In the large group, regression of the coronary aneurysm was uncommon. However, some large coronary aneurysms regressed. Whether large coronary aneurysms regress or not may be influenced by the affected segment or the length of the affected area.

Regression groups fall into two apparent subgroups. One is regression without intimal thickening, which occurs in aneurysms <4.0 mm and that regress within 1 year. All aneurysms <4.0 mm in diameter in a coronary angiogram performed less than 100 days after the onset of KD regressed and did not develop cardiac sequelae. This observation supports the data of our previous intravascular ultrasound study that there is no late intimal thickening in aneurysms <4.0 mm in diameter in the acute phase. Strictly speaking the term regression should be confined to this group.

The other subgroup is "apparent" regression with intimal thickening [19, 21, 23]. Apparent regression produces apparent normalization angiographically but with decreased coronary artery diameter due to intimal thickening. Recently, we observed acute myocardial infarction in patients with apparent regression. Although the cause of acute myocardial infarction is unknown, abnormalities of the coronary arterial wall probably predispose to the episode.

Acute stage aneurysms in KD usually involve the proximal segment of the coronary arteries. Bifurcation aneurysms of the left main coronary artery, which are often detected, are also characteristic of KD. In our study, thickening at the bifurcation of the left main coronary artery did not correlate strongly with the diameters of the coronary arteries in the first coronary angiograms [23].

For bifurcation lesions, the incidence of stenotic lesions was low compared with that of branch lesions. This may be explained by the difference in arterial types. Coronary arteries are muscular, whereas the ascending aorta is an elastic vessel. The most proximal portion of the left main artery is of a transitional structure. We speculate that the effect of acute vasculitis and its subsequent course of regression after the inflammation may differ in elastic vessels compared to muscular arteries. The characteristics of structure at the bifurcation may also explain the difference in behavior.

Usually, an aneurysm at the bifurcation >10 mm in diameter is not localized to the bifurcation but extends into either the left anterior descending or the left circumflex arteries. We believe that the development of stenosis or occlusion in a bifurcation aneurysm is strongly dependent on the degree of involvement of the branches. In one patient with a long left main trunk, localized stenosis appeared in the left main trunk after a large aneurysm at the bifurcation.

We developed fate maps for coronary arterial dilatation based on a coronary arterial diameter ≥4.0 mm in the acute phase for branch and bifurcation lesions. These fate maps should facilitate the optimal follow-up and treatment of patients with coronary arterial lesions after KD. Currently, measurement of the coronary arterial diameter in the acute phase by two-dimensional echocardiography is precise, and the value correlates highly with measurements by angiography. We believe that the results of this study will help in the prediction of the fate of coronary aneurysms by two-dimensional echocardiography without angiographic studies [2, 4].

When the diameters of the coronary aneurysms are the same in the medium group and the large group, the fate of the coronary aneurysms will not always be the same. The affected segment may determine the fate of the coronary artery due to additional

factors. Furthermore, the factors that determine the fate of coronary aneurysms may derive from differences between patients. Clarification of such factors may be useful in the future in the treatment of sequelae due to KD.

Study Limitations

The study is limited by the fact that the treatment in the acute phase and in the late period varied in this patient population. However, the study entry point is the presence of coronary dilatation at the first angiogram. Although acute treatment may influence the incidence of aneurysms, it is unclear whether it influences their long-term fate. We think that our fate maps indicate the result of the treatment by antiplatelet agents. The treatment was similar to the usual treatment for patients with coronary arterial lesions due to KD, The influence of the antiplatelet agents on intimal thickening of coronary arterial wall in the long-term period is unclear. We stress that a primary goal of our study was to define the population of post-KD patients at greatest risk for late sequelae and we believe we have achieved this goal.

Although we used the absolute dimension in the initial coronary angiogram for the predictive value of stenotic lesions, correction of the dimension by body surface area might be better. Our study did not include patients who had coronary angiograms within 2 months of the onset of KD, and few patients had onset of KD at 3 months. The predictive value causing stenotic lesions in the aneurysms of the acute phase for these small infants must be investigated. Furthermore, we should consider a possible decrease in the diameter of the aneurysm within the first 100 days.

Conclusion

The threshold for coronary aneurysms causing stenosis is 6.0 mm in coronary angiograms performed less than 100 days after the onset of KD. We speculate that acute dilatation of more than 6.0 mm indicates a high probability of irreversible change in the coronary arterial wall, leading to subsequent stenosis or occlusion.

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References

1. Akagi, T, Rose, V, Benson, LN et al. (1992) "Outcome of coronary artery aneurysms after Kawasaki disease" J Pediatr 12l: 689-694

2. Arjunan, K, Daniels, SR, Meyer, RA et al. (1986) "Coronary artery caliber in normal children and patients with Kawasaki disease but without aneurysms. An echocardiographic and angiocardiographic study" J A Coll Cardiol 8: 1119-1124 ChemPort

3. Fujiwara, H, Hamashima, Y (1978) "Pathology of the heart in Kawasaki disease" Pediatrics 62: 100-107 PubMed

4. Hiraishi, S, Misawa, H, Takeda, N et al. (2000) "Transthoracic ultrasonic visualization of coronary aneurysm, stenosis and occlusion in Kawasaki disease" Heart 83: 400-405

5. Kato, H, Ichinose, E, Yoshioka, F et al. (1982) "Fate of coronary aneurysms in Kawasaki disease: serial coronary angiography and long-term follow-up study" Am J Cardiol 49: 1758-1766
ChemPort PubMed

6. Kato, H, Koike, S, Yamamoto, M et al. (1975) "Coronary artery aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome" J Pediatr 86: 892-898
ChemPort PubMed

7. Kato, H, Sugimura, T, Akagi, T et al. (1996) "Long-term consequences of Kawasaki disease" A 10 to 21 year follow-up study of 594 patients. Circulation 94: 1379-1385
ChemPort

8. Kawasaki, T (1967) "Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children" Jpn J Allergy 16: 178-222
Comment: [in Japanese]
ChemPort

9. Kawasaki, T, Kosaka, F, Ozawa, S et al. (1974) "A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan" Pediatrics 54: 271-276
ChemPort PubMed

10. Kurisu, Y, Azumi, T, Sugahara, T et al. (1987) "Variation in coronary dimension (distensible abnormality) after disappearing aneurysm in Kawasaki disease" Am Heart J 114: 532-538
crossref ChemPort PubMed

11. Nakano, H, Ueda, K, Saito, A et al. (1985) "Repeated quantitative angiograms in coronary arterial aneurysm in Kawasaki disease" Am J Cardiol 56: 846-851
crossref ChemPort PubMed

12. Naoe, S, Takahashi, K, Masuda, H et al. (1991) "Kawasaki disease with particular emphasis on arterial lesions" Acta Pathol Japonica 41: 785-797
ChemPort

13. Onouchi, Z, Shimazu, S, Kiyosawa, N et al. (1982) "Aneurysms of coronary arteries in Kawasaki disease: an angiographic study of 30 cases" Circulation 66: 6-21
ChemPort PubMed

14. Sasaguri, Y, Kato, H (1982) "Regression of aneurysms in Kawasaki disease: a pathological study" J Pediatr 100: 225-231
ChemPort PubMed

15. Sugimura, T, Kato, H, Inoue, O et al. (1994) "Intravascular ultrasound of coronary arteries in children: assessment of the wall morphology and the lumen after Kawasaki disease" Circulation 89: 258-265
ChemPort PubMed

16. Suzuki, A, Kamiya, T, Arakaki, Y et al. (1994) "Fate of coronary arterial aneurysms in patients with Kawasaki disease" Am J Cardiol 74: 822-824
crossref ChemPort PubMed

17. Suzuki, A, Kamiya, T, Ono, Y et al. (1988) "Myocardial ischemia in Kawasaki disease: follow-up study by cardiac catheterization and coronary angiography" Pediatr Cardiol 9: 1-5
ChemPort PubMed

18. Suzuki, A, Kamiya, T, Tsuda, E, et al. (1997) Natural History of Coronary Artery Lesions in Kawasaki Disease, Elsevier, Amsterdam, pp 211-221

19. Susuki, A, Yamagishi, M, Kimura, K et al. (1996) "Functional behavior and morphology of the coronary artery wall in patients with Kawasaki disease assessed by intravascular ultrasound" J Am Coll Cardiol 27: 291-296
crossref ChemPort PubMed

20. Takahashi, M, Mason, W, Lewis, A (1987) "Regression of coronary aneurysms in patients with Kawasaki syndrome" Circulation 75: 387-397
ChemPort PubMed

21. Tatara, K, Kusakawa, S (1987) "Long-term prognosis of giant coronary aneurysm in Kawasaki disease: an angiographic study" J Pediatr 111: 705-710
ChemPort PubMed

22. Tsuda, E (2003) "Intravascular ultrasound in Kawasaki disease" Res Adv Cardiol .: 21-28

23. Tsuda, E, Kamiya, T, Kimura, K et al. (2002) "Coronary artery dilatation exceeding 4.0 mm during acute Kawasaki disease predicts a high probability of subsequent late intima-medial thickening" Pediatr Cardiol 23: 9-14
SpringerLink ChemPort PubMed

24. Yanagawa, H, Nakamura, Y, Yashiro, M (2002) "Results of the nationwide epidemiologic survey of Kawasaki disease in 1999 and 2000 in Japan" J Pediatr Practice 65: 332-342
Comment: [in Japanese]

CARDIOVASCULAR MEDICINE

Dilated coronary arterial lesions in the late period after Kawasaki disease

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Objectives: There are two types of late coronary dilated lesions after Kawasaki disease: new aneurysms and expanding aneurysms. The development of coronary dilated lesions late after Kawasaki disease was investigated.

Methods: Between 1978 and 2003, 562 patients with coronary arterial lesions underwent selective coronary angiography on at least two occasions.

Results: Of the 562 patients studied, 17 new dilated or expanding lesions were found in 15 patients (3%, 11 boys, four girls). The time of detection of new aneurysms after Kawasaki disease ranged from 1.9–19.2 years (median 11.4 years) and their diameters ranged from 2.0–6.5 mm (median 4.4 mm). Thirteen new aneurysms occurred in vessels in which previous aneurysms had regressed and all new aneurysms were associated with localised stenosis. A new aneurysm at the bifurcation or in the branches was seen in 14 (93%) and 13 were eccentric (87%). Of two expanding aneurysms, one involved the right coronary artery in one patient and the other the left anterior descending coronary artery. One expanding aneurysm increased from 4.4 mm to 19.5 mm over 17 years, and the other expanding aneurysm increased from 10 mm to 15 mm in one year.

Conclusions: Neither new nor expanding aneurysms have caused cardiac events. New aneurysms often develop as a pre-stenotic or post-stenotic dilatation secondary to localised stenosis. New and expanding aneurysms may be caused by haemodynamic factors in addition to the abnormality of the coronary arterial wall after severe acute vasculitis. Coronary arterial wall abnormalities were stenosis as well as, rarely, dilatation of the vessels in the late period. It is important to recognise that the changes of the coronary arterial wall persist late after regression of a large aneurysm.

