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ORIGINAL ARTICLE

Coronary Artery Bypass Grafting and Percutaneous Coronary Intervention after Kawasaki Disease: The Pediatric Canadian Series

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Abstract Coronary artery (CA) aneurysms are serious complications of Kawasaki disease (KD) responsible for ischemic events. Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are reported with limited data on indications and comparative efficacy. Retrospective multicenter comparison of CA intervention following KD is performed in this study. Twenty two cases were available from 5 centers, of whom 11 underwent CABG, 10 PCI and 1 systemic thrombolysis. Age at intervention (8.3 ± 3.9 vs 11.3 ± 4.9 years, $p = 0.14$) and interval from diagnosis (5.6 ± 4.1 vs 6.5 ± 4.7 years, $p = 0.64$) were similar between CABG and PCI. Interventions were based on angiography in 15 patients or cardiac event in 7, with no difference between CABG and PCI ($p = 0.24$). Patients with CABG were more likely to undergo multivessel intervention (73 vs 10 %, $p = 0.006$). None of the patients needed reintervention after CABG, compared to 6 after PCI and 1 after systemic thrombolysis ($p = 0.004$). Signs of ischemia on stress testing or MIBI were present in 15 patients before intervention and persisted in 9 patients following last intervention, in a significantly higher proportion after CABG than PCI (80 vs 17 %, $p = 0.01$). In this series, CABG, which mostly involved multivessel intervention, was superior to PCI. Nevertheless, larger-scale studies may help define patient selection criteria for a beneficial PCI approach.

Keywords Kawasaki disease · Coronary artery bypass · Percutaneous coronary intervention · Coronary aneurysm

Introduction

Coronary artery (CA) aneurysm is a serious complication of Kawasaki disease (KD). CA aneurysms are at risk of thrombosis and progressive stenosis, which can lead to ischemic heart disease, myocardial infarction and sudden cardiac death [1, 2]. Patients with giant aneurysm (classically defined with a diameter >8 mm) are at highest risk, with up to 48 % risk of acute myocardial infarction, myocardial ischemia or death on long-term follow-up [3]. Cumulative rates of coronary artery intervention in patients with giant aneurysm in a single-center retrospective study from 1972 to 2011 in Japan were 28, 43 and 59 % at 5, 15 and 25 years [4].

Experience with coronary artery bypass grafting (CABG) has been described mainly in Japan, with reports of long-term outcomes [5, 6]. A 25 years' survival rate of 95 % [95 % confidence interval (CI), 88–98] was reported in a series of 114 patients, with a cardiac event-free rate of 60 % [95 % CI 46–72] at 25 years [5]. The most frequent cardiac events in this series were percutaneous coronary intervention (PCI) and reoperation. The superiority of arterial graft patency at 20 years (87 % for internal

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thoracic artery grafts [95 % CI 78–93] vs 44 % [95 % CI 26–61] for saphenous vein grafts) shifted the surgical trend away from venous bypass grafts. PCI was adopted more recently for KD patients with good short-term outcomes, but higher rates of reintervention [7–10]. Nevertheless, only one report [8] compared outcomes of CABG and PCI. The aim of the study was to describe and compare coronary artery interventions performed in Canada after Kawasaki disease, indication for procedure and patients' outcome.

Method

Population

This was a multicenter study enrolling academic pediatric cardiology centers in Canada to identify patients who had coronary artery interventions following KD. A questionnaire was sent to the head of the pediatric cardiology divisions to identify patients with coronary intervention. All 12 centers responded to the questionnaire: 6 (50 %) had cases with CA interventions at time of survey and 5/6 (83 %) reported their experience in this study, which excluded a single patient. Patients' charts were reviewed for clinical course with echocardiography, stress testing, angiography, interventional catheterization and cardiac surgery. This study was approved by the ethics review board of all participating institutions and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Coronary artery aneurysms were defined as a localized dilatation of a portion or diffuse segments of the coronary artery and classified as giant if internal diameter was > 8 mm at any time during follow-up. The description of stenosis and thrombus was based on CA angiography. Ischemia was based on exercise stress test (ST segments anomalies and/or localized wall motion abnormalities) and/or myocardial perfusion imaging (reversible perfusion defects). Patients were classified based on initial coronary artery procedure (CABG, PCI or medical treatment). All interventions and treatments were at the discretion of the treating physician. The primary endpoint of this report was the need for reintervention or death. Secondary endpoints were the presence or persistence of ischemia, and cardiac events (chest pain, dyspnea, syncope, cardiac arrest).

