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Original Article

Chronological changes in stenosis of translocated coronary arteries on angiography after the arterial switch operation in children with transposition of the great arteries: comparison of myocardial scintigraphy and angiographic findings

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Abstract *Background:* The peri-operative mortality of the arterial switch operation in neonates with transposition of the great arteries is considerably low; however, long-term outcomes of translocated coronary arteries still remain one of the most crucial issues. *Methods and results:* A total of 110 neonates with transposition of the great arteries after arterial switch operation were evaluated; three (2.7%) late deaths occurred. The remaining 107 patients except for one underwent follow-up angiography. Angiography showed coronary artery stenosis in nine (8.4%), with right coronary artery lesions in two and left main trunk lesions in seven. In two patients, right coronary artery stenosis regressed during follow-up. In left main trunk lesions, the severity of stenosis improved in four, did not change in one, and progressed to total occlusion in two patients. In children with coronary artery stenosis, myocardial scintigraphy showed perfusion defects in five out of six (83%) with left main trunk with ⩾75% stenosis and in four out of four with left main trunk stenosis ⩾90%. In contrast, patients whose coronary artery stenosis disappeared during follow-up had no perfusion defects on scintigraphy. *Conclusions:* Regression of ostial stenosis of the transplanted coronary artery on angiogram was observed. The stenosis regressed over time in six patients; two coronary arteries with 99% stenosis and delayed angiographic enhancement of the distal coronary artery resulted in total occlusion within 1 year after the arterial switch operation. Combination of angiography and myocardial scintigraphy could be useful to differentiate deceptive stenosis from progressive stenosis.

Keywords: Transposition of the great arteries; arterial switch operation; coronary artery stenosis; myocardial scintigraphy

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In the past decade, the peri-operative mortality of the arterial switch operation in neonates with transposition of the great arteries is reported to be considerably low.[1–9] Even in low birth weight infants, arterial switch operation was performed with acceptable morbidity and mortality;[10] however, long-term outcomes of translocated coronary arteries still remain one of the most crucial issues.[1–9,11,12] In fact, most peri-operative or late deaths result from coronary obstructive events. Sudden late death secondary to acute myocardial infarction has been reported in 1–2% of hospital survivors after arterial switch operation and it usually occurs within 6 months after the operation.[1,2,12] Losay et al[1] reported no deaths after 5 years in 1095 survivors. Coronary arterial obstruction was reported to be caused by intimal thickening, thrombosis, coronary kinking, stretching, twisting, extrinsic compression, or by an intramural coronary artery.[2,11–16] There have been few reports on the long-term morbidity or mortality associated with coronary obstructive disorders after arterial switch operation in patients with transposition of the great arteries.[1–4] Furthermore, there is little information on the

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chronological changes in coronary stenosis after arterial switch operation. In the present study, we focussed on the long-term outcome and chronological change of translocated coronary arteries using follow-up coronary angiography and myocardial scintigraphy.

Patients and methods

The observational study period was from January, 1981 to June, 2010. Between January, 1981 and June, 2009, a total of 202 patients with transposition of the great arteries underwent arterial switch operation at the National Cerebral and Cardiovascular Center in Japan. Patients with double-outlet right ventricle and subpulmonic ventricular septal defect were excluded from the study. Of the 202 patients, 110 underwent arterial switch operation during the neonatal period (median age, 9 days; with a range from 2 to 30 days). The surgical technique for arterial switch operation at the National Cerebral and Cardiovascular Center was standard and has been previously described.[11] They were observed for >6 months after the arterial switch operation. A total of 83 children had transposition of the great arteries with an intact ventricular septum, and 27 had ventricular septal defect including four aortic arch obstructive anomalies. Coronary artery variation was classified according to Shaher's classification: 78 children (72%) had type 1, 16 had type 2, five had type 3, seven had type 4, two had type 5, one had type 7, and one had type 9. In all, three late deaths (2.7%) occurred that ranged from 314 to 396 days after surgery. In one case, the autopsy revealed a coronary obstruction, and the other two patients died of infection and an unknown cause, respectively. The remaining 107 patients were followed-up until June, 2010. The observational period ranged from 9 months to 23 years with a median of 11 years.