See end of article for authors' affiliations

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The vasculitis of Kawasaki disease (KD) causes coronary aneurysms in about 10% of patients early after the onset.[1] Aneurysms usually change their shape after the acute phase, but some may persist for years whereas others either regress or evolve into stenotic lesions.[2–4] Usually, the diameters of persistent aneurysms may increase slightly because of somatic growth or they may decrease because of intimal thickening of the vascular wall.[5–8] In the late period of KD either new aneurysms or expanding aneurysms are unusual but have been reported.[9–12] We investigated the characteristics of the dilated lesions and their time of appearance and speculate about their cause.

PATIENTS AND METHODS

Between 1978 and 2003, after giving informed consent, 562 patients with coronary arterial lesions underwent selective coronary angiography on at least two occasions. The protocol was as follows. Coronary angiography for patients with coronary arterial lesions was performed immediately after the acute phase of KD. All patients underwent a second coronary angiography after one year and subsequent follow up coronary angiography was done at 3–5 year intervals depending on the findings. If the aneurysms regressed, subsequent coronary angiography was not done but the patients were followed up in the outpatient clinic by non-invasive imaging including echocardiography and electron beam computed tomography. If coronary arterial lesions were suspected on non-invasive imaging, coronary angiography was considered at that time. Some patients who attended our hospital late after the acute KD episode were also included. Those patients did not undergo coronary angiography immediately after the acute phase.

RESULTS

We found 17 lesions in 15 patients that were coronary dilatations developing late after KD (3%, 11 boys, four girls). All 15 had received anticoagulant treatment. Eight patients underwent coronary artery bypass grafting (CABG), and one patient underwent percutaneous balloon angioplasty. Late coronary artery dilatations after KD can be divided into two groups: new aneurysms and expanding aneurysms.

New aneurysms

We found 15 new aneurysms in 13 patients in the coronary arteries as follows: right coronary artery (RCA), three; left anterior descending coronary artery (LAD), eight; left circumflex artery, three; and left main trunk, one. Fourteen of 15 new aneurysms were in the proximal vessel segments. In 10 lesions, there had been a pre-existing aneurysm at the same site in the initial coronary angiography. Pre-existing aneurysms had been detected by echocardiography in the acute phase for three lesions. Acute stage status for the two remaining new aneurysms was unknown. The diameter of all pre-existing aneurysms exceeded 7 mm.

The age at onset of KD ranged from 3 months to 7.0 years (median 15 months). The interval from the onset of KD to the latest coronary angiography ranged from 4.4–22.1 years (median 12.5) and the time of first detection of new aneurysms ranged from 1.9–19.2 years (median 11.4 years) (table 1). The interval from the onset of KD to the first

Abbreviations: CABG, coronary artery bypass grafting; KD, Kawasaki disease; LAD, left anterior descending coronary artery; RCA, right coronary artery

Table 1 Characteristics of the new aneurysms

Age (years)	Sex	Interval from KD (months)	Segment	Diameter (mm)	LS (%)	Pre-existing aneurysm	Branching or bifurcation location	Eccentric
1.9	M	1.5	LCX 15	4.1	90	Yes	Branch	No
4	M	3.7	LAD 6	2.0	75	Yes	Branch	Yes
7	F	6.2	RCA 2	3.0	90	Yes	Branch	Yes
10	F	9.8	LAD 6	5.2	90	Yes	Branch	Yes
11	M	4.4	RCA 1	4.2	75	Yes	Branch	Yes
12	F	10.2	LAD 6	4.7	90	Yes	Branch	Yes
5	M	4.3	LMT 5	3.8	75	Yes	No	No
14	M	13	LAD 6	4.4	50	Yes	Branch	Yes
14	M	13	RCA 1	4.9	75	Yes	Branch	Yes
12	M	12	LAD 6	6.5	50	Unknown	Branch	Yes
17	F	16	LCX 11	2.5	25	Yes	Branch	Yes
17	F	13	LAD 6	5.4	25	Yes	Branch	Yes
7	M	6.2	LAD 6	5.1	50	Yes	Bifurcation	Yes
11	M	9.9	LCX 13	3.2	90	Unknown	Bifurcation	Yes
19	M	15.8	LAD 6	5.6	25	Yes	Bifurcation	Yes

F, female; KD, Kawasaki disease; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LMT, left main trunk; LS, localised stenosis; M, male; RCA, right coronary artery

detection ranged from 1.6–16.3 years (median 9.9 years). The time of the first appearance of localised stenosis ≥ 25% ranged from 1.0–16.3 years (median 5.4 years). In five lesions a new aneurysm and localised stenosis first appeared at the same time. For the remaining eight lesions the interval from the first appearance of localised stenosis to the appearance of new aneurysms ranged from 0.6–6.4 years (median 3.3 years).

The diameter of the new aneurysms ranged from 2.0–6.5 mm (median 4.4 mm). In nine of 11 lesions on follow up coronary angiography, the diameter of the new aneurysms was slightly increased, the increase ranging from 0.4–2.3 mm. After CABG, one new aneurysm with a diameter of 2.0 mm resolved, whereas the diameter of the other new aneurysm decreased slightly.

All new aneurysms had associated localised stenosis. The degree of stenosis was 25% in three patients, 50% in three, 75% in four, and 90% in five. Twelve lesions were post-stenotic and three pre-stenotic (table 1). A new aneurysm at the bifurcation or in the branches was seen in 14 patients (93%) (fig 1). In this study, branches referred to the small branching vessels from the major branches. Bifurcation referred to the bifurcation between the LAD and the diagonal branch or the bifurcation between the posterolateral and posterodescending branch. Thirteen new aneurysms were eccentric. None of the new aneurysms caused cardiac events, although the coronary artery of some patients was revascularised.

Three cases of new aneurysms

One girl developed KD when 4 months old. Giant aneurysms were seen on the RCA and the left coronary artery by two dimensional echocardiography. At coronary angiography four months after the onset the left coronary artery the aneurysm was smaller. An angiogram recorded seven years after the onset showed a 50% localised stenosis in the LAD and occlusion of the RCA (fig 2). She had not experienced chest pain. Ten years after the onset there was a new aneurysm with associated 90% localised stenosis in the LAD. The pressure gradient estimated by the velocity at the localised stenosis by two dimensional echocardiography was 31 mm Hg (fig 3). She underwent a CABG to the LAD. One year later the estimated pressure gradient was 4 mm Hg at the same lesion. The diameter of the new aneurysm decreased from 5.2 to 4.5 mm.

A boy had KD at the age of 15 months. Although he had severe heart failure he did not undergo coronary angiography at the time. An angiogram five years after the acute episode showed segmental stenosis in the RCA. Twelve years after the onset there was a new aneurysm with associated 50% localised stenosis in the LAD. Seven years later the findings were almost the same, although the aneurysm was slightly larger (fig 4). Figure 5 shows the intravascular ultrasound findings in the new aneurysm. In the proximal portion of the aneurysm intimal thickening was severe, in the aneurysm itself it was slight, and distally eccentric intimal thickening was detected.

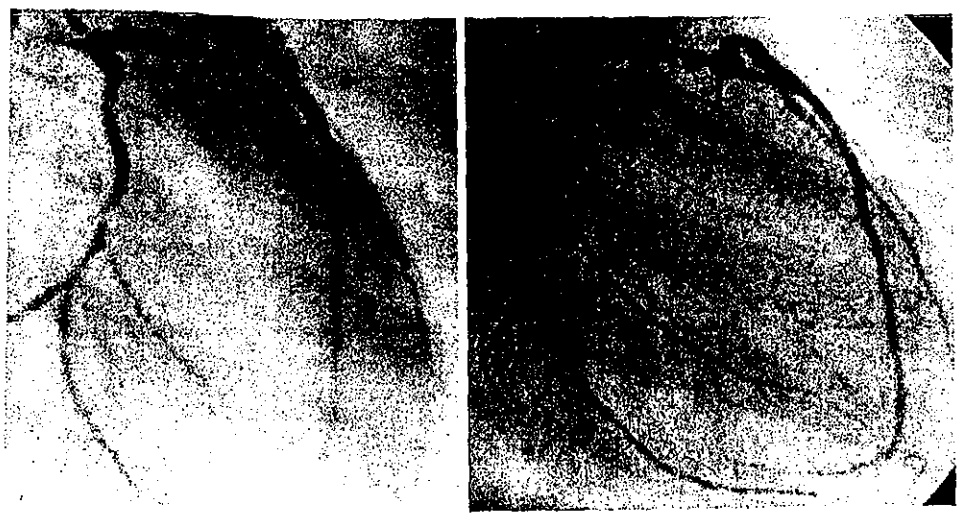

Figure 1 New aneurysm at bifurcation. Angiograms at (left) 8 years and (right) 7 years.

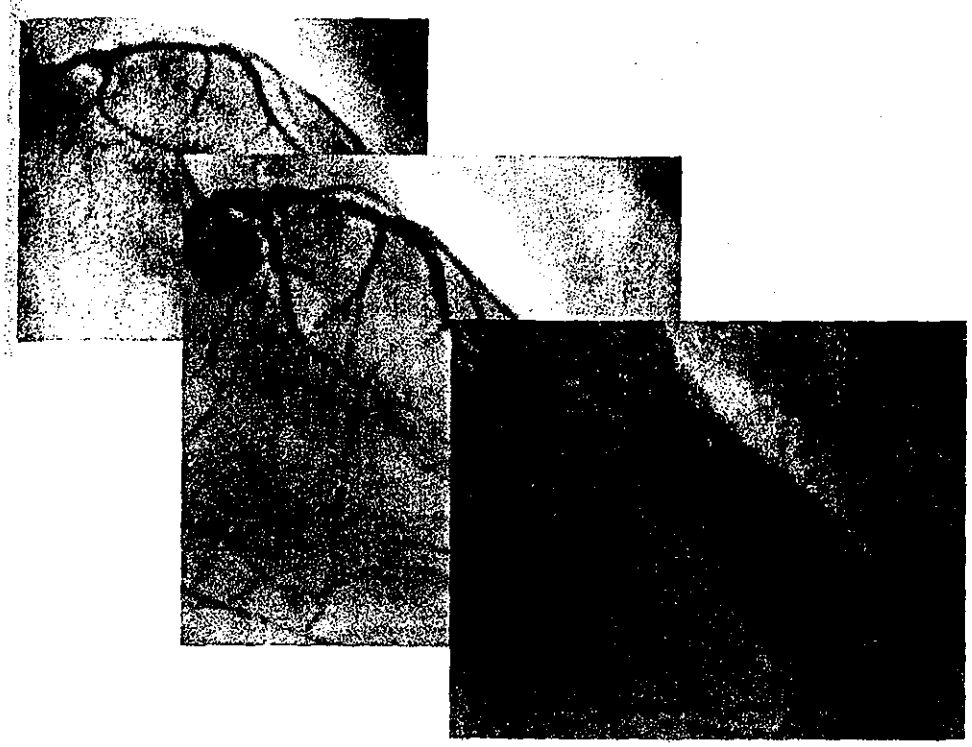

Figure 2 New aneurysm with severe localised stenosis that developed as a post-stenotic dilatation. Angiograms at (top) 2 years, (middle) 7 years, and (bottom) 10 years. The angiogram showed a new aneurysm with severe localised stenosis.

