

Right Coronary Artery May Grow Even Better than Normal After Arterial Switch Operation for Complete Transposition of the Great Arteries

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1 (1) Title page

2 Title; Right coronary artery may grow even better than normal after arterial switch

3 operation for complete transposition of the great arteries

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18 (2) Abstract

19 **Background:** It is unclear if coronary arteries properly grow in patients who underwent
20 arterial switch operation for complete transposition of the great arteries. The purpose of
21 this study was to clarify the mode of coronary growth and size in these patients.

22 **Methods:** Eighteen patients who underwent arterial switch operation for complete
23 transposition of the great arteries from 2000 to 2012 in our institution, and in whom
24 coronary angiography was performed in late operative phase, were enrolled in this study.

25 Growth of coronary arteries was evaluated by cubage of coronary arteries based on
26 analyses with coronary angiography. Coronary arteries were divided into small segments
27 and each segment was approximated by a truncated right circular cone. The sum of the
28 cubage of each truncated cone in one coronary artery was approximated as total cubage
29 of the coronary. the coronary cubage index was then calculated by dividing total cubage
30 of a coronary artery by the patient's body surface area. The coronary cubage indexes of
31 the enrolled patients were compared with that of control patients with healed Kawasaki
32 disease.

33 **Results:** The left coronary cubage indexes of the complete transposition of the great
34 arteries group and the control group were 1.05 ± 0.34 and 0.94 ± 0.34 ($p=0.598$),

35 respectively, and no significant difference was found between groups. On the contrary,
36 the right cubage index of the complete transposition of great arteries group was
37 significantly larger than the control group (1.08 ± 0.44 and 0.54 ± 0.37 , respectively;
38 $p=0.007$), and total coronary cubage index (left coronary index + right coronary index) of
39 the complete transposition of the great arteries group was also larger than the control
40 group as well (2.13 ± 0.7 and 1.47 ± 0.6 , respectively; $p=0.026$).

41 **Conclusion:** The left coronary arteries after arterial switch operation for complete
42 transposition of great arteries grow as large as normal; however, the right coronary
43 arteries possibly grow even larger.

44 311words

45

46 Key words: arterial switch operation; complete transposition of the great arteries; Jatene

47 operation; coronary artery;

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52 (3) Main text

53 **Introduction**

54 Complete transposition of the great arteries (d-TGA) can be safely corrected in neonates

55 by the arterial switch operation (ASO) and long-term survival is satisfyingly good [1,2].

56 On the contrary, concerns regarding coronary arteries after ASO still last; Turner reported

57 that myocardial flow reserve may be impaired in patients with anatomic left anterior

58 descending artery (LAD) abnormalities [3], and Mavroudis reported that one-third of

59 patients who underwent ASO required reoperations for lesions related with coronary

60 arteries [4]. Particularly, the size of left coronary artery has often been studied and

61 discussed [1,5,6] because it potentially might cause failing ventricle, however the clinical

62 question if coronary arteries properly grow in patients who underwent ASO is still unclear.

63 The purpose of this study was to clarify the mode of coronary growth and size in these

64 patients.

65

66 **Patients and Methods**

67 *Study design and patient population*

68 This was a retrospective cohort study performed at a single Japanese center in human

69 subjects. We identified 18 patients who underwent ASO for d-TGA from 2000 to 2012 in
70 our institution, and in whom coronary angiography (CAG) was performed in late
71 operative phase; in 4-7 years after ASO to evaluate coronary growth and pathology.
72 Mean age and body surface area (BSA) aged 11-191 days (median;18 days) at the
73 ASO. Eleven of them had d-TGA with intact ventricular septum (d-TGA/IVS) and seven
74 had d-TGA with ventricular septal defect (d-TGA/VSD). Eight patients with Kawasaki
75 disease, who were confirmed to have no coronary pathological lesions by CAG, were
76 selected and also enrolled in this study as age-, and BSA-adjusted control subjects. This
77 study was reviewed and approved by the institutional review board at Yokohama City
78 University. Informed consent was obtained from all patients' parents or legal guardians.

79

80 *Angiographic analyses*

81 Growth of coronary arteries was evaluated by cubage of coronary arteries based on
82 analyses with CAG. Coronary arteries were divided into small segments on CAG and
83 each segment was approximated by a truncated right circular cone. A cubage (mm^3 ; C)
84 of each truncated cone can be calculated with proximal and distal radiuses (mm ; r, R)
85 and length (mm ; L) of each segment using the following mathematical formula.

