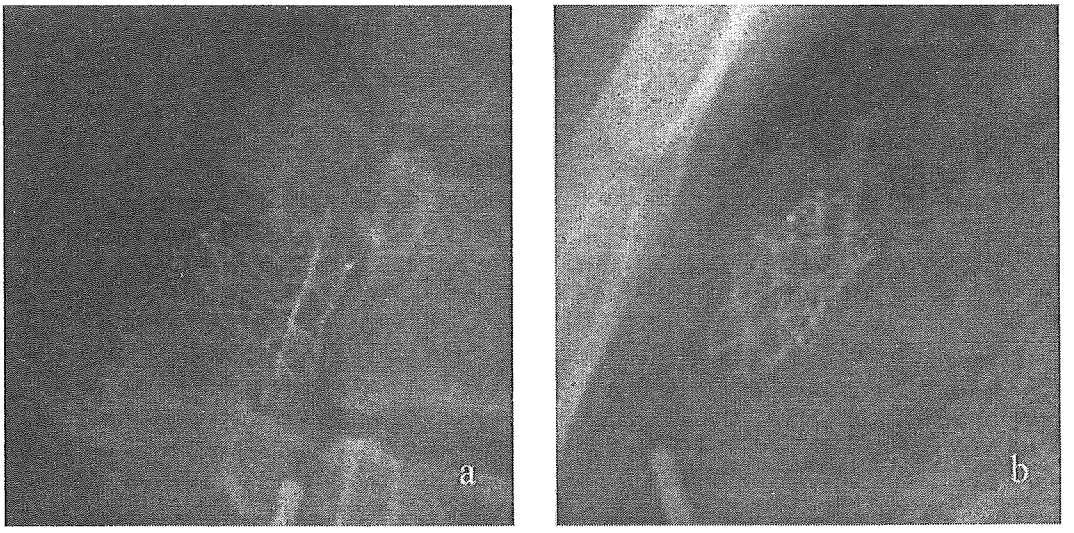

Fig. 2. Fractured stent 7 months after implantation in case 1. Anteroposterior (a) and lateral (b) view.

stenosis (PS) (Fig. 1a and b). We implanted a P188 stent on a 14 mm Z-Med balloon (NuMED, New York; Fig. 1c and d). At follow-up catheterization 7 months later, we found flattening of the stent (Fig. 2). Subsequently, we implanted two P308 stents on a 10 mm Opta 5 (Cordis) simultaneously anterior to the distorted stent (Fig. 3a), as we were concerned that a single P308 stent in the main PA might jail the bifurcation. However, compression of both stents, particularly the anterior one, developed 1 month after implantation (Fig. 3b). Although we implanted two more P308 stents on a 10 mm Opta 5 inside each distorted stent (Fig. 3c), they were gradually

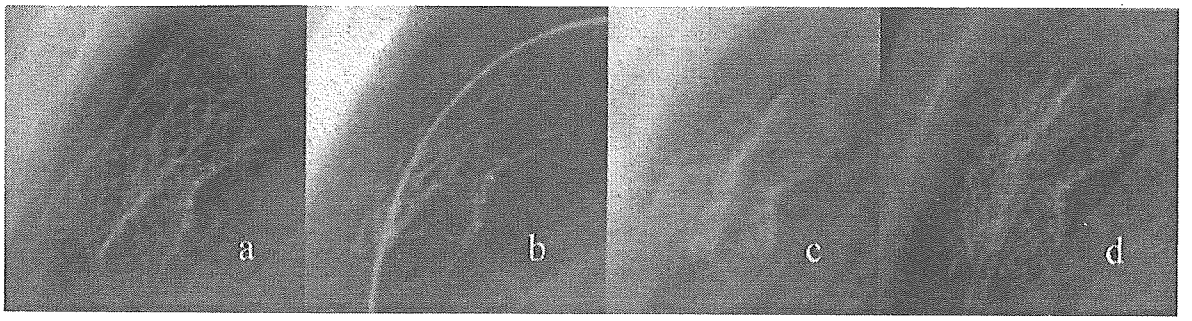

Fig. 3. Further implantation of stents in case 1. (a) Two P308 stents were implanted anterior to the collapsed one. (b) Compression of these stents. (c) Two more P308 stents inside each distorted stent. (d) Recompression of these stents.

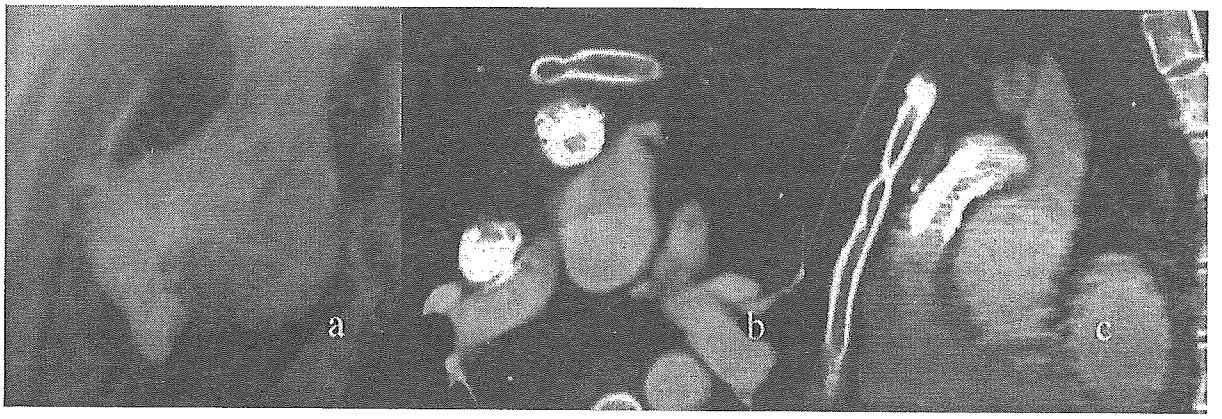

Fig. 4. Aortography (a) and CAT scan (b and c) of case 1. Stent was compressed between a markedly dilated pulsating sinus of valsalva and the sternum.

recompressed (Fig 3d). Aortography (Fig. 4a) and CAT scan (Fig. 4b and c) showed that the stent was compressed between a markedly dilated sinus of valsalva and the sternum. She is awaiting surgery.

Case 2

An 11-year-old boy developed stenosis of the superior vena cava after a Williams operation [8] for partial anomalous pulmonary venous connection (Fig. 5a), and we implanted a P308 stent on a 12 mm Ultra-thin diamond (Boston Scientific, Natick, MA) with complete elimination of the pressure gradient (Fig. 5b and c). Although follow-up angiography after 14 months showed no restenosis, a chest X-ray after 27 months documented longitudinal compression of the stent (Fig. 5d). A CAT scan showed a semicircular cross-section of the stent with flattening of the side in contact with the ascending aorta (Fig. 5e). He has been carefully observed and there has been no hemodynamic deterioration so far.

DISCUSSION

Stent placement is now a widely accepted procedure to dilate stenotic lesions associated with congenital heart disease, particularly in postoperative patients [7,9–11]. The Palmaz stent (Cordis) was originally used for such situations [9]. There are several reports of late fracture of other stents, particularly when implanted in the aorta [3–5]. However, late distortion of the Palmaz stent in extracardiac lesions is rare [6,7]. Knirsch et al. [6] reported longitudinal fracture of a stent implanted in a left pulmonary artery stenosis associated with the maneuver of Lecompte. The situation in our two patients is similar to their patient. In case 1, a markedly dilated sinus of valsalva was in close contact with the main pulmonary artery. A P188 stent dilated to 14 mm may have had insufficient radial strength in such a situation. Additionally, implantation of two stents in the narrow space between the sinus of valsalva and sternum may explain the further fracture, as collapse of the stent closer to the sternum was more marked. In case 2, although the stent has not fractured, the CAT scan clearly shows its semicircular cross-section with flattening of the side in contact with the ascending aorta. Judging from the case of Knirsch et al. [6] and ours, even the Palmaz stent may not have sufficient radial strength when implanted in lesions in close contact with the pulsating aorta. In the Lecompte maneuver, the main pulmonary artery and its