Another boy had KD at the age of 5 months. Two months after the onset angiograms showed aneurysms of the RCA and the LAD. Nine years after the acute illness an angiogram showed a 50% localised stenosis in the RCA. At 14 years there was a new aneurysm with 75% localised stenosis in the RCA and a new aneurysm with 25% localised stenosis in the LAD (fig 6).

Expanding aneurysms

Two expanding aneurysms were found, one in segment 1 of the RCA and the other in segment 6 of the LAD. One aneurysm of the RCA had decreased from 7.8 mm to 4.4 mm a year after its onset but subsequently enlarged to 19.5 mm over the next 17 years (fig 7). The other patient with an expanding aneurysm had KD when 11 years old. The

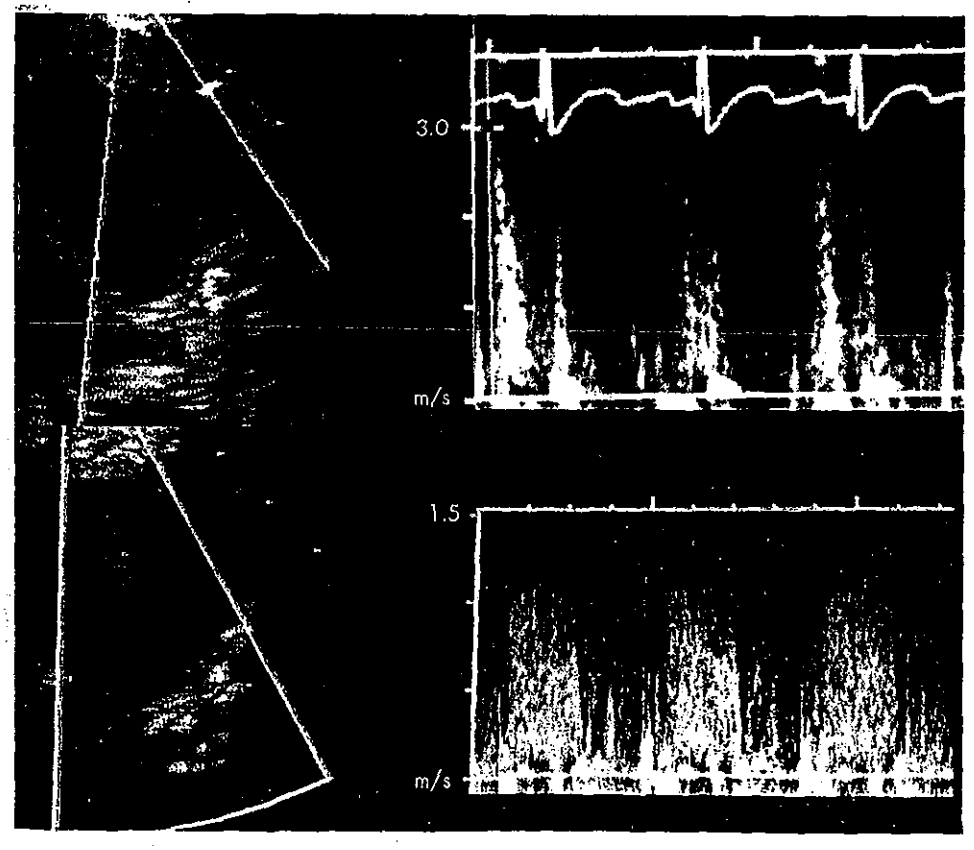

Figure 3 Pressure gradient at localised stenosis estimated by Doppler echocardiography. (Top) Echocardiogram before coronary artery bypass grafting (CABG) at 10 years. The velocity at the localised stenosis was 2.8 m/s. (Bottom) Echocardiogram after CABG. The velocity at the localised stenosis was 1.0 m/s.

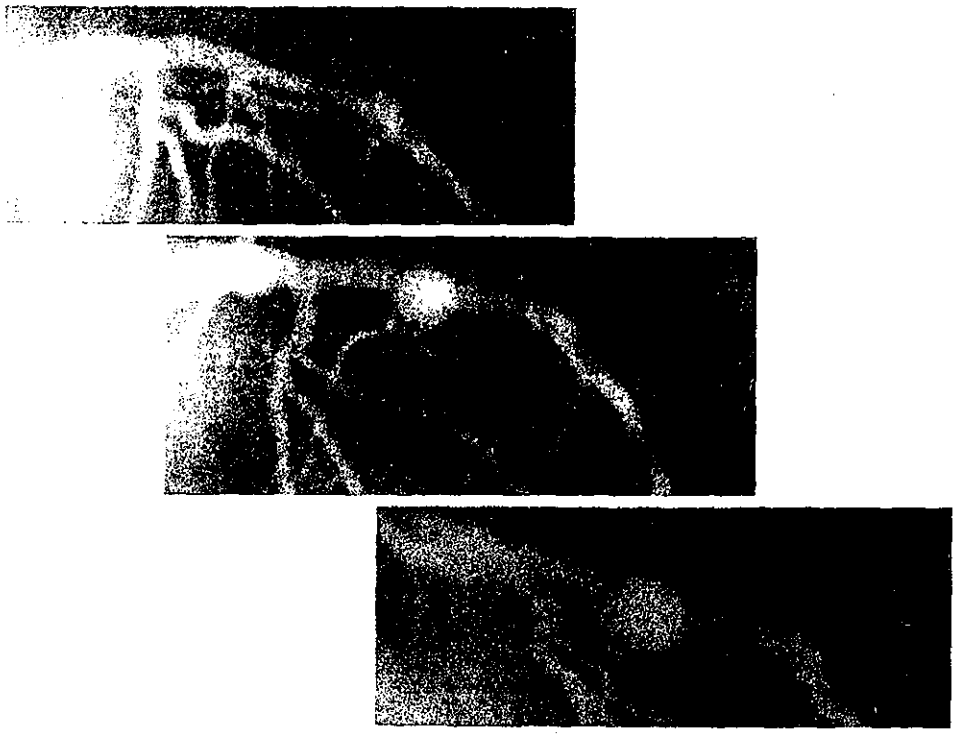

Figure 4 New aneurysm related to branching portion. Angiograms at (top) 5 years, (middle) 2 years, and (bottom) 19 years.

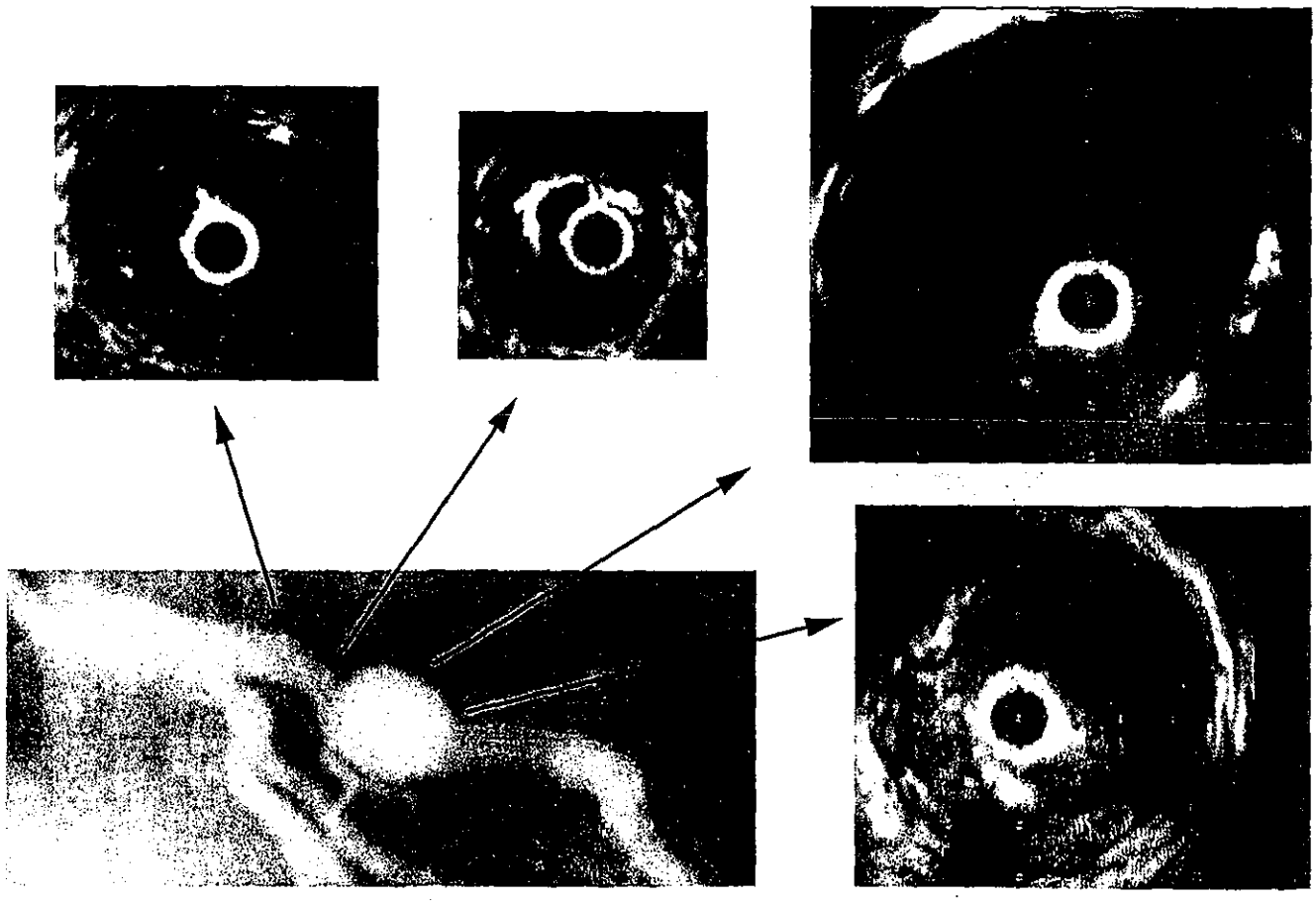

Figure 5 Intravascular ultrasound findings of a new aneurysm.