86
$$C = \frac{\pi}{3} \times L \times (r^2 + rR + R^2) \text{ mm}^3$$

87 The sum of the cubage of each truncated cone in one coronary artery could be
88 acceptable approximation of total cubage of the coronary (T). (Fig 1)

89
$$T = \sum (C_1 + C_2 + C_3 + \dots + C_n)$$

90 Left main trunk and right coronary artery were analyzed on frontal view, and left anterior
91 descending artery, first diagonal branch and circumflex system were analyzed on lateral
92 view. Figure 2 shows a sample of CAG analysis (Fig 2). Coronary cubage index was
93 calculated by dividing total cubage of a coronary artery by the patient's BSA. $BSA (m^2)$
94 was calculated by multiplying 0.007184 by $Weight(kg)^{0.425}$ and $Height(cm)^{0.725}$
95 according to the DuBois and DuBois formula [7].

96 Radiuses and lengths were measured on CAG with OsiriX DICOM viewer version 4.1.2
97 (Pixmeo SARL. Bernex, Switzerland). Data collection and cubage calculations were
98 performed with Excel software (Microsoft Corporation, Remond, WA, USA).

99

100 *Statistical analysis*

101 All statistical analyses were performed with IBM SPSS statics 20. Continuous variables
102 were expressed as mean \pm standard deviation and were compared using the student's t

103 test. Categorical variables are expressed as absolute numbers or percentages and were
104 compared using chi-square testing. The level of statistical significance was set at $p < 0.05$.

105

106 **Results**

107 *Patients demographics*

108 The list of all 18 patients with d-TGA is given in Table 1. Briefly, 10 out of 18 patients
109 were boys, the median age and BSA at the time of coronary angiography was 6.2 years
110 and 0.75 m^2 , respectively (Table 1). The median age at the time of ASO was 18 days
111 (range; 11-48 days), excluding a case who underwent Aubert-Imai operation as a two-
112 stage surgery at the age of 191 days. d-TGA/IVS was diagnosed in 11 patients and d-
113 TGA/VSD was in 7 patients. Coronary anatomies were classified by Shaher's
114 classification [8]; Shaher type 1 was confirmed in 11 patients, type 2A in 3, and type 5A
115 in 3. The median age and BSA of control (Kawasaki) group was 6.0 years and 0.77 m^2 ,
116 respectively, that were almost same as those of TGA group. No stenosis nor occlusion
117 of coronary artery was detected by CAG in both groups.

118

119 *Coronary cubage indexes (cubage(mm^3) / BSA(m^2))*

120 The left coronary cubage indexes of d-TGA group and control group were 1.05 ± 0.34
121 and 0.94 ± 0.34 ($p=0.598$), respectively, and no significant difference was found between
122 groups. On the contrary, the right cubage index of d-TGA group was significantly larger
123 than control group (1.08 ± 0.44 and 0.54 ± 0.37 , respectively; $p=0.007$), and total
124 coronary cubage index (left coronary index + right coronary index) of d-TGA group was
125 larger than control group as well (2.13 ± 0.7 and 1.47 ± 0.6 , respectively; $p=0.026$). (Table
126 2)

127

128 **Discussion**

129 ASO is a standard surgical strategy for d-TGA described by Jatene and Lecompte [9,10]
130 which is technically demanding especially in translocation of coronary arteries. Previous
131 studies reported that there possibly could be abnormal myocardial perfusion in children
132 after ASO [3]; however, the mode of coronary arteries growth and function after ASO are
133 still unclear. Yatsunami showed the left coronary arteries were smaller than normal after
134 ASO and that the dominant, large right coronary artery does not fully compensate [5].
135 On the contrary, Turner advocated that anatomic coronary growth is normal in almost
136 90% coronary arteries after ASO [3]. Our results of this present study differ from these

137 previous reports; the left coronary arteries after ASO grew as large as normal (Kawasaki),
138 and the right coronary arteries grew even larger.