A total of 106 of 107 patients (99%) underwent angiography 1 month to 14 years (median, 1.0 year) after arterial switch operation. Subsequent follow-up angiography was performed in 59 of those ranging from 1 to 4 times. In our institution, the coronary arteries of infants <1-year old are evaluated by aortography with appropriate angulation, whereas selective coronary angiography are added if necessary in children who are ⩾1-year old and <5-years old. Both aortography and selective coronary angiography are used in children who are ⩾5-years old. A coronary obstruction was semi-quantitatively evaluated as 0, 25, 50, 75, 90, or 99% stenotic or totally occluded based on the American Heart Association classification. Myocardial perfusion was evaluated by SPECT with (^{99m}Tc) tetrofosmin with dipyridamole loading and at rest. Myocardial scintigraphy was performed during the same hospitalisation; two independent examiners semi-quantitatively evaluated myocardial perfusions on each segment. Evaluation of the ventricular septum was excluded because of enrolment of children with ventricular septal defects. The severity of the myocardial perfusion was graded into four degrees from mild, moderate, severe, to complete defect. A more than mild perfusion defect with dipyridamole loading was regarded as a significant finding in the present study. Written informed consent was obtained from all patients or patients' guardians before catheter examinations.

Results

The patients' characteristics are shown in Table 1. Although peri-operative coronary artery events such as ST depression or hypokinesis of the left ventricular wall were found in four children, only one child had a congestive heart failure-related symptom. Angiography showed coronary arterial involvement in nine (8.4%) patients at 1–16 months after the arterial switch operation. The coronary lesions are summarised in Table 2. The coronary lesions were detected at all ostia, at the right coronary artery in two patients, and at the left main trunk in seven patients. Right coronary artery stenosis in two patients improved over time. In patient 1, the

Table 1. Patients' profile with coronary artery involvements.

Patients	Gender	TGA type	Shaher type	Age at ASO	EC	Symptom
1	Female	II	1	7 days	None	None
2	Male	I	1	11 days	Perioperative EC	None
3	Female	I	1	2 days	None	None
4	Male	II	5a (modified Aubert)	13 days	None	None
5	Male	I	1	13 days	None	None
6	Male	I	1	5 days	Perioperative EC	None
7	Male	II	1	5 days	None	None
8	Male	I	1	5 days	Perioperative EC	Congestive heart failure
9	Male	II	1	8 days	Perioperative EC	None

ASO = arterial switch operation; EC = episode of cardiac event associated with coronary artery; TGA = transposition of the great arteries

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Table 2. Coronary involvements by angiographic assessment and myocardial scintigraphy.

	First examination			Second examination			Third examination			Fourth examination		
Patients	CAL	PD	Interval	CAL	PD	Interval	CAL	PD	Interval	CAL	PD	Interval
1	RCA 75%	(–)	1.3	RCA 0%	(–)	6.0						
2	RCA 90%	No study	0.1	RCA 0%	(–)	2.4	RCA 0%	(–)	13.0			
3	LMT 50%	(–)	1.2	LMT 0%	(–)	3.3						
4	LMT 75%	(–)	0.2	LMT 25%	(–)	1.0	LMT 0%	(–)	4.9			
5	LMT 50%	(–)	1.0	LMT 25%	(–)	3.2	LMT 0%	(–)	6.1			
6	LMT 90%	Ant-Lat	0.1	LMT 75%	Ant-Lat	0.6	LMT 50%	Ant-Lat	1.4	LMT 25%	Ant-Lat	2.8
7	LMT 50%	Lat	1.0	LMT 50%	Ant-Lat	1.9						
8	LMT 99%	Ant-Lat	0.1	LMT occ.	Ant-Lat	0.9						
9	LMT 99%	No study	0.1	LMT occ.	Ant-Lat	0.6						

Ant = anterior wall; CAL = coronary arterial lesions evaluated by angiography; Interval = period from arterial switch operation (year); Lat = lateral wall; LMT = left main trunk; PD = perfusion defect evaluated by myocardial scintigraphy; RCA = right coronary artery