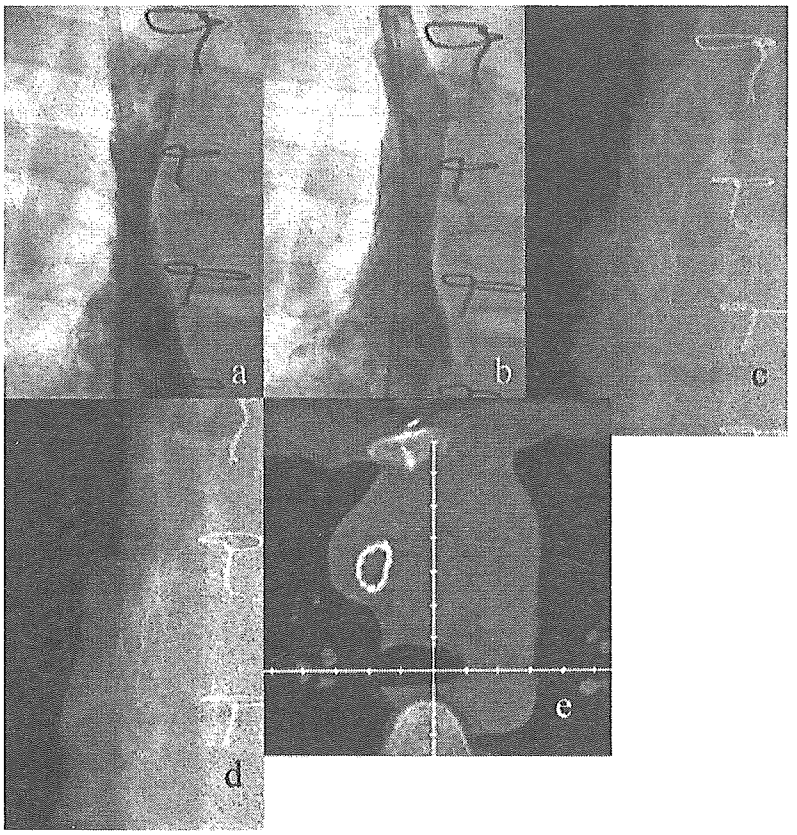

Fig. 5. Angiogram of superior vena cava before (a) and after (b) implantation of a P308 stent in case 2. Chest X-ray just (c) and 27 months (d) after stent implantation. Longitudinal compression was observed on chest X-ray at 27 months. e: CAT scan showed semicircular cross-section of the stent with flattening of the side adjacent to ascending aorta.

bifurcation are close to the ascending aorta, while in the setting of Williams procedure [8], when the transected superior vena cava is sutured to the right atrial appendage, the ascending aorta could be located close to the superior vena cava. As continuous pressure from the pulsation of the adjacent ascending aorta may cause late distortion of the stent, we should determine anatomical relationships between the lesion and the aorta before implanting a stent in such lesions. Careful follow-up is essential. As far as we could determine from the literature concerning long-term follow-up after stent implantation, including implantation for stenosis after the arterial switch operation, late stent distortion in such lesions is rare [12,13]. Consequently, other technical issues, such as manual crimping of the stent on the balloon and selection of the balloon diameter, may influence radial strength after implantation.

In conclusion, even the Palmaz stent, which is believed to have sufficient radial strength, may be distorted when implanted in a lesion adjacent to a pulsating aorta.

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STEEP STENT'S ANGLE TO THE REFERENCE VESSEL PROMOTES NEOINTIMA

By Masataka Kitano, MD; Satoshi Yazaki, MD, Hideshi Tomita, MD; Koji Kimura MD; Toshikatsu Yagihara, MD; Shigeyuki Echigo, MD

Background

Although mid-term results of stent implantation for postoperative or native peripheral pulmonary artery stenosis (PPS) in patients with congenital heart disease has been reported to be effective and safe, repeat stent dilation has often been performed because of somatic growth of patients, stent deformity by external compression, or in-stent stenosis with neointimal proliferation.[1-5] We previously reported that small stent diameter implanted in peripheral pulmonary artery was one of risk factors for neointimal hyperplasia.[6,7] We also have the impression that steep stent's angle to the reference vessel or residual waist of stent's body will promote neointimal proliferation around the corners (Figure 1). Therefore, we studied the relationship between stent's angle to the reference vessel and the neointimal proliferation around the corner in patients with PPS.

Methods

We retrospectively studied angiograms of 30 lesions in 21 consecutive patients who underwent stent implantation for right or left branch pulmonary artery stenosis and follow-up catheterization from September 1997 to October 2004. Age and body weight at implantation ranged from 0.8 to 18 years (median 8 years) and from 7.8 to 77 kg (median 24 kg), respectively. Underlying heart disease included 14 patients after repair of Tetralogy of Fallot, 2 patients after arterial switch operation for transposition of the great arteries, and the others. Two patients after total cavopulmonary connection procedure were excluded from the study. One or two of Palmaz P308, P188, P128, or Corinthian IQ stents were implanted in the lesions. We selected diagnostic angiograms which have 0 to 30 degrees of rightward and 0 to 40 degrees of cranial angulation for right pulmonary arteriograms, and 10 to 40 degrees of leftward and 0 to 40 degrees of cranial angulation in the case of left pulmonary arteriogram.

MLD-0	7.7± 1.7 mm
MinIT-6m	0.28 ± 0.15 mm
MaxIT-6m	1.1 ± 0.30 mm
Ang-o	23 ± 14°
CornetIT-6m	0.70 ± 0.50 mm

Table 1. Results of 5 Parameters. These data are presented as mean ± standard deviation. MLD-0, minimum luminal diameter of stent immediately after stent implantation; MinIT-6m, minimum intimal thickness of stent 6 months after stent implantation MaxIT-6m, maximum intimal thickness of stent 6 months after stent implantation; Ang-0, the angle between stent's outline and the reference vessel's outline immediately after stent implantation; CornerIT-6m, maximum intimal thickness at the corner 6 months after stent implantation.

On the angiograms, we collected the following data: Minimum luminal diameter of stent immediately after stent implantation (MLD-0), minimum intimal thickness of stent 6 months after stent implantation (MinIT-6m), maximum intimal thickness of stent 6 months after stent implantation (MaxIT-6m), the angle between stent's outline and the reference vessel's outline immediately after stent implantation (Ang-0), and maximum intimal thickness around the corner 6 months after stent implantation (CornerIT-6m) (Figure 2). Although there can be up to 4 points of Ang-0 in an angiogram, Ang-0 can not be measured

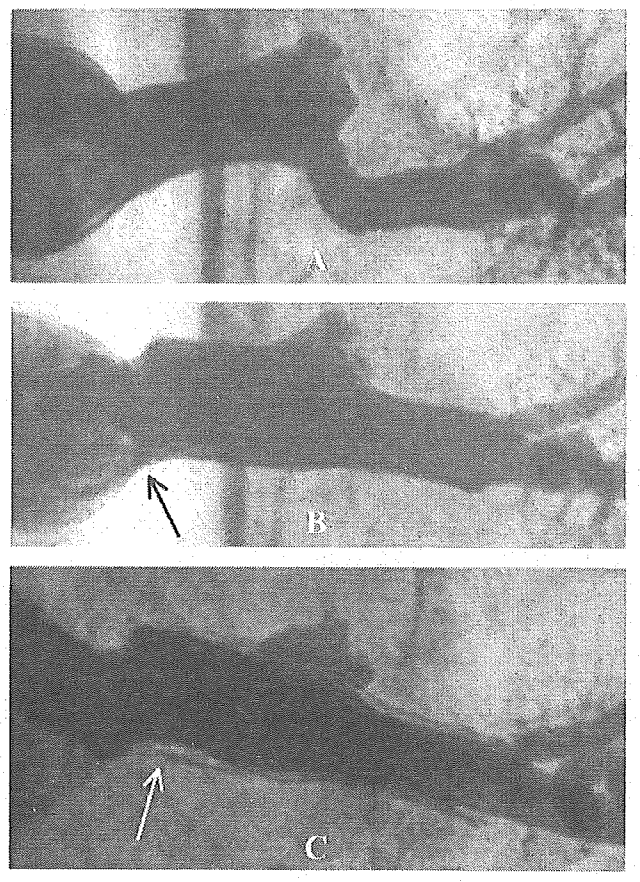

Figure 1. Left pulmonary arteriograms of a patient with left pulmonary artery stenosis after operation for tetralogy of Fallot. Panel A, B, and C are angiograms before stent implantation, immediately after stenting, and 6 months after implantation, respectively. There was steep angle between the medial outline of the stent and the reference vessel's outline immediately after stenting (black arrow). Six months later, neointimal hypertrophy was recognized around the corner (white arrow).