139 From the embryologic point of view, the development of the coronary vasculature starts
140 from the appearance of round blood islands on epicardium, and then these islands
141 preferentially develop in the sulci of the heart surface and form a rudimentary plexus
142 [11,12]. This coronary plexus grows and climbs superiorly, and then develops the
143 coronary network. The coronary stems are formed from the coronary network and
144 attaches to the aortic root. Based on the embryologic and anatomical differences of
145 relationship of great arteries and ventricles between the normal and the d-TGA fetus, the
146 reasons underlying our results should be discussed in taking the logical fetal circulation
147 into account. The oxygen saturation of the blood distributed in the ascending aorta is
148 65%, mixture of the blood from foramen ovale with an oxygen saturation of about 85%
149 and that from pulmonary veins with an oxygen saturation of about 60% in the normal
150 fetus [13]. On the contrary, the blood ejected by the right ventricle to the ascending aorta
151 have an oxygen saturation of about as low as 45%; mixture of blood from placenta with
152 an oxygen saturation of about 85% and that from systemic circulation with an oxygen
153 saturation of about 35%, that is similar to that of the pulmonary artery in the normal fetus

154 [13]. Therefore, the oxygen saturation of the blood distributed in the coronary artery of
155 the d-TGA fetus would be lower than that of the normal fetus [13]. Based on this logic,
156 total coronary blood flow of the d-TGA fetus should consequently be 1.5 times higher
157 than that of the normal fetus to provide the proper oxygen delivery. One can then
158 hypothesize that coronary arteries of d-TGA possibly grow the same as or even better
159 than the normal due to the higher coronary flow.

160 Previous studies documented that the right coronary arteries are larger than the left,
161 which consists with our results. It is questioned why this phenomenon happens. The right
162 coronary artery flow has been documented to increase with a positive correlation to
163 systolic right ventricular pressure in children with congenital heart defect [14]. The right
164 ventricles corresponding to systemic circulation in d-TGA should have higher systolic
165 pressure than normal. The right coronary artery flow then consequently increase,
166 therefore, we could hypothesize that it leads to enlarged right coronary arteries.
167 Moreover, the fact that the distance between the right coronary stems and the aortic root
168 which is located anterior to the main pulmonary artery in TGA fetus is shorter than normal
169 might increase the right coronary flow.

170 Hemodynamically and anatomically different circumstances of the coronary artery

171 development is considered to play major roles for the results of the present study as
172 described above. Although these factors mainly affect within embryos and neonates
173 before correction, we believe that they can substantially impact to the coronary artery
174 growth even years after ASO.

175

176 *Study limitations.*

177 This study included single center data and the numbers of the subjects are small.
178 Regardless of the type of coronary artery anatomy in d-TGA, the coronary cubage was
179 comprehensively evaluated. But impacts of coronary artery anatomy to the coronary
180 growth could not be evaluated because of small samples. Observational period was as
181 short as 5-7 years in this study. Longer observation of larger cohorts of patients is then
182 necessary to evaluate the coronary artery growth more properly. Also, the impact of
183 embryonic circulation on coronary artery growth even after the corrective surgery has to
184 be studied from the point of gene expression.

185

186 **Conclusion**

187 The left coronary arteries after ASO for d-TGA grow as large as normal; however, the

188 right coronary arteries possibly grow even larger. Further evaluation with long
189 observation of larger cohorts is mandatory for verifying these results.

190

191 **Abbreviations**

192 d-TGA: Complete transposition of the great arteries, ASO: arterial switch operation, LAD:
193 left descending artery, CAG: coronary angiography, BSA: body surface area, VSD:
194 ventricular septal defect, IVS: intact ventricular septum

195

196 **Declarations**

197 *Ethical Approval and Consent to participate*

198 This study was approved by the institutional review board at Yokohama City University.
199 Informed consent was obtained from all patients' parents or legal guardians.

200

201 *Consent for publication*

202 Consent for publication was obtained from all patients' parents or legal guardians.

203

204 *Availability of supporting data*

205 All data are available.

206

207 *Competing interests*

208 All authors declare that they have no competing interests.

209

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212

213 *Authors' contributions*

214 DM and YI designed the study. DM and MoG wrote and submitted the manuscript. DM,

215 YI, MaG, NT, SK, KK, TM, SY, TC collected and analyzed data together. SS and MM

216 supervised this study. All authors read the final version of this article and approved for

217 publication.