Statistical Analysis

Quantitative variables were expressed as mean ± SD or median [range], and categorical variables as frequencies or percentages. The Shapiro–Wilk test was used to test for normal distribution. Comparison of patients with PCI and CABG was performed using the Student's t test for continuous variables with normal distribution or the Mann–Whitney U test for continuous variables with non-normal distribution. The Fisher exact or the Chi-square tests were used for categorical distribution comparison. The McNemar test was used for comparison before and after the procedure. The survival curve was generated using the Kaplan–Meir method, and the differences were assessed using the log-rank test. All analyses were performed with SPSS Statistics version 23 (IBM, Chicago, Illinois). A two-tailed p value of <0.05 was set for statistical significance.

Results

There were 23 patients with CA intervention following KD in Canada, 22 of whom are reported herein (16/22 (76 %) were males). PCI was the initial procedure for 10 (45 %) patients, CABG for 11 (50 %) patients and medical treatment (systemic thrombolysis) for 1 (5 %) patient (Fig. 1).

Baseline Characteristics

At time of initial diagnosis of KD, patients were 3.3 ± 3.3 years old on average; 8/22 (33 %) presenting incomplete clinical diagnostic criteria. Patients with CABG were younger at initial diagnosis of KD (2.6 ± 3.8 vs 4.3 ± 2.4 years, $p = 0.04$). Intravenous immunoglobulin (IVIG) was given to 19 (86 %) patients, on average 11.6 ± 7.4 days after onset of fever. Delayed diagnosis resulting in delay in IVIG administration (>10 days of fever) was the case for 9 (47 %) patients. IVIG resistance, defined as the persistence or recurrence of fever 36 h after the end of IVIG perfusion, was reported in 12 (63 %) patients. Only half of the patients (11/22) received anti-inflammatory aspirin at onset of the disease, more so in patients who subsequently underwent PCI (8/10 vs 2/11, $p = 0.009$). Otherwise, antiplatelet aspirin dose was chronically administered in 17 (85 %) patients. Corticosteroids were received by 9 (41 %) patients, not related to IVIG resistance ($p = 0.65$) nor to IVIG delay ($p = 0.35$) (Table 1).

All patients had at least one CA aneurysm on echocardiography, and 18/20 (90 %) had giant aneurysm according to the classical definition. Selective CA angiography before the procedure confirmed the presence of aneurysms in all patients, on the right CA for 19/22 (86 %) patients and the left CA in all 22 patients. Multivessel CA aneurysmal disease was found in similar proportion between patients with CAGB and PCI (11/11 vs 7/10, $p = 0.09$). Stenosis was diagnosed in 19 (86 %) patients, thrombosis in 19 (86 %) patients and both stenosis and thrombosis in 16 (73 %) of patients, without difference between CABG and PCI.