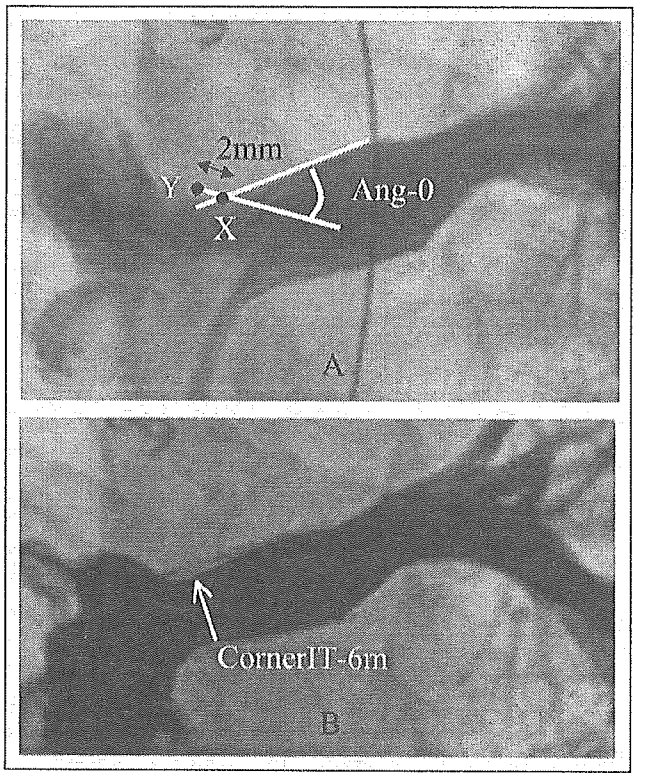

Figure 2. Left pulmonary arteriograms of a patient with left pulmonary artery stenosis after arterial switch operation for transposition of the great arteries. Panel A and B are angiograms immediately after stent implantation and 6 months after implantation, respectively. Point X and Y represent an end point of the stent's outline and the point with a length of 2mm from the point X on the reference vessel's outline, respectively. The angle between the stent's outline and the line extended from the point Y through the point X was measured as Ang-0. And maximum intimal thickness around the corner (arrow) 6 month after implantation was measured as CornerIT-6m.

where there is overinflation in the 4 points. All data were presented as mean ± standard deviation. Then we analyzed the correlation between Ang-0 and CornerIT-6m, MinLD-0 and MinIT-6m, and MLD-0 and MaxIT-6m. The linear regression and Pearson collection index were used for statistical analysis. A p value less than 0.05 was considered statistically significant.

Results

Table 1 shows measured results of 5 parameters. Figures 3 and 4 suggest the relationship between Ang-0 and CornerIT-6m. There is significant correlation between Ang-0 and CornerIT-6m (Figure 3, $\gamma = 0.78$, $n = 84$, $p < 0.001$). Similarly, significant correlation between the two was recognized in each of 4 separate parts which consisted of the proximal or the distal parts on the medial or the lateral outlines of stent (Figure 4). Figure 5 demonstrates the relationship of MLD-0 to MaxIT-6m and to

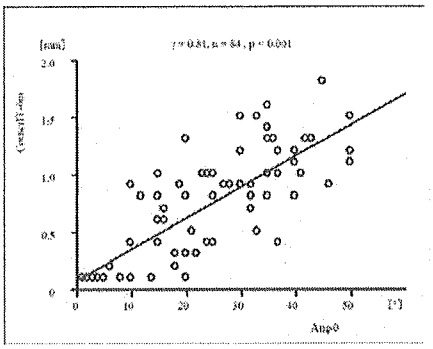

Figure 3. The relationship between Ang-0 and CornerIT-6m. Ang-0, the angle between stent's outline and the reference vessel's outline immediately after stent implantation; CornerIT-6m, maximum intimal thickness around the corner 6 months after stent implantation.

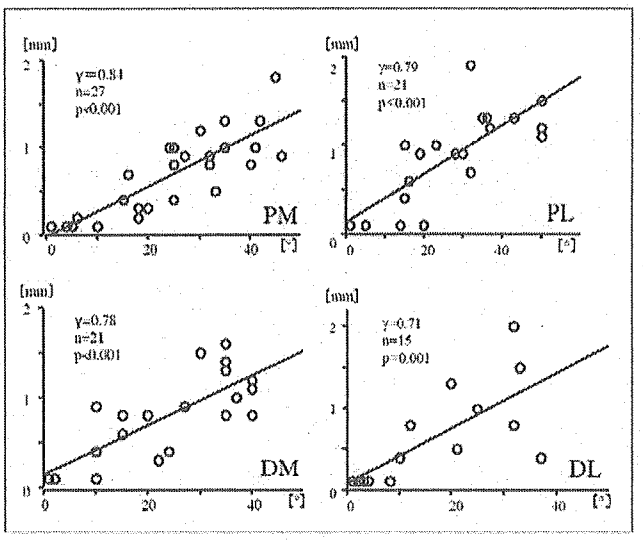

Figure 4. The relationship between Ang-0 and CornerIT-6m in the following 4 separate parts: PM, the proximal part on the medial outline of stent; PL, the proximal part on the lateral outline of stent: DM, the distal part on the medial outline of stent; DL, the distal part on the lateral outline of stent. The horizontal and vertical axes on each panel indicate Ang-0 and MaxIT-6m, respectively.

Ang-0, the angle between stent's outline and the reference vessel's outline immediately after stent implantation; CornerIT-6m, maximum intimal thickness at the corner 6 months after stent implantation.

MinIT-6m. We did not recognize significant correlation between MLD-0 and MaxIT-6m (p=0.055), but between MLD-0 and MinIT-6m (γ = 0.74, n = 30, p < 0.001).

Discussion

Although stent's angle to the reference vessel measured on an angiogram does not completely conform with the true angle between the stent and the reference vessel, we consider this difference to be trivial because there is a relatively strong correlation between Ang-0 and CornerIT-6m. Therefore, we regard steep stent's angle to the reference vessel as a risk factor for neointimal hyperplasia around the corner. Neointimal proliferation seems to be promoted by steep angle not only at the edge of stent, but also at the body of stent. Figure 6 shows right pulmonary arteriograms in a patient who had implantation of 3 pieces of stents for right pulmonary artery stenosis after operation for tetralogy of Fallot. Twelve months after stent implantation, neointimal proliferation was recognized distal to where overlapping of two stents formed a significant angle. It was also reported that there was neointimal hyperplasia immediately proximal and distal to any residual stenosis ("waist") within the stent.[3] Although Ing et al suggested that local eddy currents and turbulence created by the waist might cause microscopic vessel wall injury and resulted in more severe intimal hyperplasia, [2] we do not agree on their opinion.

From the result that there is significant correlation between MLD-0 and MinIT-6m, we regard small stent's diameter as one of risk factors for neointimal hyperplasia. However, other factors also have influence on this because the correlation is not strong. We think that the fact that there is significant correlation not between MLD-0 and MaxIT-6m, but between MLD-0 and MinIT-6m, resulted from the influence of steep angle or overinflation of stent on neointimal proliferation around these parts.

It is difficult to explain why steep stent's angle to the reference vessel promotes neointimal proliferation around that corner. Intravascular ultrasound images were not obtained in most of the patients because this study was retrospective. However ,according to a study of the relationship between local variations in shear stress and neointimal thickness after implantation of wallstents in

"It is difficult to explain why steep stent's angle to the reference vessel promotes neointimal proliferation around that corner."

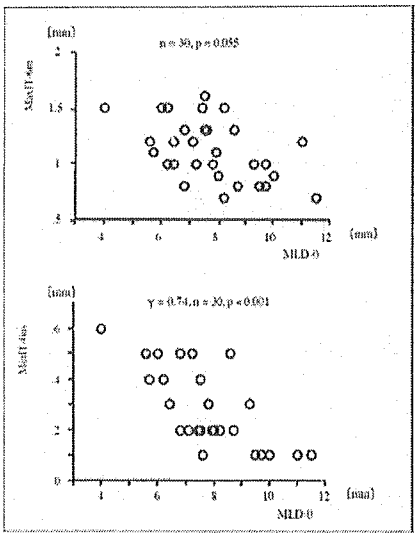

Figure 5. The relationship of MLD-0 to MaxIT-6m (upper panel) and to MinIT-6m (lower panel).