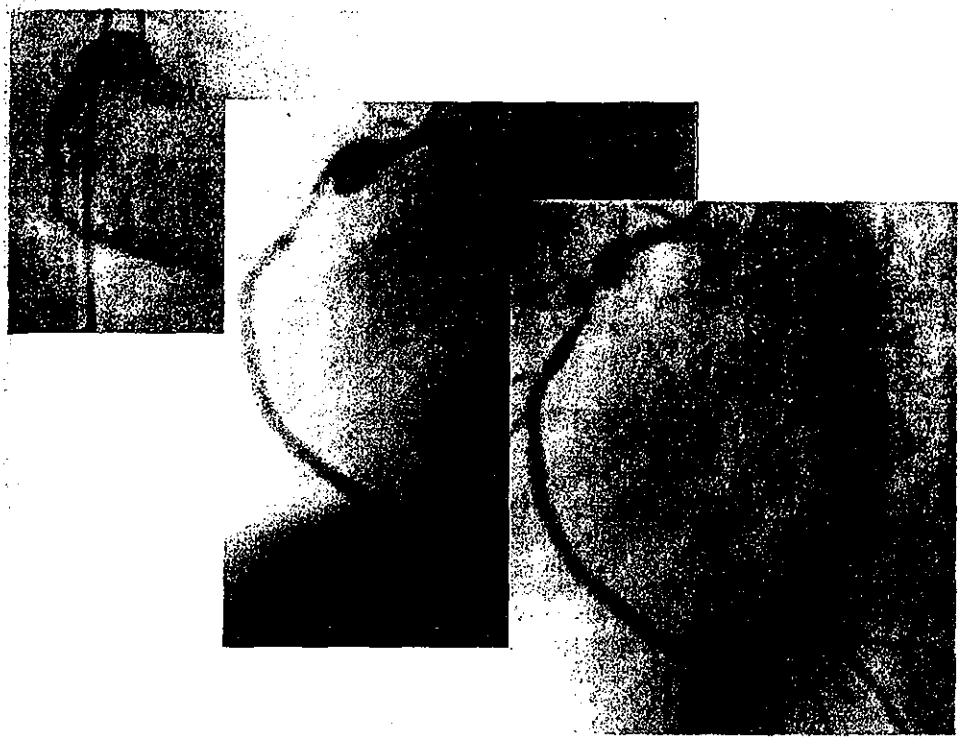

Figure 6 New aneurysm that developed as a pre-stenotic dilatation. Angiograms (top) two months, (middle) nine years, and (bottom) 14 years after onset.

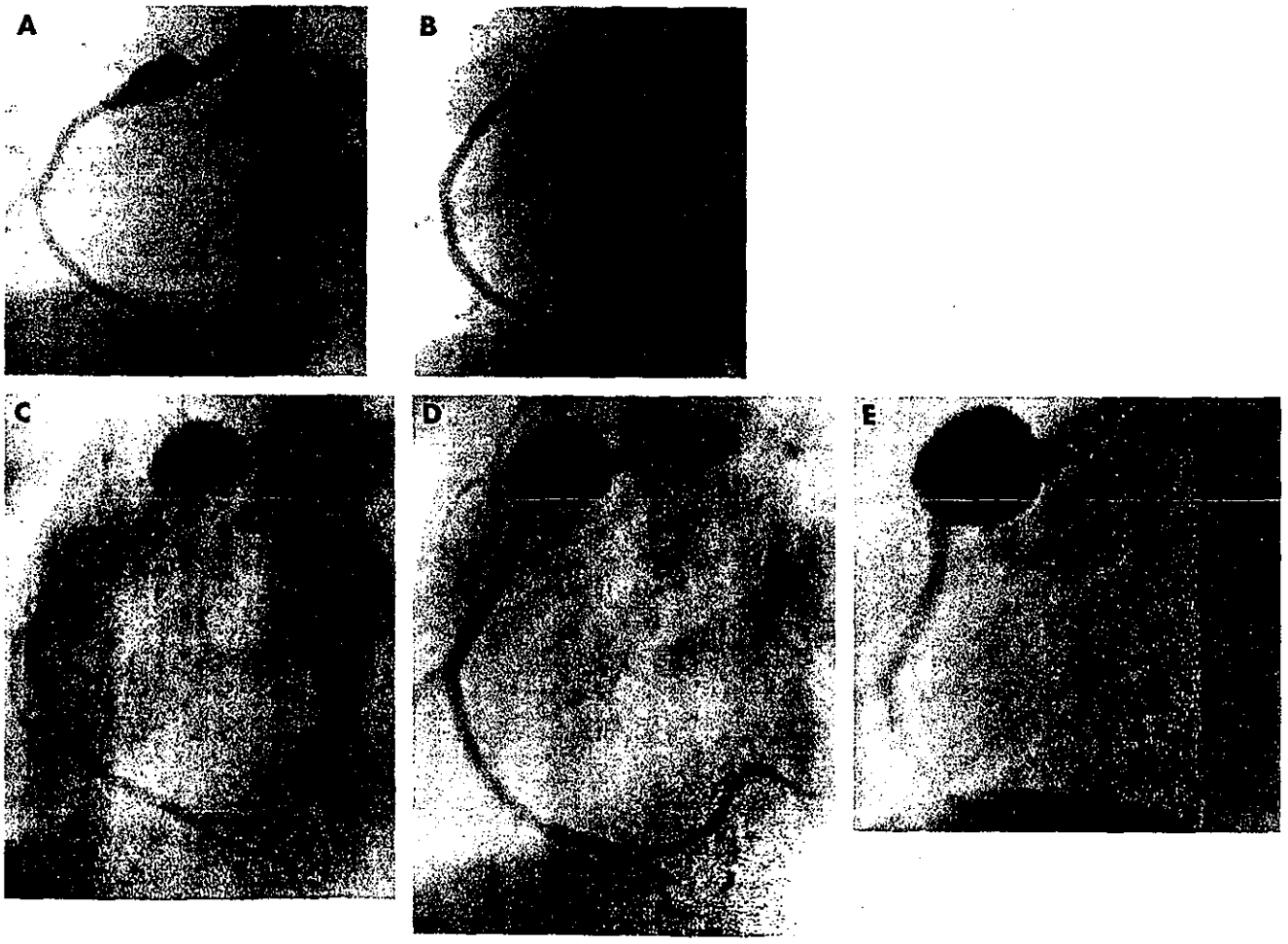

Figure 7 Angiographic follow up of an expanding aneurysm in a patient who had Kawasaki disease at the age of 18 months. Angiograms at (A) age 22 months (aneurysm diameter 7.8 mm), (B) 2 years 9 months (4.4 mm), (C) 10 years (9.6 mm), (D) 14 years (16.3 mm), and (E) 20 years (19.5 mm).

aneurysm increased from 10 mm to 15 mm in one year. Localised stenosis was not present in the two cases of expanding aneurysms and both patients were asymptomatic.

DISCUSSION

We found that new aneurysms developed in the same location at which there had been a pre-existing aneurysm. New aneurysms were aneurysms that redeveloped after previous regression. All pre-existing aneurysms were large and we hypothesised that the structure of the coronary arterial wall was irreversibly damaged by the severe acute inflammation. Most new aneurysms were associated with the appearance of severe localised stenosis. The pressure gradient generated by severe localised stenosis causes abnormal blood flow profiles, and these haemodynamic abnormalities exacerbate the existing damage from severe vasculitis. New aneurysms related to severe localised stenosis may be caused by pre-stenotic or post-stenotic dilatation. Furthermore, haemodynamic factors at the bifurcation and branches may predispose patients without severe localised stenosis to irregularity of the coronary wall. The wall properties at the bifurcation and branches may also favour aneurysm formation, as histologically the wall at a branching point is different from walls in other locations.[12]

Usually, the remodelling of localised stenosis after a large aneurysm caused by KD comprises severe intimal thickening.[5–8] It was thought that the coronary arterial wall of localised stenosis consisted of intimal thickening after regression of a large aneurysm; however, in this study the coronary arterial wall abnormalities late after KD were not only stenosis but also dilatation of the vessels, although such development was rare. Dilated coronary arterial lesions in the late period after KD indicated that the coronary arterial wall was irregular late after acute vasculitis. Although the cause is unknown, a small, weak portion in the thickened and firm wall may develop in the damaged coronary arterial wall after severe vasculitis caused by KD. The weak portion may be related to branching and may be dilated by the haemodynamic force of severe localised stenosis.

As most new aneurysms first appear during adolescence, growth of the coronary artery in relation to rapid somatic growth may also be a factor in causing new aneurysms. We must realise that the abnormality of the coronary arterial wall after regression of a large aneurysm consists not only of a thickened and firm portion but also a portion of partial thinning and weakness. This finding is useful for percutaneous coronary intervention, CABG, and long term follow up of patients with a history of a large aneurysm caused by KD.

Similarly, we believe that abnormalities of the coronary arterial wall contribute to the development of expanding aneurysms. Expanding aneurysms are proximal and subject to similar strong haemodynamic forces as is the aorta.[13]

The prevalence of dilated lesions in adult atherosclerosis and the occurrence of new aneurysms in cerebral aneurysms have been reported with a suggested incidence of 0.3–4.7%.[13–18] Haemodynamic factors, including hypertension, bifurcation wall characteristics, and weakening of the wall by atherosclerosis, were cited as causes. Some of these factors may also be common to the dilated coronary arterial lesions late after acute KD.

All new aneurysms were small or of medium size and, in our experience, neither new nor expanding aneurysms have led to clinical events. However, a patient with a new aneurysm and severe localised stenosis leading to occlusion has been reported on, although he remained asymptomatic.[11] The occurrence of cardiac events depends on the degree of localised stenosis. On the other hand, if a new aneurysm occurs in some cases, the progression of localised stenosis must be anticipated. A patient with an expanding aneurysm who was operated on to prevent rupture has also been reported on.[12] Acute myocardial infarction secondary to a large aneurysm certainly is possible. Such patients must be followed up closely and be given anticoagulants.

We emphasise the abnormalities of the coronary arterial wall in the appearance of new aneurysms. Therefore, although some of the new aneurysms were small, we called them "aneurysms" in this study on the basis of their shape. We must not ignore the abnormality of the coronary wall after apparent regression of a large aneurysm to prevent cardiac events in the future. Furthermore, we must develop a better understanding of long term changes in the vascular wall after severe acute vasculitis of KD.

Conclusion

New aneurysms and expanding aneurysms imply that the coronary arterial wall is abnormal late after previous regression. We suspect that new and expanding aneurysms result from haemodynamic factors in addition to partial weakening of the coronary wall late after acute severe vasculitis.