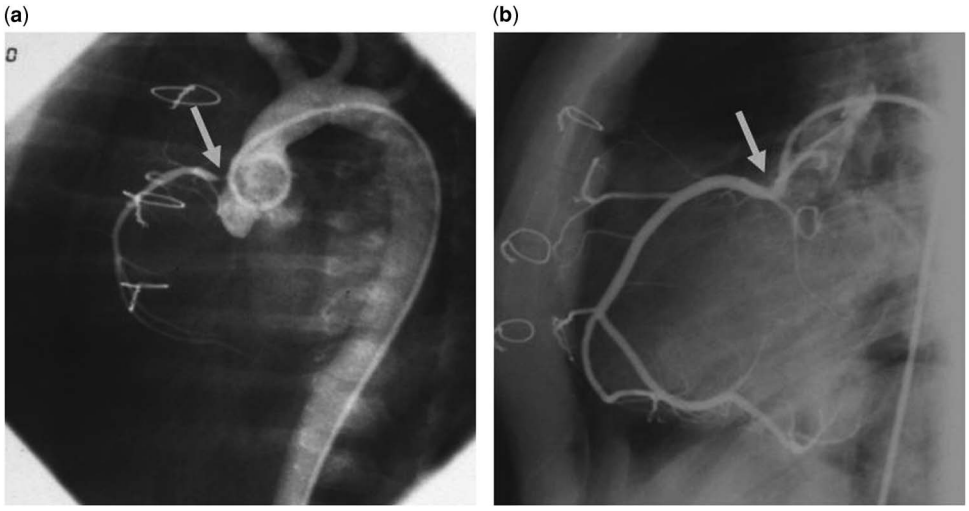

Figure 1.
*Chronological change of coronary stenosis on angiography in case 2: (**a**) 90% stenosis (arrow) was shown at the orifice of the right coronary artery 2 months after the arterial switch operation; (**b**) Stenosis could not be detected by follow-up angiography (arrow) 13 years after the arterial switch operation.*

proximal right coronary artery showed 75% stenosis 15 months after the arterial switch operation, but the stenosis could not be detected at the 6-year follow-up examination. Similarly, although 90% stenosis of the right coronary artery orifice was present 1 month after the arterial switch operation in patient 2 (Fig 1a), it disappeared at both the 2-year and the 13-year follow-up angiographies (Fig 1b). In patients with left main trunk lesions, the degree of stenosis improved in four children, did not change in one child, and progressed to complete occlusion in two children based on follow-up angiography. In patient 3, the left main trunk stenosis was 50% 14 months after the arterial switch operation, but it disappeared at the 3-year follow-up angiography. In patients 4, 5, and 6, the left main trunk stenosis at the initial angiography was regarded as 75, 50, and 90%, respectively; however, it regressed to 25% at 12 months and to no stenosis at 4 years in patient 4, 25% at 3 years and to no stenosis at 6 years in case 5, and 75% at 7 months, 50% at 16 months, and 25% at 33 months in case 6 (Fig 2a and b). On the contrary, severe 99% obstruction in patients 8 and 9 deteriorated to total occlusion at 10 and 7 months after the arterial switch operation, respectively. In patient 7, left main trunk stenosis did not change during the observation period.

The results of myocardial scintigraphy with (^{99m}Tc) tetrofosmin in children with coronary arterial involvement are shown in Table 2. In two right coronary artery lesions, myocardial scintigraphy did not show any perfusion defect. In seven patients with left main trunk lesions, myocardial scintigraphy showed a perfusion defect in five out of six (83%)

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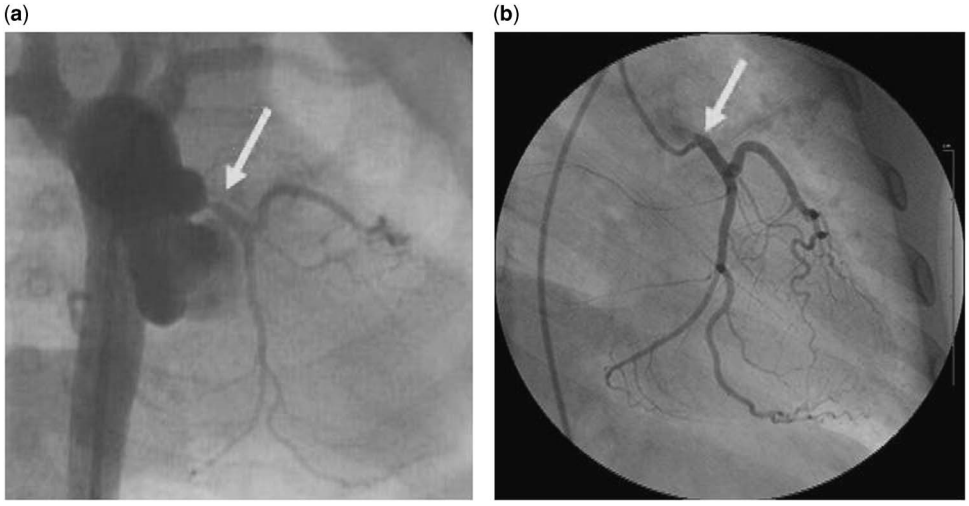