MLD-0, minimum luminal diameter of stent immediately after stent implantation; MaxIT-6m, maximum intimal thickness of stent 6 months after stent implantation; MinIT-6m, minimum intimal thickness of stent 6 months after stent implantation.

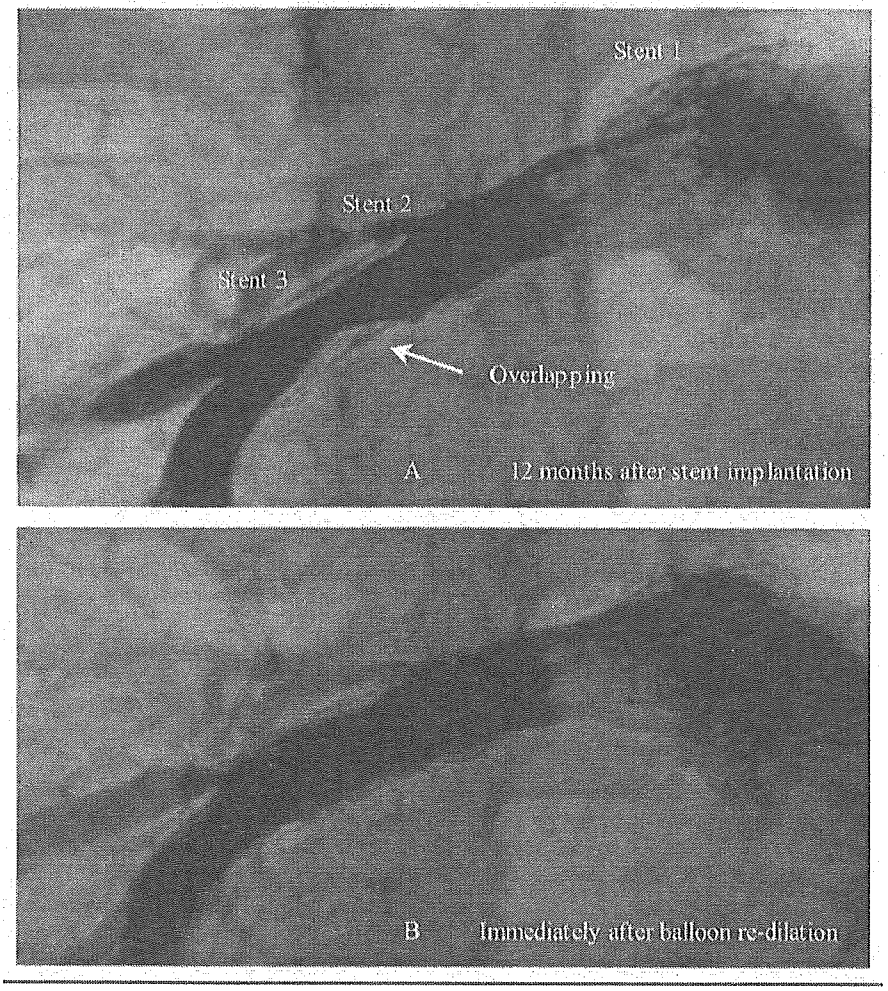

Figure 6. Right pulmonary arteriograms of an patient who had implantation of 3 pieces of stents for right pulmonary artery stenosis after operation for tetralogy of Fallot. 12 months after stent implantation, neointimal proliferation was recognized on the distal side of where overlapping of the two stents (arrow) formed some degrees of angle (Panel A). This stenosis was improved by balloon re-dilation (Panel B).

human coronary arteries, low shear stress locations demonstrated more neoinmal growth than locations with high shear stress.[8] An animal study of neointimal growth in polytetrafluoroethylen (PTEF) grafts also showed that larger amounts of intima were recognized in low shear stress parts than in high shear stress parts.[9] Another animal study of neointimal growth in balloon expandable stents implanted into carotid arteries showed that low flow promoted in-stent intimal hyperplasia.[10] Taking these results into consideration, low shear stress may be the main cause for neointimal hyperplasia. In the curving part of the artery, higher shear stress is generally raised on the outside than the inside in the vessel wall. We consider the corner that is steep stent's angle to the reference vessel or residual steep angle of stent's body as the inside of a curving vessel, therefore, neointima may proliferate around there.

Conclusion

Steep stent's angle to the reference vessel is one risk factor for neointimal proliferation around the corner in patients with PPS. In the case of stenting in a curving vessel, we recommend implanting a flexible stent and dilating it using a high pressure-balloon catheter with a banana shape to minimize neointimal proliferation in the vessel wall.

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"Steep stent's angle to the reference vessel is one of risk factors for neointimal proliferation around the corner in patients with PPS."

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Original Article

Dilated cardiomyopathy after pacemaker implantation in complete heart block

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Abstract

Background: The aim of this study was to evaluate the clinical features of patients with congenital complete heart block (CCHB) who developed dilated cardiomyopathy (DCM) after pacemaker implantation (PMI) and to determine factors predicting DCM development.

Method: A total of 15 patients were reviewed retrospectively. They were classified into two groups, one consisted of four patients who were diagnosed as having CCHB *in utero* or at birth and who developed DCM after PMI (DCM group) and the other consisted of 11 patients who did not (non-DCM group).

Results: Maternal autoantibodies were found in two of the DCM group and in five of the non-DCM group. Perfusion defects in myocardial imaging were detected in all DCM patients and in five non-DCM patients. DCM developed 2 to 43 months after PMI and three DCM patients died of heart failure 7 to 48 months after PMI. In pathological studies, endocardial or interstitial fibrosis was present in all DCM patients and in one of two in the non-DCM group. No significant differences between the two groups were found in age at PMI, atrial or ventricular rate, end-diastolic dimension and ejection fraction of the left ventricle before PMI, and width of QRS after PMI.

Conclusion: Although it was suspected that the patients with CCHB had myocardial involvement before PMI, there was no significant factor predicting the risk of DCM after PMI. In addition to cardiac rhythm abnormalities, careful attention should be paid to cardiac function in CCHB patients after PMI.

Key words complete heart block, dilated cardiomyopathy, pacemaker implantation.

Congenital complete heart block (CCHB) without intracardiac structural abnormalities is potentially lethal, however, with effective management during the prenatal, neonatal and infantile periods, and prompt initiation of cardiac pacing, the prognosis is considered benign.[1,2] Nevertheless, despite appropriate initiation of cardiac pacing, some patients develop dilated cardiomyopathy (DCM) after pacemaker implantation (PMI).[3,4,5] We also encountered four patients with isolated CCHB who developed DCM after PMI.

Our purpose in this retrospective study was to evaluate the clinical features of these patients, hoping to identify factors that might predict the development of DCM despite adequate PMI.

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Subjects and methods

Classification

In total, 47 patients were identified in National Cardiovascular Center, Osaka, Japan, as CCHB after PMI, and 15 patients with isolated CCHB were classified into two groups, one consisted of four patients who were diagnosed as having CCHB *in utero* or at birth and who developed DCM after adequate PMI (DCM group). The other group consisted of 11 patients with a similar clinical course as the DCM group but who did not develop DCM (non-DCM group).

None of the cases had anatomical cardiac abnormalities, including coronary anomalies. Pacemaker implantation was indicated due to arrhythmia (long QT syndrome, polymorphic premature ventricular contraction and/or atrial flutter) in four cases (two cases in DCM group), and low-output syndrome, congestive heart failure, syncope and/or ventricular volume overload due to severe bradycardia in the remaining 11 cases (two in the DCM group). With the exception of case 6,

PMI was performed with epicardial leads. Patients were diagnosed as having dilated cardiomyopathy clinically, based on symptoms of low-output syndrome and congestive heart failure, with cardiomegaly on chest X-ray and volume overload and low ejection fraction of the left ventricle at cardiac catheterization or on echocardiography. Finally, they had pathological findings compatible with DCM.