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REFERENCES

1 **Yanagawa H,** Nakamura Y, Yashiro M. [Results of the nationwide epidemiologic survey of Kawasaki disease in 1999 and 2000 in Japan]. *J Pediatr Pract* 2002;65:332–42 (In Japanese).
2 **Akagi T,** Rose V, Benson LNA, *et al.* Outcome of coronary artery aneurysms after Kawasaki disease. *J Pediatr* 1992;121:689–94.
3 **Suzuki A,** Kamiya T, Tsuda E, *et al. Natural history of coronary artery lesions in Kawasaki disease.* Shannon: Elsevier Science Ireland, 1997:211–21.
4 **Kato H,** Sugimura T, Akagi T, *et al.* Long-term consequences of Kawasaki disease: a 10 to 21 year follow-up study of 594 patients. *Circulation* 1996;94:1379–85.
5 **Naoe S,** Takahashi K, Masuda H, *et al.* Kawasaki disease: with particular emphasis on arterial lesions. *Acta Pathol Jpn* 1991;41:785–97.
6 **Sugimura T,** Kato H, Inoue O, *et al.* Intravascular ultrasound of coronary arteries in children: assessment of the wall morphology and the lumen after Kawasaki disease. *Circulation* 1994;89:258–65.
7 **Tsuda E,** Kamiya T, Kimura K, *et al.* Coronary artery dilatation exceeding 4.0 mm during acute Kawasaki disease predicts a high probability of subsequent late intima-medial thickening. *Pediatr Cardiol* 2002;23:9–14.
8 **Tsuda E.** Intravascular ultrasound in Kawasaki disease. Advanced technology in cardiology. Kerala: Global Research Network, 2003:21–8.
9 **Iwatani H,** Okuno M, Ono Y, *et al.* Prognosis of the cases with localized stenosis occurred from aneurysms on the coronary angiography. *Prog Med* 1989;9:2019–25.
10 **Tomita H,** Fuse S, Chiba S. Images in cardiology. Delayed appearance of coronary aneurysms in Kawasaki disease. *Heart* 1998;80:425.
11 **Yasukawa K,** Sonobe T, Yamamoto W, *et al. The evolution of newly* developed coronary aneurysm in the chronic stage of Kawasaki disease and the usefulness of MRCA. *Prog Med* 2003;23:1778–83.
12 **Kobayashi T,** Sone K, Shinohara M, *et al.* Giant coronary aneurysm of Kawasaki disease developing during postacute phase. *Circulation* 1998;98:92–3.
13 **Hartnell GG,** Parnell BM, Pridie RB. Coronary artery ectasia: its prevalence and clinical significance in 4993 patients. *Br Heart J* 1985;54:392–5.
14 **Velican C,** Velican D. Some particular aspects of the microarchitecture of human coronary arteries. *Atherosclerosis* 1979;33:191–200.
15 **Kitzis I,** Kornowski R, Miller HI. Delayed development of a pseudoaneurysm in the left circumflex artery following angioplasty and stent placement, treated with intravascular ultrasound-guided stenting. *Cathet Cardiovasc Diagn* 1997;42:51–3.
16 **Hashimoto N,** Handa H, Nagata I, *et al.* Experimentally induced cerebral aneurysms in rats. Part V. Relation of hemodynamics in the circle of Wills to formation of aneurysms. *Surg Neurol* 1980;13:41–5.
17 **Ilia R,** Kafri C, Carmel S, *et al.* Angiographic follow-up of coronary artery ectasia. *Cardiology* 1995;86:388–90.
18 **Takahashi K,** Ohyanagi M, Ikeoka K, *et al.* Clinical course of patients with coronary ectasia. *Cardiology* 1999;91:145–9.

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Pediatric Cardiology

Total Anomalous Pulmonary Venous Return with the Circular Pulmonary Venous Connection: Outcome of Common Pulmonary Venous Agenesis

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Abstract. A rare case of total anomalous pulmonary venous return, in which the right and left peripheral pulmonary veins connected circularly and there was no central part of the pulmonary vein or the common pulmonary vein, is presented. To our knowledge, total anomalous pulmonary venous return with circular pulmonary venous connection has not been reported previously in the literature. It is thought that the complex connection between peripheral pulmonary veins with the absence of the central part of the pulmonary vein as well as the common pulmonary vein results from common pulmonary venous agenesis.

Keywords: Total anomalous pulmonary venous return — Common pulmonary vein — Asplenia

Case Report

A female neonate, born at 33 weeks of gestation and weighing 2640 g, received mechanical ventilation due to persistent severe cyanosis. Echocardiography showed asplenia, atrioventricular septal defect, common atrium, left ventricular hypoplasia, double-outlet right ventricle, subpulmonary stenosis, and bilateral superior vena cava (SVC). Two abnormal transverse vessels, one of which drained into the left SVC and the other into the right SVC, were found but neither the central part of the pulmonary vein (CPPV) nor the common pulmonary vein (CPV) were detected. Pulmonary arteriography revealed the absence of the CPPV as well as the CPV and the circular connection between right and left peripheral pulmonary veins that drained into both SVCs through three separate bridging vessels (two right vessels and one left vessel). Each bridging vein seemed stenotic at its junction with the SVC (Fig. 1).

A procedure to relieve the pulmonary venous obstruction was performed. The junction of the left bridging vein and the left SVC was enlarged using a Gore-Tex patch and the right midportion of the pulmonary venous circle was directly anastomosed to the common atrium. Although she recovered from critical hypoxia (PaO_2 elevated from 17 to 35 mmHg), she developed hypoxic spells caused by infundibular stenosis. On day 2 after the first operation a right modified Blalock–Taussig shunt was added, but 4 days later after the second operation she died due to decreasing ventricular contraction.

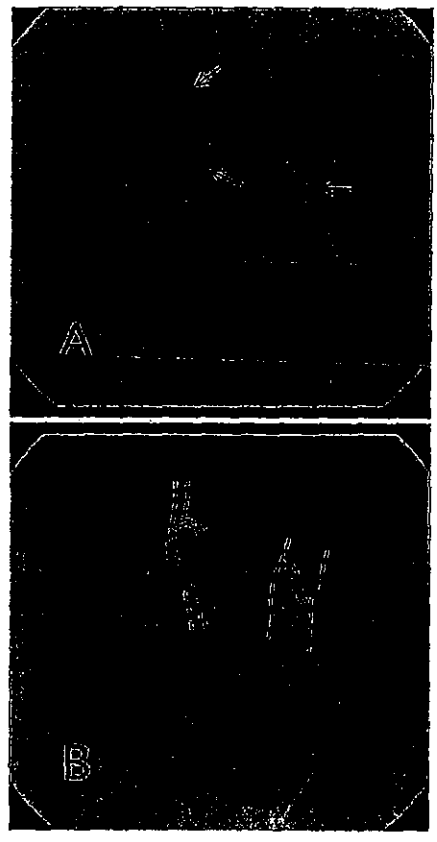

Fig. 1. (A) Angiogram showing the absence of any central part of the pulmonary vein as well as the common pulmonary vein and the circular connection between the right and left peripheral pulmonary veins that drain into both bilateral superior vena cava (*SVC*) through three separate bridging vessels. Each bridging vein seems stenotic at its junction with the SVC (*arrows*). (B) Broken lines and solid lines indicate bilateral SVC and bridging veins, respectively.

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Discussion

From the embryologic stand point, the pulmonary venous plexus engages with the splanchnic plexus and communicates with cardinal veins and the umbilicovitelline system. The CPV grows from the left atrium and connects with the pulmonary venous plexus. This direct connection allows atrophy of primitive complex systemic venous channels and provides normal pulmonary venous drainage to the left atrium through four central parts of the pulmonary vein (right upper, right lower, left upper, and left lower CPPV) [1, 2, 5]. It is believed that total anomalous pulmonary venous return results from abnormal development of the CPV and persistence of the embryologic pulmonary–systemic venous anastomosis [1].

In this case, the right and left peripheral pulmonary veins connected circularly and there was no CPPV or CPV. It is thought that the complex connection between peripheral pulmonary veins results from either agenesis of the CPV or early atrophy of the CPV connecting to the primitive pulmonary venous plexus, and it is also associated with asplenia. Sutherland et al. [4] reported a case of the latter with asplenia: an atretic strand extended from the common atrium to the CPPV, which directly connected to four other central parts of the pulmonary vein (right upper, right lower, left upper, and left lower CPPV). Then, the left lower CPPV connected to the right middle CPPV and drained into the SVC [4]. Ritter et al. [5] reported a case of the former in which there was no CPPV but there were complex connections between peripheral pulmonary veins [3]. We consider that our case is similar to the former one because of the absence of the CPPV; that is, the complex connection between peripheral pulmonary veins without forming the CPPV resulted from common pulmonary venous agenesis.

References

1. Delisle G, Ando M, Calder AL, et al. (1976) Total anomalous pulmonary venous connection: report of 93 aoutopsied cases with emphasis on diagnostic and surgical consideration. *Am Heart J 91*:99–122
2. Neill CA (1956) Development of the pulmonary veins: with reference to the embryology of anomalous pulmonary venous return. *Pediatrics 18*:880–887
3. Ritter S, Tani LY, Shaddy RE, Pagotto LT, Minich LLA (2000) An unusual variant of total anomalous pulmonary venous connection with varices and multiple drainage sites. *Pediatr Cardiol 21*:289–291
4. Sutherland RD, Korns ME, Pyle RR, Edwards JE (1970) Intrapulmonary vein contributing a segment of venous supply of contralateral lung. *Chest 57*:182–184
5. Van Praagh R, Corsini I (1969) Cor triatriatum: pathologic anatomy and a consideration of morphogenesis based on 13 postmortem cases and a study of normal development of the pulmonary vein and atrial septum in 83 human embryos. *Am Heart J 78*:379–405

Blood Pressure Dynamics During Simulated Ventricular Tachycardia in Patients After Right Ventricular Outflow Tract Reconstruction Mainly for Tetralogy of Fallot Compared With Patients After Ventricular Septal Defect Closure

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We studied hemodynamic changes during simulated ventricular tachycardia using ventricular pacing. Hemodynamic deterioration during pacing is more significant in patients after right ventricular outflow tract reconstruction, especially in adults, than after closure of a ventricular septal defect. The cardiac autonomic nervous system has a significant impact on hemodynamics during simulated ventricular tachycardia. ©2004 by Excerpta Medica, Inc.

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Late arrhythmias after definitive repair for congenital heart disease assume great importance, especially in adult patients[1] and are a major determinant of late morbidity and mortality.[2] Imbalance of cardiac autonomic nervous activity is a risk factor for arrhythmias, and baroreflex function has a significant role in arterial blood pressure (BP) recovery during ventricular tachycardia (VT) in adult patients.[3–5] Impaired baroreflex function is associated with symptoms and intolerance of tachyarrhythmia[6,7] and may cause hemodynamic deterioration and lethal ventricular fibrillation. Most postoperative patients with congenital heart disease exhibit abnormalities of the cardiac autonomic nervous system, especially impaired baroreflex function in complex anatomy patients.[8,9] This impairment may adversely influence hemodynamics during VT in these patients, who often also have residual hemodynamic abnormalities, causing volume and/or pressure overload. It is likely that the abnormal hemodynamics have a significant impact on BP change during VT. Because there are no studies addressing hemodynamics during tachyarrhythmias in patients with congenital heart disease, our purpose in the present study was to measure BP changes during ventricular pacing (simulated VT) and determine relations among BP changes, cardiac autonomic nervous activity, and hemodynamics at rest in patients with a history of right ventricular outflow tract reconstruction (RVOTR) for congenital heart disease.