Figure 2.
*Chronological change of coronary stenosis on angiography in case 4: (**a**) 75% stenosis (arrow) was shown at the orifice of the left main trunk 2 months after the arterial switch operation; (**b**) Obvious stenosis could not be detected by follow-up angiography (arrow) 4.9 years after the arterial switch operation.*

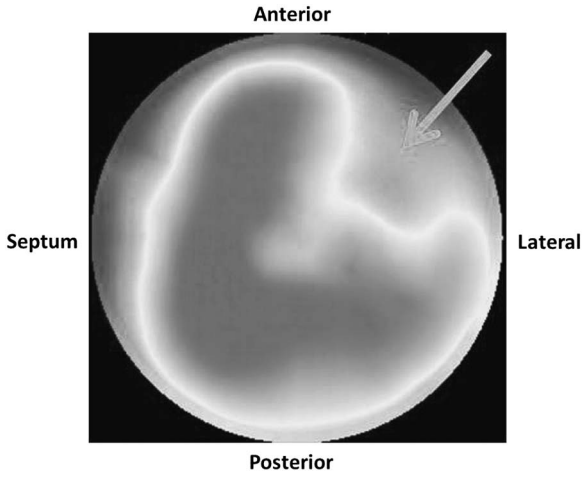

Figure 3.
Myocardial scintigraphy in case 9. A moderate perfusion defect was shown at the antero-lateral wall (arrow).

with left main trunk stenosis ⩾75% and in four out of four patients with left main trunk stenosis ⩾90% (Fig 3). In contrast, patients 1–5 who showed angiographical regression of coronary arterial lesions over time had no perfusion defects on myocardial scintigraphy at any time during the study period. In cases 1, 6, and 7, perfusion defect was somewhat fill-in at rest by re-injection of an isotope. In cases 8 and 9, perfusion defect did not change at rest by re-injection of the isotope.

Discussion

Coronary arterial obstruction in the early stage was associated with intimal proliferation, the intramural coronary artery, re-implanted coronary deformation such as stretching, twisting, and kinking, and extrinsic compression.[14–16] Therefore, most of the hospital or early deaths after arterial switch operation were directly or indirectly associated with the surgical manipulation as coronary re-implantation;[1] however, long-term chronological changes of lesions in the translocated coronary arteries could be affected by coronary artery growth, a change in the relationship between an adjacent organ and the coronary artery, or intimal proliferation or regression. Angiography was widely recognised as the gold standard to evaluate coronary arterial lesions after an arterial switch operation in patients with transposition of the great arteries; however, it could have a limitation in demonstrating the precise morphology of the coronary arteries because of the size of small infants and peculiarities of the coronary anatomy in transposition of the great arteries.[11]

In the present study, angiographical regression of ostium stenosis of the transplanted coronary artery was observed in six out of nine patients. The "coronary artery stenosis" on angiography can include coronary kinking, stretching, or twisting, which can be changed over time. These aetiologies could have the potential to be resolved with body growth. When the "coronary artery stenosis" is due to intimal proliferation, coronary artery growth might overcome intimal proliferation. When the aetiology of the stenosis is extrinsic compression by glue or haematoma at the time of surgery, angiographical findings could be relieved because of its absorption. The "coronary artery stenosis" on angiography should be considered not always equal to actual coronary stenosis. Therefore, the indication for surgical or catheter intervention should depend not