Clinical data accumulation

From the patient records, we obtained the following clinical data: gender, age at PMI, the presence or absence of maternal autoantibodies (anti-SSA antibody, anti-SSB antibody and antinuclear antibody) and the presence or absence of perfusion defects in 201-thallium or technetium-99 m myocardial imaging (MI). MI was performed in one patient in the DCM group twice at 0.4 and 59.9 months, and in four patients in the non-DCM group five times between 0.8 and 52.1 months before PMI. All four patients in the DCM group underwent MI five times between 0.8 and 43.9 months, and in four patients in the non-DCM group five times between 0.8 and 120.5 months after PMI. Ventricular and atrial heart rate was obtained from an electrocardiogram, which was done at 0–0.7 months (mean, 0.2 months) in the DCM group and 0–1.3 months (mean, 0.5 months) in the non-DCM group before PMI, and 3.7–48.8 months (mean, 22.9 months) and 19.1–270.8 months (mean, 115.6 months) after PMI. Pacing mode, pacing rate, width of QRS after initial PMI and the location of ventricular pacing were also recorded.

End-diastolic dimension (LVDd) and fractional shortening (%LVFS, %) of the left ventricle were obtained from an echocardiogram performed 0–2.4 months (mean, 0.6 months) in the DCM group and 0–2.8 months (mean, 0.9 months) in the non-DCM group before PMI, and 3.6–48.8 months (mean, 22.9 months) and 19.1–264.6 months (mean, 101.7 months) after PMI. The LVDd was expressed as a sex-matched percentage of the normal body surface area-predicted value (%LVDd, %).

We also reviewed the pathological findings at myocardial biopsy or autopsy. Endocardial or interstitial fibrosis was classified into four grades: no fibrosis (none), slight, moderate and severe.

We compared clinical data between the DCM group and the non-DCM group.

Data analysis

Comparisons between the two groups were performed using the Mann–Whitney *U*-test or Fisher's exact test. A *P*-value of < 0.05 was considered statistically significant.

Results (Tables 1, 2)

Dilated cardiomyopathy group

The patients were all male. The oldest patient (case 4) had a history of atrial flutter. PMI was done just after birth in two patients, at 2 months old in one patient, and at 7 years old in one patient. Maternal autoantibodies were present in two of the four patients. The ventricular rate before PMI was 44–53 bpm (mean, 47 bpm) and the atrial rate was 101–188 bpm (mean, 151 bpm). %LVDd was 116–143% (mean, 125%), and slight volume overload of the left ventricle was found in all. %LVFS was decreased to 18 and 21 in two patients, although severe congestive heart failure was not present in any patient. Single chamber pacing was employed in the three patients paced from infancy. Dual chamber pacing was used in one older patient. The initial pacing rate was 120 bpm in the three patients with single chamber pacing. DCM developed 2–43 months after PMI. A severe decrease in left ventricular contractility with dilatation was found (mean %LVFS, 8; mean %LVDd, 156%). Three patients died 7–48 months after PMI. The survivor is being treated with beta-blocker, angiotensin-converting enzyme inhibitor and diuretics. MI was done in one patient before PMI and in all patients after the development of DCM, and localized perfusion defects (PD) were found in all. In the one patient, there was no PD at 59.9 month before PMI, but a PD was detected 58 month later. There was a PD in all examinations in the DCM group except for one patient scanned at 0.8 month after PMI.

Biopsy or autopsy was done in all patients. All four patients showed slight to severe endocardial or interstitial fibrosis, and endocardial fibroelastosis was present in two patients. Trivial inflammatory cell infiltration was present in only one patient, but it was not thought to indicate myocarditis.

Non-dilated cardiomyopathy group

These 11 patients were all alive. In the patients who underwent PMI as a neonate or in early infancy, the indications for PMI were poor feeding and poor bodyweight gain due to bradycardia, and two patients (case 11, 14) had fetal distress and hydrops foetalis. Of the patients who received PMI when older (cases 6, 10, 12), the indications for PMI were volume overload of the left ventricle, and in one patient (case 6), a history of syncope. Autoantibodies were present in five and localized PD were found in all five patients in whom MI was done. Myocardial biopsy revealed interstitial fibrosis in one of two patients.

Comparison between groups

Comparing factors before PMI, no statistically significant differences were found in age at PMI or ventricular rate

Table 1 Patient profiles before pacemaker implantation

Patient	Gender	F/U period (mo)	Age at PMI (mo)	Auto-antibody	Before PMI				
					ECG		Echocardiography		MI
					HR (bpm)	P rate (bpm)	%LVDd (%)	%LVFS (%)	PD-location
DCM group									
1	m	37	2	(–)	45	188	121	32	ND
2	m	7	0	(–)	53	172	116	18	ND
3	m	48	0	(+)	49	143	143	21	ND
4	m	8	7 years 9 months	(+)	44	101	121	45	(+)
Mean ± SD		25 ± 20	23 ± 46		47 ± 4	151 ± 38	125 ± 12	29 ± 4	
non-DCM group									
5	f	274	2		40	149			ND
6	f	107	11 years 4 months		47	93	130	41	(+) – apical
7	f	199	0		53	135	99	30	ND
8	f	192	0		59	185			ND
9	m	164	1 year 7 months	(+) SSA	31	90	139	27	(+) – apical
10	f	75	2 years 9 months		50	115		35	(+) – anterolateral
11	f	102	0		55	115	155		ND
12	f	85	5 years 4 months	(+) SSA, ANA	38	85	124	44	(+) – apical
13	m	70	0	(+) SSA, ANA	52	136	121	32	ND
14	m	69	0	(+) SSA, ANA					ND
15	m	25	0	(+) SSA	53	109	124	44	ND
Mean ± SD		132 ± 76	23 ± 42		47 ± 8	121 ± 30	127 ± 16	36 ± 3	

ANA, antinuclear antibody; DCM, dilated cardiomyopathy; ECG, electrocardiography; f, female; F/U, follow-up; HR, heart rate; LVDd, end-diastolic dimension of left ventricle; LVFS, fractional shortening of left ventricle; m, male; MI, myocardial imaging; Mo, month; ND, not done; PD, perfusion defect; PMI, pacemaker implantation; SSA, anti-SSA antibody.

between the two groups. Atrial rate and %LVFS before PMI were not significantly different, but the atrial rate tended to be greater and %LVFS to be worse in the DCM group. Neither the initial mode of PM nor the width of QRS after PMI was significantly different between the two groups.

Discussion

CCHD is considered to have a good prognosis with appropriate management[1,6] but recently some cases that developed severe DCM despite early pacemaker implantation have been reported.[3,4] Some reports discuss risk factors for the development of DCM after adequate PMI, but the causes are unclear, making it important to evaluate the clinical features of these patients to identify factors that might predict the development of DCM despite adequate PMI.

In our study, 9% (4/47) of patients developed severe DCM after PMI, a frequency similar to previous reports.[3,6] Previous studies, concerned with DCM without CCHD, reported that approximately one-third of patients with DCM die.[7] In contrast, Udink *et al.* reported that 22% (2/9) of patients die, and Moak *et al.* also reported a 25% (4/16) mortality rate, and heart transplantation was done in 22% (2/9) and 44% (7/16), respectively, in their reports concerned with DCM with CCHD after PMI.[3,4] In our study, 75% (3/4) died, suggesting that the prognosis for patients with CCHD who develop DCM after PMI may be poorer than for DCM without CCHD.

Udink *et al.* reported that risk factors may include an early increased cardiothoracic ratio and left ventricle dilation, with little or no improvement in ventricular size with pacing, a prenatal diagnosis of CCHB, and bradycardia at birth.[3] Moak *et al.* examined possible serological, histological and electrophysiological risk factors but were unable to identify any significant predictors.[4] In our study, based on the MI and pathological findings, we suspect that the DCM patients with CCHB had pre-existing myocardial perfusion abnormalities or fibrosis of the myocardium before PMI. However, even in the non-DCM group, there were patients with suspected myocardial involvement. Thus, any relationship between myocardial involvement found in patients with CCHB and the development of DCM was unclear.