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We studied 29 patients with RVOTR (tetralogy of Fallot in 20, and other anomalies in 9) and 11 patients after closure of a ventricular septal defect (VSD). Of the patients with RVOTR, 16 were children and the others were adults; clinical and resting hemodynamic characteristics are shown in Table 1. Severe pulmonary regurgitation was present in 5 patients with tetralogy of Fallot. Diuretics and anticoagulants were given in 5 and 9 patients with RVOTR, respectively. No patients with RVOTR were receiving antiarrhythmic agents. No medications were given in postoperative patients with VSD. Of these patients, 9 patients had had an outlet VSD with right coronary cusp prolapse and 2 a perimembranous VSD with a significant shunt.

Heart rate variability and arterial baroreflex sensitivity were measured in all patients using previously reported methods.[8,9] The spectral heart rate variability was expressed as a low-frequency component (0.04 to 0.15 Hz) and a high-frequency component (0.15 to 0.40 Hz), and the logarithmic values, log (low-frequency component) and log (high-frequency component), were used. A bolus phenylephrine method was used to measure arterial baroreflex sensitivity (milliseconds/mm Hg).[10]

Cardiac catheterization was performed under light sedation to evaluate hemodynamics and ventricular function, including ventricular volume (divided by body surface area) and the ejection fraction.[8,9]

After hemodynamic evaluation, a 5Fr pacing catheter was positioned in the right ventricular outflow in all patients, ventricular pacing threshold was measured, and the heart paced at twice the pacing threshold. BP was directly recorded with a catheter inserted into the ascending aorta. Femoral venous pressure instead of central venous pressure was continuously recorded by way of a 7Fr sheath placed in the right femoral vein. Heart rate was derived from a continuous 6-lead electrocardiographic recordings.

After acceptable hemodynamic stability, the following protocol was used: (1) venous blood was taken from the femoral vein for plasma norepinephrine, (2) a rapid pacing rate at 150 beats/min for 1 minute, (3) venous blood sampling for plasma norepinephrine 15 seconds after the end of pacing, (4) recovery for 5 to 10 minutes, (5) rapid pacing rate at 180 beats/min for 1 minute, and (6) venous sampling for plasma norepi-

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TABLE 1 Clinical Characteristics of the Study Patients

Variables	RVOTR		VSD	
	Children (n = 16)	Adults (n = 13)	Children (n = 5)	Adults (n = 6)
Age (yrs)	12 ± 2	22 ± 4	12 ± 1	21 ± 3
Follow-up (yrs)	7 ± 4	13 ± 5	1 ± 0	1 ± 0
Central venous pressure (mm Hg)	6 ± 3	6 ± 2	3 ± 0	4 ± 2
Right ventricular pressure (mm Hg)	55 ± 15	58 ± 17	25 ± 5	24 ± 9
Right ventricular end-diastolic pressure (mm Hg)	8 ± 1	9 ± 2	6 ± 1	5 ± 2
Pulmonary artery pressure (mm Hg)	17 ± 5	15 ± 3	13 ± 2	10 ± 4
Right ventricular end-diastolic volume (ml/m^2)	80 ± 20	102 ± 26*	84 ± 17	71 ± 12
Right ventricular ejection fraction (%)	53 ± 8	53 ± 8	54 ± 4	54 ± 12
Left ventricular end-diastolic pressure (mm Hg)	10 ± 2	10 ± 2	10 ± 1	10 ± 5
Left end-diastolic volume (ml/m^2)	81 ± 15	102 ± 26*	85 ± 22	73 ± 6
Left ejection fraction (%)	69 ± 9	59 ± 9*	64 ± 7	65 ± 5
Pulmonary resistance (U · m^2)	2.5 ± 1.6	2.6 ± 0.7	1.6 ± 0.2	1.3 ± 0.6
Systemic resistance (U · m^2)	23 ± 5	31 ± 7*	21 ± 6	24 ± 5
Cardiac index (L/min/m^2)	3.5 ± 0.8	2.7 ± 0.6*	4.0 ± 0.7	3.3 ± 0.5

*p <0.01 vs. children (RVOTR).
Values are mean ± SD.

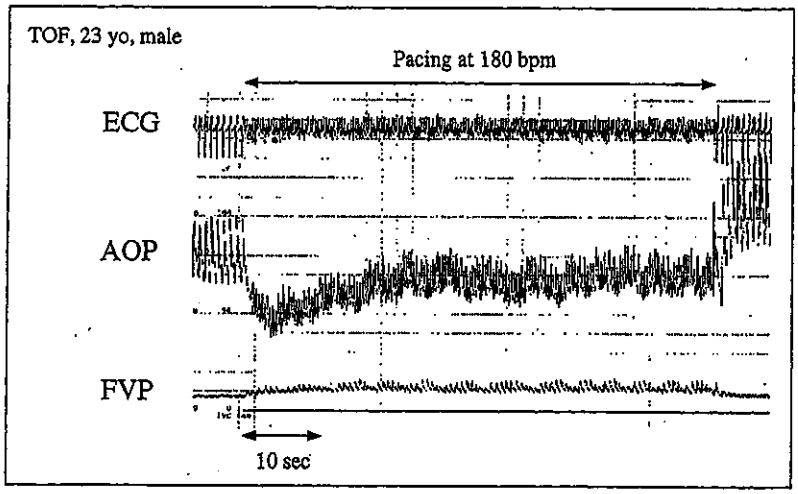

FIGURE 1. Sample tracing of surface elecrocardiogram, ascending aortic pressure (AOP), and femoral venous pressure (FVP) during 180 beats/min (bpm) ventricular pacing in a 23-year-old patient with tetralogy of Fallot (TOF).

TABLE 2 Comparison of Cardiac Autonomic Nervous Activity Among the Study Groups

Variables	RVOTR		VSD	
	Children	Adults	Children	Adults
Log (low-frequency component of heart rate variability)	1.7 ± 0.7	1.8 ± 0.5	2.1 ± 0.3	2.0 ± 0.5
Log (high-frequency component of heart rate variability)	1.4 ± 0.5	1.6 ± 0.7	1.9 ± 0.5	1.9 ± 0.6
Arterial baroreflex sensitivity (ms/mm Hg)	6.4 ± 6.0	3.9 ± 3.5	12.2 ± 3.6	14.0 ± 4.1
Plasma norepinephrine (pg/ml)	185 ± 96	169 ± 72	212 ± 71	164 ± 119

Values are mean ± SD.

nephrine 15 seconds after the end of pacing. All patients tolerated the protocol. During pacing, the initial mean BP decrease from baseline to nadir (around initial the 10 seconds; Figure 1), mean BP recovery from nadir to steady state (last 10 seconds), and steady-state mean BP were measured. Plasma norepinephrine was determined by high-performance liquid chromatography.[11]

Informed consent was obtained from all subjects and/or their parents. The study protocol was approved by the ethical committee of the National Cardiovascular Center.

Differences in hemodynamics, cardiac autonomic nervous activity, and hemodynamic variables between the 2 study groups were evaluated using the unpaired *t* test, and differences in mean BP during pacing were assessed by repeated measures of analysis of variance. Simple linear regression analysis was used to evaluate correlations between mean BP changes and hemodynamics at rest, and cardiac autonomic nervous activity indexes and stepwise multivariate linear regression analysis were used to detect major determinants of the mean BP change during pacing. Data are expressed as the mean ± SD. A p value of <0.05 was considered statistically significant.

Hemodynamics were significantly impaired in the patients with RVOTR, especially the adults, compared with the patients with VSD (Table 1).

Although there was no difference in plasma norepinephrine, arterial baroreflex sensitivity, and log (high-frequency component) were lower in the patients with RVOTR. No difference in any cardiac autonomic nervous activity was observed between the child and adult patients with RVOTR or patients with VSD (Table 2).

In all groups, at the onset of pacing, BP decreased abruptly, whereas femoral venous pressure increased followed by a gradual increase in BP (BP recovery) with some fluctuations. At the end of pacing, all patients showed stable BP with small fluctuations (Figure 1). These hemodynamic changes were accompanied by an increase in plasma norepinephrine in the 2 RVOTR groups and the adult patients with VSD (Figures 2 and 3). Although no differences in mean BP change were observed between the RVOTR and VSD groups, the mean BP changes were greater during 180 pacing than 150 pacing (p <0.005; Figures 2 and 3). Mean BP was

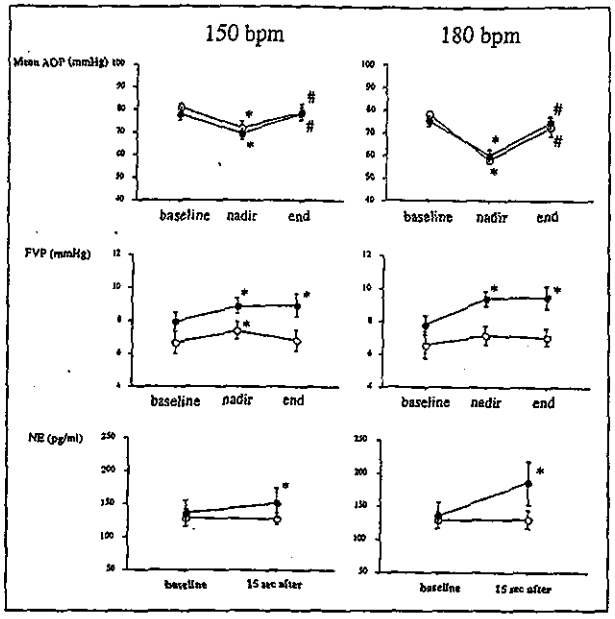

FIGURE 2. Changes in mean AOP, FVP, and plasma norepinephrine (NE) in children. *Open and closed circles*, patients after closure of VSD and those after RVOTR, respectively. *Significant versus baseline; #significant versus nadir. bpm = beats per minute; other abbreviations as in Figure 1.