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228

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Figures

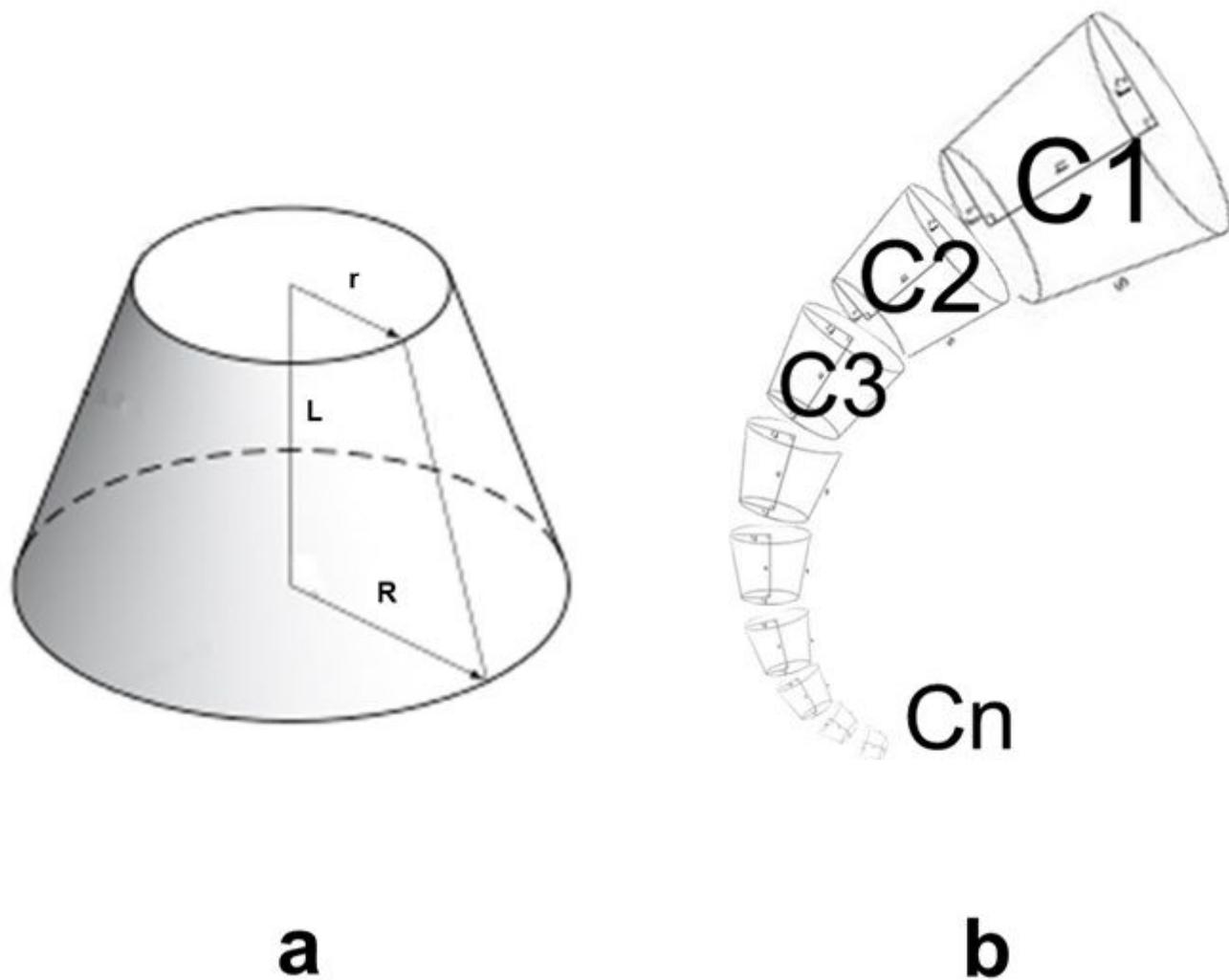


Figure 1

Approximation of coronary arteries by multiple circular truncated cones a. A cubage (C) of each truncated cone can be calculated with proximal and distal radiuses (r, R) and length (L) of each segment using the following mathematical formula. $C = \pi/3 \times L \times (r^2 + rR + R^2)$ mm³ b. The sum of the cubage of each truncated cone in one coronary artery could be acceptable approximation of total cubage of the coronary (T). $T = \sum (C_1 + C_2 + C_3 + \dots + C_n)$