Table 2 Patient profiles after pacemaker implantation

Patient	Interval from PMI to P/O of DCM (Mo)	Prognosis	Interval from PMI to death (Mo)	Pacemaker Mode	Lead position	HR (bpm)	Width of QRS (ms)	After PMI Echocardiogram %LVDd (%)	%LVFS (%)	MI PD	Biopsy/Autopsy Fibrosis	Hypertrophy
DCM group												
1	30	Death	37	VVI	RV		112	149	7	(+)	sl-moderate (EFE)	(–)
2	6	Death	7	VVI		120		176	5	(+)	severe (EFE)	(–)
3	43	Death	48	VVI	RV	120	80	155	6	(+)	severe	(–)
4	2	Alive		DDDR	RV		120	142	15	(+)	slight	(+)
Mean ± SD	20 ± 19		30 ± 21		120	104 ± 21	156 ± 14	8 ± 4				
non-DCM group												
5		Alive		VVI		100	120	107	32	ND	ND	ND
6		Alive		DDD	RV		120	107	31	ND	(+)	ND
7		Alive		VVI	RV	110	80	102	43	(+)	ND	ND
8		Alive		VVI	RV	110	100	90	25	ND	ND	ND
9		Alive		DDD			120	96	35	(+/–)	ND	(+)
10		Alive		VVI	LV	90	80	118	30	(+)	ND	ND
11		Alive		VVI	RV	110	112	86	32	ND	ND	ND
12		Alive		DDD	LV		112	105	52	ND	ND	ND
13		Alive		VVI		110	88	104	36	ND	ND	ND
14		Alive		VVI	RV	120	88	92	46	ND	ND	ND
15		Alive		VVI	RV	120	104	95	40	ND	ND	ND
Mean ± SD						109 ± 10	102 ± 15	100 ± 9	36 ± 2			

DCM, dilated cardiomyopathy; EFE, endocardial fibroelastosis; HR, heart rate; LV, left ventricle; LVDd, end-diastolic dimension; LVFS, fractional shortening of left ventricle; MI, myocardial imaging; Mo, month; ND, not done; PD, perfusion defect; PMI, pacemaker implantation; P/O, point out; RV, right ventricle.

Taylor *et al.* reported an association between autoantibodies and the development of DCM in patients with CCHB after PMI.[8] We found maternal autoantibodies in all cases that were examined in the non-DCM group while autoantibodies were not present in two cases in the DCM group. While the presence of maternal autoantibodies may be a risk factor for myocardial involvement in patients with CCHB, they are not the cause of the development of DCM. The titer of autoantibodies or the timing and period of exposure to autoantibodies *in utero* may determine the extent of myocardial damage and/or the development of DCM, though this possibility could not be examined in our study.

Clinical factors prior to PMI (age at PMI, cardiac size, cardiac function and the exact rhythm) were not associated with the development of DCM after PMI statistically, although the atrial rate and LVFS data might suggest that the DCM group was actually more ill before PMI subclinically.

Recently, the clinical benefits of cardiac resynchronization therapy for heart failure were reported.[9] In this regard, atrioventricular and/or inter/intraventricular desynchronization may be considered a cause of heart failure, and atrioventricular and inter/intraventricular resynchronization with dual chamber and/or biventricular pacing may produce hemodynamic benefits. Manolis *et al.* suggested an association between the mode and site of pacing and coronary flow.[10] In this respect, ventricular single chamber pacing is less desirable than atrial or sequential dual chamber pacing because it may be associated with abnormal conduction and pacing, and may itself be a factor in causing DCM after PMI. Of our patients, pacing was converted from single chamber pacing to dual in one (case 2), but congestive heart failure was so severe before conversion that there was no improvement. Sequential dual chamber pacing or biventricular pacing may be more effective in preventing the development of DCM after PMI. Further experience will determine whether conversion of pacing mode improves the course of congestive heart failure. To evaluate any association between pacing itself and the development of DCM after PMI, further studies in patients with acquired CHB are necessary.

Study limitation

Our study involves only a few patients in each group. Studies involving larger patient numbers may uncover factors that predict the risk of DCM after adequate PMI.

Summary

We report four CCHB cases that developed DCM after PMI. We suspect that the patients with CCHB had pre-existing myocardial perfusion abnormalities or myocardial fibrosis,

although no apparent risk factor predicting the development of DCM after PMI was identified. The presence of maternal autoantibodies may correlate with myocardial involvement. Pacing itself may be implicated in the development of DCM after PMI in patients with CCHB. Patients with CCHB require careful follow up for both arrhythmia and cardiac function after PMI, even after early and adequate PM initiation.

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Validation of the Association Between the Gene Encoding 5-Lipoxygenase-Activating Protein and Myocardial Infarction in a Japanese Population

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Background Recently, the 5-lipoxygenase activating protein gene (*ALOX5AP*) was reported to confer a risk of myocardial infarction (MI) and stroke, independent of conventional risk factors. The purpose of the present study was to validate those findings in a Japanese population.

Methods and Results The study population consisted of 1,875 subjects (males 871, females 1,004) recruited from the Suita study (control group) and 353 subjects (males 306, females 47) with MI. The promoter, all of the exons, and 3'UTR regions of *ALOX5AP* were sequenced in 96 subjects, and 8 polymorphisms were found. There were significant differences in the frequencies of the haplotypes constructed from the 2 SNPs (A162C and T8733A) between the control and MI groups. Multiple logistic analysis indicated that the homozygous genotype of the (CA) haplotype was significantly associated with a reduced risk for MI.

Conclusion The hypothesis that *ALOX5AP* contributes to susceptibility for MI was validated in a Japanese population. (*Circ J* 2005; **69:** 1029–1034)

Key Words: *ALOX5AP*; Haplotype; Myocardial infarction

Myocardial infarction (MI) is a multifactorial disease caused by environmental and genetic factors. There are an increasing number of studies that identify genes contributing to MI[1–5] for personalized prevention from the disease. Recently, the 5-lipoxygenase activating protein gene (*ALOX5AP*) was reported to confer a risk of MI and stroke, independent of conventional risk factors[6] This possibility was based on findings in genome-wide scans and subsequent case–control studies. A haplotype, HapA, defined by 4 single nucleotide polymorphisms (SNPs) and which spanned *ALOX5AP*, was shown to be associated with MI in an Icelandic population[6] and subsequently, another SNP-based haplotype within *ALOX5AP*, HapB, showed a significant association with MI in British cohorts from Leicester and Sheffield[6]

The *ALOX5AP* gene encodes the membrane-associated 5-lipoxygenase (LO)-activating protein, an important mediator of the activity of 5-lipoxygenase, a key enzyme in the biosynthesis of leukotrienes[7] Leukotrienes are not only smooth muscle constrictors but also proinflammatory mediators that are produced predominantly by inflammatory cells[8,9] Studies have indicated that inflammatory processes play an important role in the progression of atherosclerotic disease[10,11] The 5-LO pathway could be an important contributor to the pathophysiology of atherosclerosis through the formation of leukotriene (LT) B4 via an increase in vascular permeability[12] Antagonists of LTB4 have been reported to attenuate the development of atherosclerosis in apoE-deficient and LDLR-deficient mice[13] Furthermore, 5-LO has been localized to macrophages, dendritic cells, foam cells, mast cells, and neutrophilic granulocytes, and the number of cells that expressed 5-LO was markedly greater in advanced lesions[14] Leukocytes that were positive for 5-LO accumulated at distinct sites that are most prone to rupture[15] Taken together, these findings suggest that upregulation of the leukotriene pathway may contribute to the progression of atherosclerotic progression and plaque stability. However, the precise role of leukotrienes in the pathogenesis of atherothrombotic diseases awaits further investigation.

Thus, it is likely that *ALOX5AP* contributes to MI. However, we are now recognizing that the contribution of common alleles is less than expected, and any single study that considers a few thousand subjects may not be large enough to support concrete conclusions and should be viewed as providing only tentative results. The purpose of the present study was to validate the findings of DeCode genetics[6] in a Japanese population and to evaluate the possible importance of *ALOX5AP* in the pathogenesis of MI.

Methods

Study Population

The selection criteria and design of the Suita Study have been described previously[16–18] The genotypes were determined in 1,875 subjects recruited from the Suita Study between April 2002 and February 2003. The MI group consisted of 353 (males 306, females 47) randomly selected inpatients and outpatients with documented MI who were enrolled in the Division of Cardiology at the National Cardiovascular Center between May 2001 and April 2003[19]

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Table 1 Characteristics of the Study Population

	Control	MI	p-value
n	1,875	353	
Sex (% male)	46.5	86.69	<0.0001
Age (years)	64.5±0.25	58.8±0.59	<0.0001
BMI (kg/m^2)	22.8±0.07	23.9±0.16	<0.0001
C-SM (%)	44.3	61.2	<0.0001
HT (%)	40.6	53.7	<0.0001
HLP (%)	27.8	51.7	<0.0001
HDL-C (mg/dl)	59.9±0.35	44.0±0.93	<0.0001
DM (%)	6.1	39.1	<0.0001

Data are mean±standard error. Differences between the 2 groups (control vs myocardial infarction (MI)) were calculated by t-test or χ^2 analysis. BMI, body mass index; C-SM, current smoking habit; HT, hypertension; HLP, hyperlipidemia; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus.