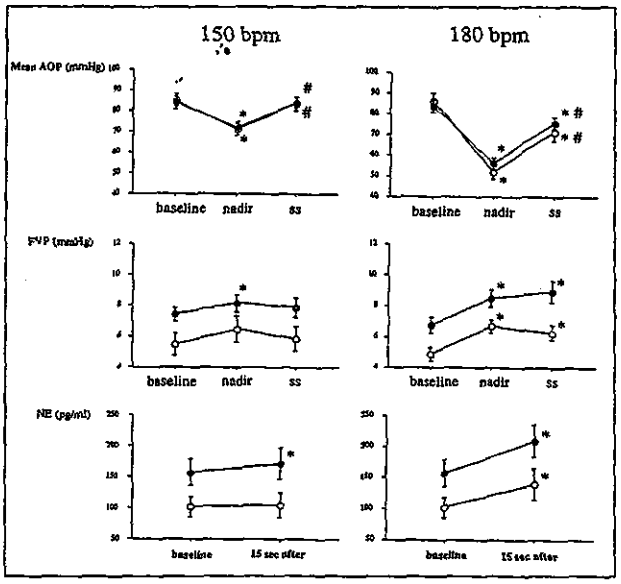

FIGURE 3. Changes in mean AOP, FVP, and plasma norepinephrine in adult patients. *Open and closed circles*, patients after closure of VSD and those after RVOTR, respectively. *Significant versus baseline; #significant versus nadir. ss = steady state; other abbreviations as in Figure 1.

greater in the adult patients than in the child patients, and, in adults, mean BP at 180 pacing was significantly lower than that at baseline.

Femoral venous pressure increased at the nadir of mean BP and tended to decrease at the end of pacing in the patients with VSD, resulting in no difference in the femoral venous pressure compared with baseline values, except for adult patients at 180 pacing. However, the femoral venous pressure at the end of pacing was significantly higher in the patients with RVOTR, except for the value at 150 pacing in adult patients (Figures 2 and 3). Plasma norepinephrine increased during both pacing periods in all patients with RVOTR; however, the increase was significant only in adult patients with VSD during 180 pacing (Figures 2 and 3).

In all patients, there was no correlation between plasma norepinephrine increase and mean BP recovery during 150 and 180 pacing. However, a significant positive relation was observed in all the adults ($r = 0.53$, $p < 0.05$) and it remained significant when the analysis was limited to adult patients with RVOTR (Figure 4).

In patients with RVOTR, high baseline mean BP was a major determinant for a greater initial mean BP decrease during 150 pacing and older age and higher baseline mean BP for the mean BP decrease during 180 pacing ($p < 0.001$ for each). Higher pulmonary artery and left ventricular end-diastolic pressures mainly determined the poor mean BP recovery during 150 pacing ($p < 0.01$), and high central venous pressure determined the poor mean BP recovery during 180 pacing ($p < 0.05$). Higher arterial baroreflex sensitivity and baseline mean BP were the major determinants for higher steady-state mean BP during 150 pacing (Figure 4), and higher baseline mean BP was the only determinant of higher mean BP at the end of 180 pacing ($p < 0.001$).

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Our major findings are: (1) despite no difference in mean BP during pacing, responses of plasma norepinephrine and femoral venous pressure were greater in the patients with RVOTR; (2) faster pacing caused a greater initial mean BP decrease, and high baseline mean BP was a major determinant for a greater mean BP decrease and higher steady-state mean BP; (3) adult patients had a greater initial mean BP decrease; and (4) in addition to impaired hemodynamics, maintained arterial baroreflex sensitivity had a significant impact on higher steady-state mean BP during 150 pacing, and the sympathetic activation (plasma norepinephrine increase) was related to the mean BP recovery during faster pacing.

BP change during VT or ventricular pacing has been studied in dogs and adult patients with VT,[3–6,12] and the pacing site has little impact on hemodynamics during VT.[3,13] Faster VT rate and impaired left ventricular contractility are the main causes of hypotension during VT.[3] Our study confirms that the VT rate greatly impacts BP dynamics in patients with congenital heart disease. It is notable that the initial BP decrease was greater in adults than in children. Because BP is mainly determined by cardiac output and vascular resistance, a higher systemic arterial resistance may explain this finding; the systemic arterial resistance correlated well with the age of our patients with RVOTR ($r = 0.59$, $p < 0.001$).

Changes in femoral venous pressure and plasma norepinephrine were greater in the patients with RVOTR than in the patients with VSD despite no difference in BP during pacing. Increased tricuspid

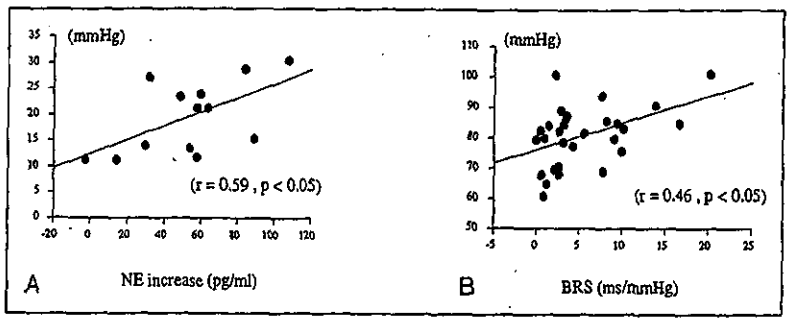

FIGURE 4. Relation between increase in plasma norepinephrine (NE) and AOP recovery during 180 beats/min ventricular pacing in adult patients with RVOTR (A) and that between arterial baroreflex sensitivity (BRS) and steady-state AOP during 150 beats/min ventricular pacing in all patients with RVOTR (B). Other abbreviations as in Figure 1.

valve regurgitation similar to mitral valve regurgitation during VT[14] and a relative increase of the pressure gradient across right ventricular outflow tract may explain the femoral venous pressure increase. In addition, impaired positive force-frequency relations may cause hemodynamic deterioration,[15] because of the significantly lower ejection fraction in some adult patients with RVOTR.[16] The hemodynamic deterioration requires sympathetic activation, especially in adult patients with RVOTR, and this compensatory response may have unfavorable influences on sustaining VT. Because spontaneous termination of VT may be infrequent in patients with impaired baroreflex function,[17] evaluation of cardiac autonomic nervous activity would be beneficial and important in following these patients.

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1. Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life. *Heart* 2001;85:438–443.
2. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosental M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet* 2000;356:975–981.
3. Smith ML, Ellenbogen KA, Beightol LA, Eckberg DL. Sympathetic neural responses to induced ventricular tachycardia. *J Am Coll Cardiol* 1991;18:1015–1024.
4. Hamdan MH, Joglar JA, Page RL, Zagrodzky JD, Sheehan CJ, Wasmund SL, Smith ML. Baroreflex gain predicts blood pressure recovery during simulated ventricular tachycardia in humans. *Circulation* 1999;100:381–386.
5. Smith ML, Joglar JA, Wasmund SL, Carlson MD, Welch PJ, Hamdan MH, Quan K, Page RL. Reflex control of sympathetic activity during simulated ventricular tachycardia in humans. *Circulation* 1999;100:628–634.
6. Landolina M, Mantica M, Pessano P, Manfredini R, Foresti A, Achwarz PJ, De Ferrari GM. Impaired baroreflex sensitivity is correlated with hemodynamic deterioration of sustained ventricular tachycardia. *J Am Coll Cardiol* 1997;29:568–575.
7. van den Berg MP, Hassink RJ, Tuinenburg AE, Lefrandt JD, de Kam PJ, Crijns HJ. Impaired autonomic function predicts dizziness at onset of paroxysmal atrial fibrillation. *Int J Cardiol* 2001;81:175–180.
8. Ohuchi H, Suzuki H, Toyohara K, Tatsumi K, Ono Y, Arakaki Y, Echigo S. Abnormal cardiac autonomic nervous activity after right ventricular outflow tract reconstruction. *Circulation* 2000;102:2732–2738.
9. Ohuchi H, Takasugi H, Ohashi H, Okada Y, Yamada O, Yagihara T, Echigo S. Stratification of pediatric heart failure on the basis of neurohormonal and cardiac nervous activities in patients with congenital heart disease. *Circulation* 2003;108:2368–2376.
10. Smyth HS, Slight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man. *Circ Res* 1969;24:109–121.
11. Mori K. Automated measurement of catecholamines in urine, plasma and hemogenates by high-performance liquid chromatography with fluorometric detection. *J Chromatogr 1981;218:631–637.*
12. Smith ML, Kinugawa T, Dibner-Dunlap ME. Reflex control of sympathetic activity during ventricular tachycardia in dogs: primary role of arterial baroreflexes. *Circulation* 1996;93:1033–1042.
13. Barold SS, Linhart JW, Hilder FJ, Samet P. Hemodynamic comparison of endocardial pacing of outflow and inflow tracts of the right ventricle. *Am J Cardiol* 1969;23:697–701.
14. Scully HD, Bello AG, Beierholm E, Frederiksen J, Weisfeldt ML, Daggett WM. The relationship between the atrial systolic-ventricular systolic interval and left ventricular function. *J Thorac Cardiovasc Surg* 1973;65:684–694.
15. Hasenfuss G, Holubarsch C, Hermann H-P, Astheimer K, Pieske B, Just H. Influence of the force-frequency relationship on haemodynamics and left ventricular function in patients with non-failing hearts and in patients with dilated cardiomyopathy. *Eur Heart J 1994;15:164–170.*
16. Waien SA, Liu PP, Ross BL, Williams WG, Webb GD, McLaughlin PR. Serial follow-up of adults with repaired tetralogy of Fallot. *J Am Coll Cardiol* 1992;20:295–300.
17. Waxman MB, Sharma AD, Cameron DA, Huerta F, Wald RW. Reflex mechanisms responsible for early spontaneous termination of paroxysmal supraventricular tachycardia. *Am J Cardiol* 1982;49:259–272.

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Pediatric Cardiology

Images in Pediatric Cardiology

Early Sympathetic Reinnervation Demonstrated by Iodine-123 Metaiodobenzylguanidine Imaging in a Child After Cardiac Transplantation

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A 2-year-old boy underwent orthotopic cardiac transplantation because of dilated cardiomyopathy. The procedure was performed at the Loma Linda University Medical Center (Loma Linda, CA, USA) when he was 17 months old. The patient returned to Japan 6 months after transplantation, and immunosuppressive therapy with cyclosporine and azathioprine was continued at our hospital. He is in good clinical condition.

We performed iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy to assess cardiac sympathetic reinnervation 6 and 12 months after the cardiac transplantation. Before receiving 37 MBq of ^{123}I-MIBG, the patient took no medication known to inhibit MIBG uptake, and thyroid uptake was blocked by potassium iodide. At the 6-month examination, partial reinnervation was observed in the basal anterior region in the left ventricle, which was confirmed by anterior planar imaging and single-photon emission computed tomography imaging (Fig. 1). At the second examination, 12 months after cardiac transplantation, the distribution of ^{123}I-MIBG uptake included the septal, apical, and lateral walls, but the inferior wall was still not visualized (Fig. 2).