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only on angiographic findings but also on the presence of myocardial ischaemia detected by myocardial scintigraphy or other imaging modalities. Although coronary stenosis progressed in some patients, in the present study, two coronary arteries with 99% stenosis with delayed angiographic enhancement of the distal coronary artery progressed to total occlusion. There was obvious myocardial ischaemia on myocardial scintigraphy within 1 year after the arterial switch operation in those patients. Thus, the aetiology of stenosis in those two patients was thought to be progressive intimal proliferation.[17,18] Surgical repair or catheter intervention should have been considered for the rescue of ischaemic myocardium without delay in those patients.[18] Ostial angioplasty or mammary artery grafting could be applied with acceptable mortality.[8] Meanwhile, the management of regressive coronary artery but persistant myocardial perfusion defect, as in patient 6, may have been due to viability of the myocardium as well as the degree of the myocardial perfusion defect and angiographic findings. Previous studies have reported that early sudden death associated with coronary involvements is not rare.[1–9] Considering both these facts and our observation together, severe stenosis with myocardial ischaemia could progress to total occlusion within 1 year after arterial switch operation and could cause sudden death, but "coronary artery stenosis" on angiography without myocardial ischaemia might not mean actual stenosis and can be be improved. Indication of surgery or catheter intervention for these patients should be carefully considered.

The morbidity of the coronary stenosis after arterial switch operation was previously reported to be 3–7.8%.[1–9,13,19] In the present study, the morbidity was 8.4%, which was a little higher compared with those studies. The morbidity of coronary involvements depends on the frequency and scrutiny of the coronary arteries on angiography. The patients after arterial switch operation are insensitive to chest pain because of the disturbance of the cardiac nerves adjacent to the great arteries by the surgical procedure.[19] Therefore, symptoms related to myocardial ischaemia are not reliable. In the present study, all patients but one routinely underwent post-operative coronary angiography at least once whether or not there were symptoms of myocardial ischaemia, and coronary arterial assessment was always carried out even when the purpose of angiography was for some other reason, such as pulmonary arterial stenosis. The diagnosis of an ostial lesion can be sometimes missed based on selective coronary angiography, because the insertion of the catheter tip into the coronary arteries could result in insufficient enhancement of the ostial segment. Aortography adjacent to the target coronary artery could be helpful to detect ostial stenosis only if appropriate angiographic angulation can differentiate the proximal portion of the coronary artery from the aortic sinus of valsalva. Thus, the combination of selective coronary angiography and appropriate angulated aortography should be adopted to avoid misdiagnosis as much as possible. Enhanced CT could also be useful to evaluate coronary arterial lesions induced by extrinsic compression;[15,16] however, it could be difficult to detect ostial stenosis because of limited spatial resolution and motion artefacts in small children. Echocardiography is another modality, but it is extremely difficult to detect coronary ostial lesions by conventional 2D echocardiography. Coronary flow reserve evaluated by Doppler echocardiography can detect these lesions and might be a promising methodology in older children.[20] Although MRI has been used to detect myocardial ischaemia in patients with arterial switch operation, the usefulness of this imaging modality has not been clearly established in the paediatric population.[21] In contrast, myocardial scintigraphy could be useful to evaluate obstructive coronary lesions in patients with arterial switch operation, although the influence of open-heart surgery itself on the myocardial perfusion scan cannot be eliminated.[22–24] In the present study, myocardial ischaemia was detected by scintigraphy in five out of six (83%) patients with left main trunk stenosis $\geqslant$75% and in four out of four (100%) with left main trunk stenosis $\geqslant$90%. All five children whose coronary arterial lesions angiographically regressed over time had no myocardial perfusion defects throughout the study. In some cases, discrepancy between the angiographic findings and the scintigraphic findings was revealed. The aetiology of the discrepancy was unclear. Coronary stenosis on angiography might not be always equal to the actual stenosis. Ostium of the translocated coronary artery after arterial switch operation was morphologically varied. Therefore, the coronary artery may not be as stenotic as it appears on the angiography with certain angle. Furthermore, scintigraphic assessment in small children might have the limitation of sensitivity. Angiographical assessment alone could have limitations for detecting myocardial ischaemia. Consequently, a combination of myocardial scintigraphy and angiography could be a useful modality to determine the necessity for surgical or catheter intervention and expect prognosis.

Study limitations

The retrospective nature of this study is an important limitation. The number of patients with coronary arterial lesions was still small. Further accumulation of experiences is necessary to reveal the relationship between coronary angiography and myocardial scintigraphy in these patients.

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Conclusions

The present study showed chronological changes in the translocated coronary arteries after the arterial switch operation. Careful observation is necessary during follow-up even when patients have no symptoms of myocardial ischaemia. A combination of angiographic assessment and myocardial scintigraphy could provide us with useful information for further interventions.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidlines on human experimentation and with the helsinki Declaration of 1975, revised in 2008.

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