Table 2 Primers for Sequence Analysis

Probe	Sequence (5'-3')
P1S	GATATCAGCTGTCCCTCCCCACTG
E1S	CTCAGGGAAGTTTCCCATGACAAGG
E2S	CAGTAGAGAGCAGCTGCTGAGTACG
E3S	CCAAGTCTCCCTTACGCATCACCG
E4S	CTTGGGTCTTTTCCTGAAGTGC
E5S	GGAGCATTGTTGAGTCCAGGGAGC
P1A	GCACAACCTGCCCTGTACAGGAAG
E1A	CAAAACCTTCAAGTTGCAGCCCTG
E2A	CACAAAGCCTCTCTGGTGAAGTCC
E3A	GCTCTCACCTCTCCAGGGCTTCAC
E4A	GCTCAGGGAAAGAAGAATCAGAGGTC
E5A	GGATTACAGGTATGAGCCACCACACC

Primers used for sequence analysis of a promoter region and all of the 5 exon regions including noncoding regions in ALOX5AP.

All the subjects enrolled in the present study provided written informed consent. The present study was approved by the Ethics Committee of the National Cardiovascular Center and by the Committee on Genetic Analysis and Gene Therapy of the National Cardiovascular Center. The characteristics of the study population are shown in Table 1. Subjects with systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or taking antihypertensive medication were categorized as having hypertension (HT). Subjects with fasting blood glucose ≥126 mg/dl, hemoglobinA1c ≥6.5%, and/or treatment for diabetes mellitus (DM) were categorized as having DM. Subjects with total cholesterol ≥220 mg/dl, triglycerides ≥150 mg/dl, and/or antihyperlipidemic medication were categorized as having hyperlipidemia (HLP).

DNA Studies

A promoter region and all of the 5 exon regions, including noncoding regions, were sequenced in 48 healthy subjects and 48 subjects with MI. Primers for sequencing are shown in Table 2. Eight polymorphisms were found and all the genotypes were determined by the TaqMan system in 1,875 control subjects and 353 subjects with MI. The probes and primers are shown in Table 3. HapA and HapB reported by DeCode,[6] which have been reported to be associated with MI and stroke, each consisted of 4 SNPs that were outside the area of our sequencing. To validate the possible importance of these haplotypes, the genotypes of 7 additional SNPs were also determined by the TaqMan system (Table 3).

Table 3 TaqMan Probes and Primers for *ALOX5AP* Genotyping

	Probe		Primer	
	VIC	FAM	F	R
A(−607)G	TTTTCTTGGAATTCAAAAA	TTTCTTGGATTCAAAAA	AAACCTTATGTGGCTGCTACTTACC	GTGCCCCAAATACTGTCCTTCT
T(−515)C	TGTGCGTGTGTGTGT	TGCGTGCGTGTGTGT	TGGAATTCAAAAAAGAAGGACAGTA	GGGCAACAGAGCAAGACTGTCT
A(162)C	CCCTTCACTCAGGG	CCCTTCAATCAGGG	CAGCGTGGTCCAGAATGGTA	TCCAAACAACCATCAAAGAAAATC
A(8640)C	AGTCCTAACCCTGATGTT	AGTCCTAACCCTGATGTTG	GCCTTTGAGCGGGTCTACACT	TTAAGGGTGGTCATCACTCCTAGAA
T(8733)C	AGCCAAGTTCTGAGCG	TGAGCCAAGCTTCTGA	ACCACCCTTAATACCACATGTCTGT	AAGCCTCTCTGGTGAAGTCCAA
G(20616)C	CCTTCCCCCTCCCAC	CCTTCCCCGCTCCCA	AGGGAAAGAAGAATCAGAGGTCCTA	CAGGAAGAGTGACAATTCAAAACAGTA
C(28506)G	CTTCTTTTTCGGAAGTGA	CTTCTTTTTGGAAGTGACT	GTCCGTTGCTGGCATATTCA	TGGAGATCGTCTTTATGTAGTTTTCAA
A(28794)G	CTATTCCCATGCATTTT	CTATTCCCGTGCATTT	GAACAAAATGATGTCATGTCAGCTC	TGGTCACAAAACATCTTCAGAGAAC
HapA1	CCACTGTTGCCCAGTGG	AGCCACTGTTACCCAGTG	ATGATTCTTCTGACAGCATCAGCT	CATGTTGCTGTGTCCATACATAGC
HapA2, HapB2	TGCAATTCTATTAACCTCAA	TGCAATTCTAATTAACCTCAA	TCACAAGATCCAGATGTATGTCCAA	ACTCTTAAGGTAGGTCTATGGTTGCAA
HapA3	AGAGCGCGTGTGATAA	CAGAGCGCATGTGATAA	TCGGAGGCCGTGTTTCAG	CCAGGGAGCAAGCATTAGCA
HapA4	AATTGCTGATGAGATCCT	AATTGCTCGATGAGATCC	TGCTTTAGTTCTTGACCTCACCAA	ACCATCTGGGTTCAAGAGAGAAAT
HapB1	CTGCCTCGGCCTC	TGCCTCAGCCTCCCA	ACATCACGTAGTGTGTTGTGTAAGAAA	ACTGTCTTGAACTCCTGACCTCAG
HapB3	AACTGAGGTAAAGATTC	AACTGAGGGTAAAGATT	TCTTTAACACCCTGTCTCCAAATACA	TGGTCCCTTCCAAAATTCATATG
HapB4	TTTTAAAAAACCGAAAGGACCA	TTTTTAAAAAACTGAAAGGACCAC	TGCACCCCCACAAATACCTACAA	ATCCTGATGGCCTGGCATT

TaqMan probes and primers used to determine the genotypes of SNPs in ALOX5AP. The nucleotides of polymorphisms are underlined. HapA and HapB are defined as follows: HapA1, SG13S376; HapA2 and HapB, SG13S114; HapA3, SG13S89; HapA4, SG13S32; HapB1, SG13S377; HapB3, SG13S41, HapB4, SG13S35 (see Reference 1).

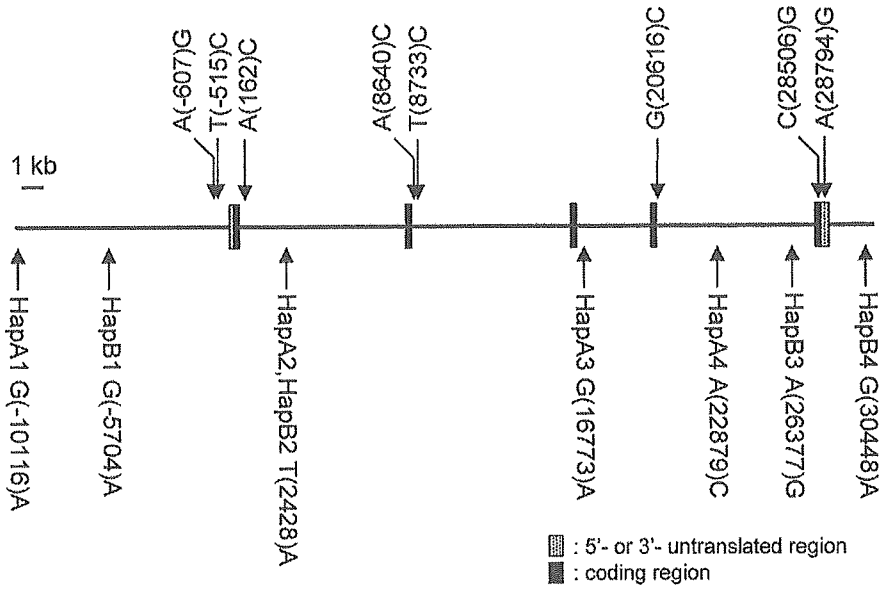

Fig 1. Schematic of the *ALOX5AP* gene and the positions of the determined polymorphisms. Gray boxes indicate the 5'- or 3'-untranslated regions, and black boxes indicate coding regions.