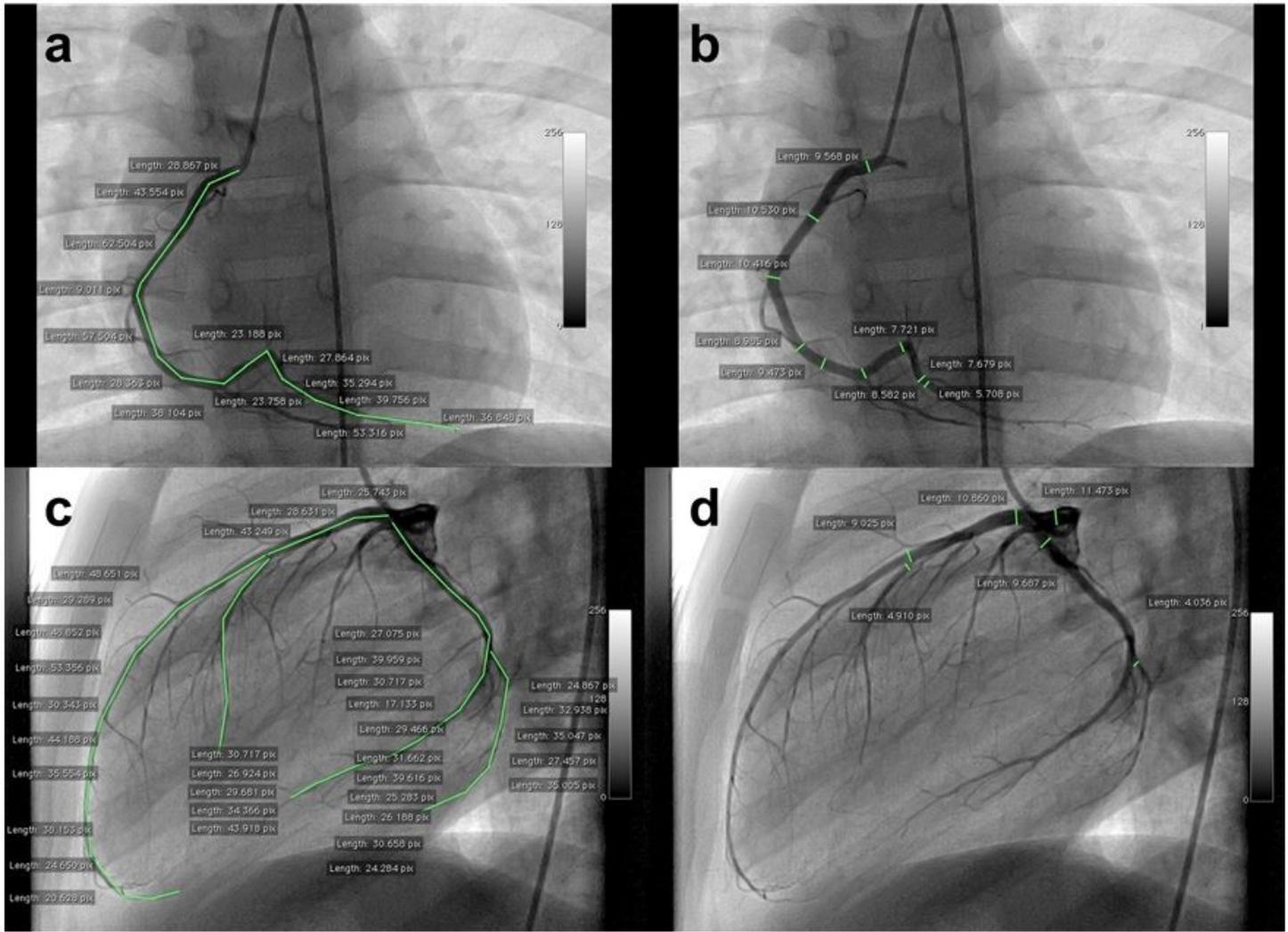


Figure 2

Angiographical analysis Radiuses and lengths of each segments of coronary arteries were measured on CAG with OsiriX DICOM viewer version 4.1.2. a, b; Right coronary artery and left main trunk were analyzed on frontal view. c, d; Left anterior descending artery, first diagonal branch and circumflex system were analyzed on lateral view.

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