Previous studies showed that cardiac uptake of ^{123}I-MIBG was not demonstrable in adults less than 1 year posttransplantation [1–4]. However, in our

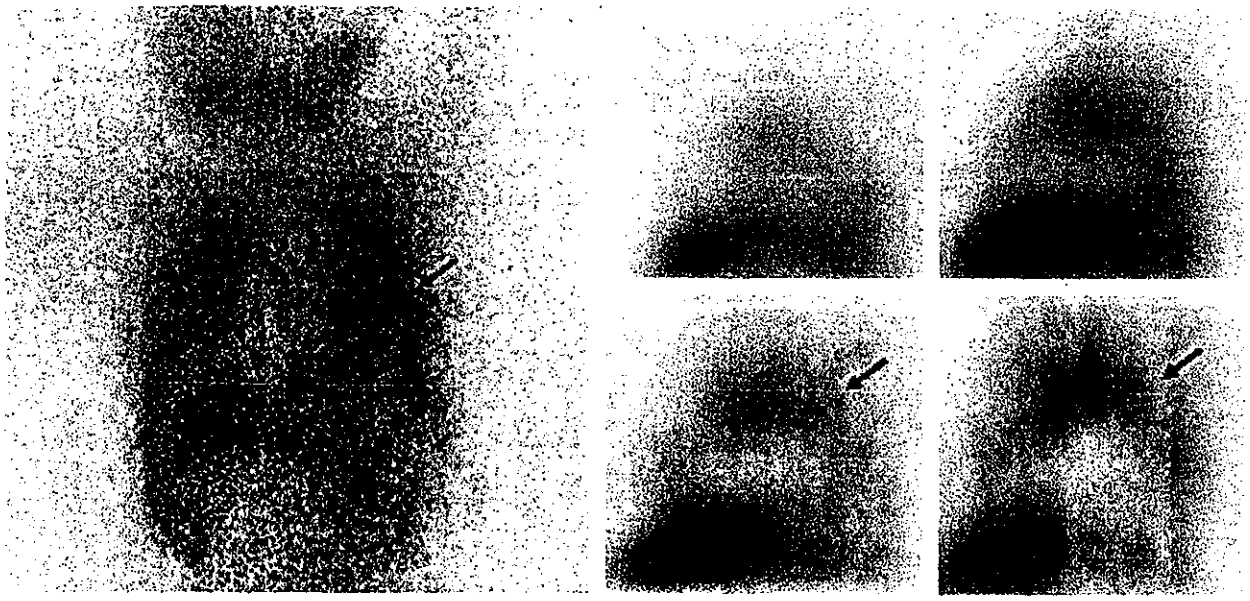

Fig. 1. Anterior planar and short-axis single-photon emission computed tomography images with iodine-123 metaiodobenzylguanidine (*MIBG*) 4 hours after injection. Regional MIBG uptake is seen in the basal anterior left ventricle (*arrows*) 6 months after the cardiac transplantation.

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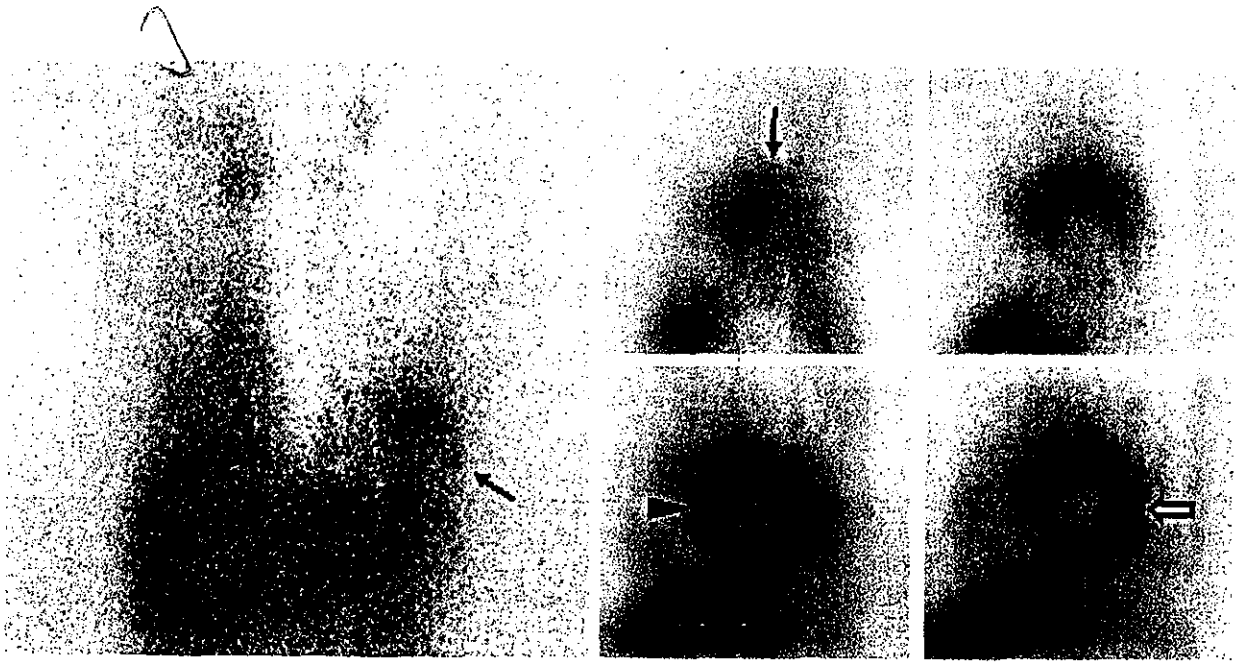

Fig. 2. A second iodine-123 metaiodobenzylguanidine study was performed 12 months after the cardiac transplantation, which showed further growth toward the apical (*arrow*), septal (*arrow head*), and lateral (*open arrow*) regions.

patient, cardiac ^{123}I-MIBG uptake was clearly evident 6 months after cardiac transplantation, and at 12 months uptake showed obvious expansion. The present finding demonstrates, for the first time, that early (within 6 months after transplantation) sympathetic reinnervation is possible, at least in children.

References

1. Dae MW, De Marco T, Botvinick EH, et al. (1992) Scintigraphic assessment of MIBG uptake in globally denervated human and canine hearts—implications for clinical studies. *J Nucl Med 33*:1444–1450
2. De Marco T, Dae M, Yuen-Green MSF, et al. (1995) Iodine-123 metaiodobenzylguanidine scintigraphic assessment of the transplanted human heart: evidence for late reinnervation. *J Am Coll Cardiol 25*:927–931
3. Estorch M, Camprecios M, Flotats A, et al. (1999) Sympathetic reinnervation of cardiac allografts evaluated by ^{123}I-MIBG imaging. *J Nucl Med 40*:911–916
4. Toba M, Ishida Y, Fukuchi K, et al. (1998) Sympathetic reinnervation demonstrated on serial iodine-123-metaiodobenzylguanidine SPECT images after cardiac transplantation. *J Nucl Med 39*:1862–1864

Pediatric Cardiology

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Improvement of Left Ventricular Function After Changing the Pacing Site in a Child with Isolated Congenital Complete Atrioventricular Block and Dilated Cardiomyopathy

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Abstract We report a case of isolated congenital complete atrioventricular block with left ventricular dysfunction after pacemaker implantation that improved after the pacing site was changed. During the neonatal period, a pacemaker wire was implanted on the right ventricular epicardium and pacing was initiated. Decreased ejection fraction and a perfusion defect around the septum on myocardial scintigraphy were observed during follow-up. Induced left bundle branch block was thought to be causing interventricular asynchrony, and the pacing site was change to the left ventricular epicardium. Ejection fraction improved and the perfusion defect resolved. Lead relocation may be useful for left ventricular dysfunction that develops during right ventricular pacing.

Keywords Congenital complete atrioventricular block - Pacemaker implantation - Dilated cardiomyopathy - Myocardial scintigraphy - Interventricular aynchrony - Left bundle branch block

Most patients with isolated congenital complete atrioventricular block (CCAVB) eventually require pacemaker implantation (PMI) and the prognosis has been considered relatively benign. Recent evidence suggests that a subset of patients with isolated CCAVB develop dilated cardiomyopathy (DCM) despite early pacemaker implantation [4, 11]. We describe a 5-year-old girl with isolated CCAVB who developed left ventricular dysfunction resembling DCM 5 years after pacemaker implantation. Her left ventricular function improved after the pacing site was changed.

Case Report

The patient was diagnosed as having complete atrioventricular block at 38 weeks of gestation because of fetal bradycardia. Her mother had no past history of

autoimmune disease and her serum antinuclear antibody, anti-Ro/SSA antibody, and anti-La/SSB antibody were all negative. The patient was born at 38 weeks and 3 days of gestation by normal vaginal delivery with a birth weight of 2620 g. Her Apgar score was 7 at 1 minute and 8 at 5 minutes.

Because her heart rate was 50 beats per minute (bpm) and did not increase even with crying, a pacemaker wire was implanted on the right ventricular epicardium and VVI (120 ppm) pacing was started. Although she was doing well without pacing failure and had normal growth during follow-up, echocardiographic parameters of left ventricular function gradually deteriorated. At 5years of age, she was admitted to our hospital because of suspected DCM and impending pacemaker battery failure. On admission,there were no remarkable physical findings except the operative scar of PMI. Serum HANP (Human Atrial Natriuretic Peptide) and BNP (Brain Natriuretic Peptide) were within the normal range. Her cardiothoracic ratio on chest roentgenogram was 55%, and an electrocardiogram showed complete atrioventricular block with constant pacing rhythm and complete left bundle branch block (LBBB) with a QRS duration of 140 msec. Echocardiogram showed that the interventricular septal wall motion was depressed, with a left ventricular end diastolic dimension of 39.5 mm (117% of normal) and an ejection fraction of 53%. She underwent ^{99m}Tc myocardial scintigraphy to assess myocardial perfusion and quantitative gated single photon emission computed tomography (QGS) to determine left ventricular function. Perfusion defects on ^{99m}Tc myocardial scintigraphy were revealed from the septum to the inferior segment, and the ejection fraction on QGS was 39% with hypokinesis in the same segments (Fig. 1). A myocardial biopsy of the right ventricle showed moderate degenerative and fibrous changes compatible with DCM. During cardiac catheterization, we compared the cardiac index on VVI pacing with that on DDD pacing, but there was no significant difference. We thought that artificial LBBB with induced interventricular asynchrony had contributed to her left ventricular dysfunction, and that a DDD pacing mode would be more physiological than VVI. She underwent a generator exchange with pacemaker lead implantation on the left ventricular epicardium, and left ventricular DDD mode pacing was initiated. Biventricular pacing systems are not available in Japan, so we chose to change the pacing site to the left ventricle. Two weeks after the operation, her electrocardiogram had changed from LBBB to complete right bundle branch block with a QRS duration of 140 msec, and an echocardiogram showed improved septal wall motion with an ejection fraction of 76%. One month after the operation, the perfusion defects on ^{99m}Tc myocardial scintigraphy had resolved and her ejection fraction on QGS improved to 53% without hypokinesis (Fig. 2).