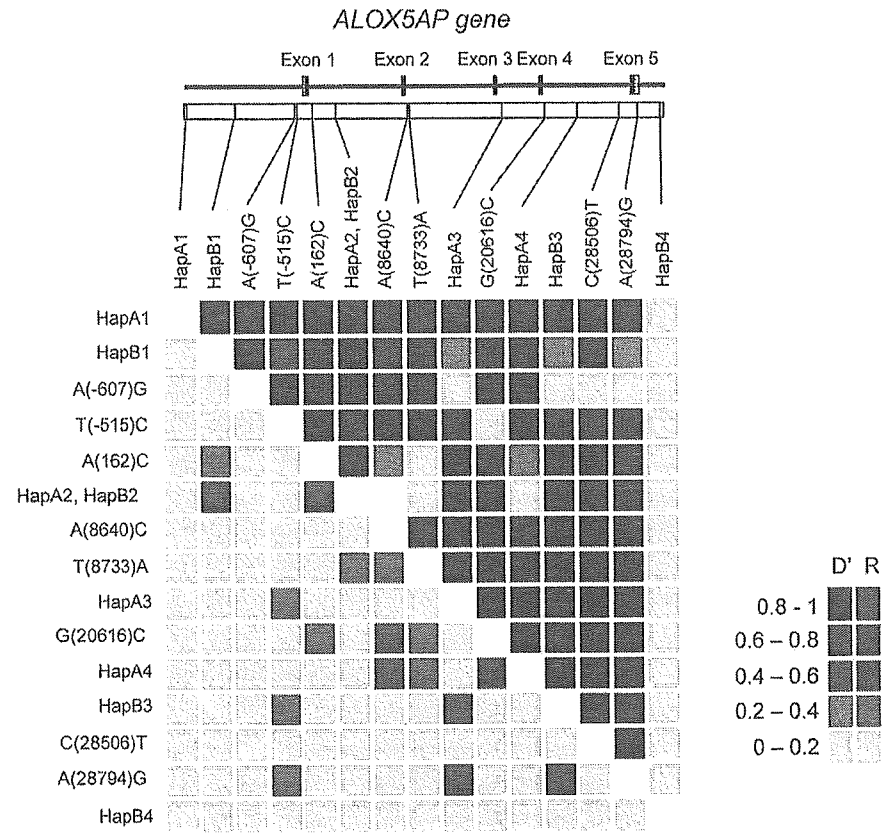

Fig 2. Linkage disequilibrium among the SNPs in the *ALOX5AP* gene. Two measures of LD are shown: D'-values in the upper right triangle and R-square values in the lower left triangle. Color-coded scales for D'-values or R-square values (measures of LD strength) are provided on the right.

Statistical Analysis

Values are expressed as mean ± standard error of the mean. All statistical analyses were performed with the JMP statistical package (SAS Institute Inc, Cary, NC, USA) unless otherwise stated. Multiple logistic analysis was performed to obtain predictors for MI. R-square values between polymorphisms and haplotype frequencies in the control and MI groups were analyzed using the SNPAlyze Pro

Table 4 Genotype Frequencies of Each Polymorphism in *ALOX5AP* in the Total Group and in Males

Polymorphism	Control			MI			P_1 value	P_2 value	Control males			MI males			P_1 value	P_2 value
	Major	Hetero	Miner	Major	Hetero	Miner			Major	Hetero	Miner	Major	Hetero	Miner		
A(−607)G	1,843	31	1	342	11	0	0.1893	0.4430	854	17	0	295	11	0	0.1201	0.1167
T(−515)C	1,859	15	0	346	2	0	0.6451	0.5695	863	8	0	299	2	0	0.6713	0.5876
A(162)C	491	939	445	105	179	68	0.1294	0.2706	240	428	203	93	150	63	0.4989	0.4470
A(8640)C	800	833	237	146	167	39	0.5250	0.5009	371	381	118	124	146	35	0.4035	0.4553
T(8733)C	605	903	364	113	179	61	0.5697	0.3391	294	413	163	97	157	52	0.5061	0.3207
G(20616)C	1,122	651	102	210	127	16	0.7331	0.8127	510	313	48	181	111	14	0.8151	0.7954
C(28506)G	1,862	12	0	353	0	0	0.0415	0.7168	866	5	0	306	0	0	0.0823	0.8010
A(28794)G	1,847	26	1	344	7	0	0.5980	0.7270	859	11	1	299	6	0	0.5133	0.5663
HapA1 (G(−1011 6)A)	1,873	1	0	352	0	0	0.5573	0.9375	871	0	0	305	0	0		
HapA2, HapB2 (T(2428)A)	792	844	239	138	173	39	0.2976	0.1480	370	384	117	123	145	35	0.4675	0.4325
HapA3 (G(16773)A)	1,848	26	1	346	7	0	0.6031	0.7313	859	11	1	300	6	0	0.5156	0.5703
HapA4 (A(22879)C)	800	832	242	145	168	39	0.4285	0.3791	373	382	116	123	146	36	0.4620	0.4838
HapB1 (G(−5704)A)	1,249	561	64	221	121	10	0.2426	0.1756	573	266	32	200	96	9	0.8119	0.8653
HapB3 (A(26377)G)	1,847	27	1	343	9	0	0.3032	0.7148	858	12	1	298	7	0	0.4260	0.5632
HapB4 (G(30448)A)	1,875	0	0	353	0	0			871	0	0	306	0	0		

Major, Hetero and Minor indicate major genotype, heterozygous genotype, and minor genotype, respectively. For example, in the case of polymorphism A(−607)G, major, hetero, and minor refer to the AA, AG, and GG genotypes, respectively. The numbers of each genotype of each SNP are shown. P_1 values were calculated by χ^2 analysis and P_2 values were calculated by multiple logistic analysis including age, sex, BMI, HT, HLP, DM, and C-SM as independent variables (See Table 1 for abbreviations).

statistical package (version 3.2, Dynacom Inc). Diplotypes were also estimated by the SNPAlyze Pro statistical package.

Results

Sequence analyses in 96 subjects revealed the existence of 8 polymorphisms in Japanese. The genotypes of these 8 polymorphisms were determined by the TaqMan system in 1,875 control subjects and 353 MI subjects. Seven additional genotypes were also determined by the TaqMan system to validate the possible importance of HapA and HapB, as reported by DeCode.[6] A schematic of *ALOX5AP* and its polymorphisms are shown in Fig 1. The LD values calculated by D'- or R-square values among these SNPs are shown in Fig 2.

Genotype frequencies in the control and MI groups are shown in Table 4. P_1 values were calculated by chi-square analysis and P_2 values were calculated by multiple logistic analysis including age, sex, body mass index (BMI), HT, HLP, DM, and current smoking (C-SM) as independent variables.

The allele frequencies of the SNPs comprising HapA and HapB were significantly different between the Icelandic and Japanese populations. The allele frequencies of HapA1, HapA3, HapB3, and HapB4 were significantly less in Japanese, and some of the HapA and HapB haplotype frequencies were too small for conducting meaningful association studies in Japanese. Thus, we conducted haplotype analyses based on the polymorphisms found in our study population.

The allele frequencies of the A162C, A8640C, T8733A, and G20616C polymorphisms exceeded 0.15 (Table 4). The polymorphisms A8640C, T8733A, and G20616C are in tight LD (Fig 2). Therefore, we constructed haplotypes with A162C and one of the polymorphisms from A8640C, T8733A, and G20616C, and compared haplotype frequencies between the control and MI groups. The most significant difference in haplotype frequency ($p<0.0001$ [1,000 permutations]) was observed in the haplotype constructed by the A162C and T8733A polymorphisms (Table 5). The haplotype (AA) was less frequent in the control than in the MI group (20.0% vs 25.8%, p=0.003 [1,000 permutations] The haplotype (CA) was more frequent in the control than in the MI group (23.6% vs 16.9%, p=0.001 [1,000 permutations]. Similar trend was also observed in male subjects only (Table 5).

Next, diplotypes of the study population were estimated and the characteristics of the subjects with the homozygous genotype of the (CA) haplotype and the others are shown in Table 6. The influence of the haplotypes on susceptibility to MI was assessed by multiple logistic analysis in which age, sex, C-SM, BMI, HT, HLP, and DM were included as independent variables. The homozygous genotype of the (CA) haplotype was significantly associated with reduced risk for MI (p=0.0431, odds ratio=0.4436, 95% confidence interval=0.189–0.926) over other genotypes. However, multiple logistic analysis did not conclude that the homozygous genotype of the (AA) haplotype was associated with increased risk for MI (p=0.2901).

Discussion

The purpose of the present study was to validate in a Japanese population the association between *ALOX5AP*