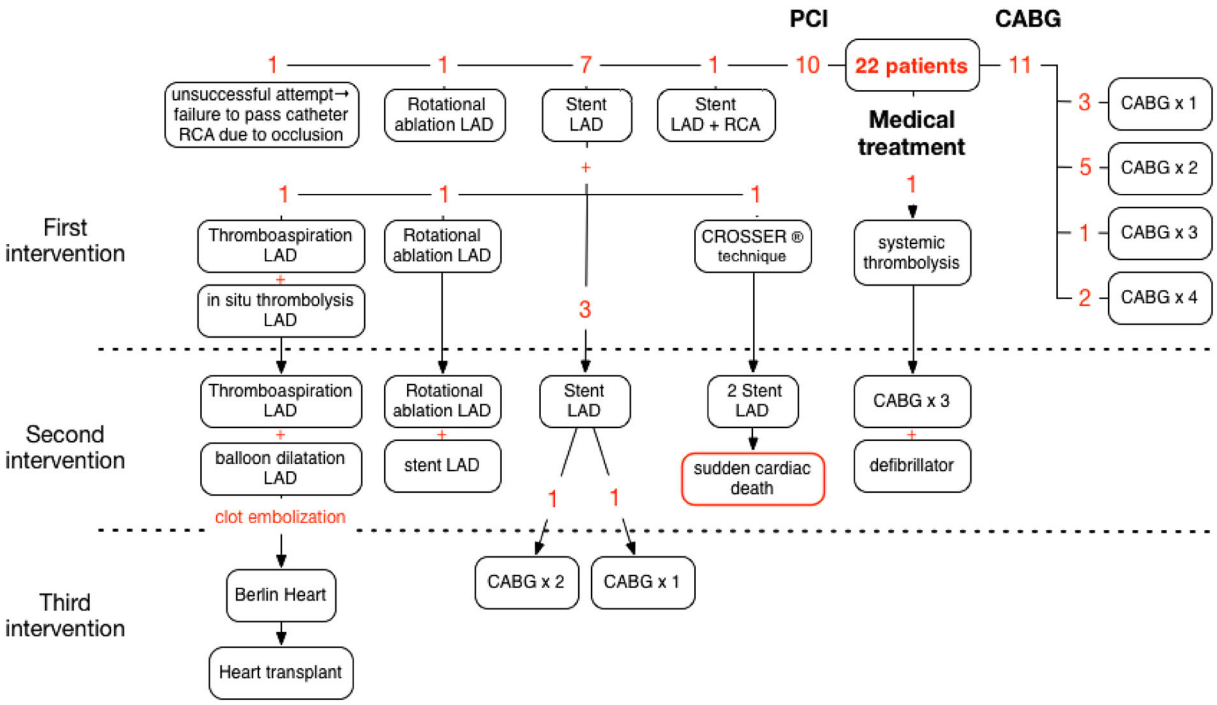

Fig. 1 Coronary artery interventions performed in Canada and course of events

Table 1 Patients' characteristics at diagnosis

Patients' characteristics at KD diagnosis	CABG	PCI	*p* value
Age at KD diagnosis (years)	2.6 ± 3.8	4.3 ± 2.4	0.04
Male *n* (%)	8 (80)	8 (80)	1.00
Complete KD *n* (%)	6 (60)	8 (80)	0.63
Day of fever at diagnosis (days)	13.3 ± 10.8	10.8 ± 5.9	0.55
Anti-inflammatory aspirin at onset *n* (%)	2 (18)	8 (80)	0.009
IVIG *n* (%)	8 (73)	10 (100)	0.21
IVIG delay *n* (%)	2 (25)	6 (60)	0.19
IVIG resistance *n* (%)	6 (75)	5 (50)	0.37
Steroids *n* (%)	8 (73)	0 (0)	0.001
Multiple vessel disease *n* (%)	11 (100)	7 (70)	0.09
Stenosis *n* (%)	8 (73)	10 (100)	0.21
Thrombosis *n* (%)	9 (82)	9 (90)	1.00

CABG coronary artery bypass grafting, *IVIG* intravenous immunoglobulins, *KD* Kawasaki disease, *PCI* percutaneous coronary intervention

There was no difference in medical treatment before the intervention between patients with PCI and CABG, with 17 (77 %) of patients anticoagulated with either heparin or warfarin (Table 2). Cardiac events before the intervention were reported in 8 (36 %) patients (4/11 CABG vs 4/10 PCI group; $p = 1$), consisting of chest pain in 6 patients, dyspnea in 1 patient and chest pain with dyspnea in 1 patient. These events occurred on average 3.7 ± 4.3 years after KD diagnosis. Reversible ischemia before the procedure was found in 15 (68 %) patients, with no difference between the CABG and PCI groups (8/11 vs 6/10, $p = 0.66$). Fixed perfusion defects on nuclear scan were present in 6/13 (46 %) patients before the procedure, with no difference between CABG and PCI ($p = 0.56$).

Intervention

Age at initial procedure was 9.3 ± 4.8 years, comparable between patients with PCI and CABG (11.3 ± 4.9 vs 8.3 ± 3.9 years, $p = 0.14$), on average 5.6 ± 4.5 years after diagnosis (6.5 ± 4.7 vs 5.6 ± 4.1 years, $p = 0.64$) (Table 3). From the 10 patients who had PCI, 4 (40 %)

Table 2 Medical treatment before and after intervention

Medical treatment	Before intervention		After intervention	
	CABG	PCI	CABG	PCI
Aspirin	8 (80.0)	8 (80.0)	8 (80.0)	8 (80.0)
Clopidogrel	4 (36.4)	2 (20.0)	2 (18.2)	5 (50.0)
Anticoagulation[a]	9 (81.8)	7 (70.0)	9 (81.8)	5 (50.0)
Beta blockers	6 (54.5)	2 (20.0)	6 (54.5)	6 (60.0)
ACE inhibitors	1 (9.1)	0 (0.0)	1 (9.1)	2 (20.0)
Statins[†]	2 (18.2)	2 (20.0)	5 (45.5)	6 (60.0)

No statistical difference in medical treatment between patients with CABG and PCI

ACE inhibitors angiotensin-converting enzyme inhibitors, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention

[†] $p = 0.02$ before versus after intervention

[a] Heparin or Warfarin

were < 10 years old at time of procedure, compared to 7/11 (64 %) patients with CABG, $p = 0.40$. First CA interventions were performed between 1995 and 2014 (1996–2014 for PCI and 1995–2013 for CABG). A similar proportion of patients between PCI and CABG had intervention before 2000 (2 patients with PCI vs 2 patients for CABG, $p = 0.63$) and after 2010 (4 patients with PCI vs 3 patients with CABG, $p = 0.44$). The only patient with medical intervention (systemic thrombolysis) was less than 1 year of age at time of procedure and had first intervention in 1988. Intervention was performed following a cardiac event in 7 (32 %) patients or based on angiography findings for the others, without difference according to the type of initial procedure (4/11 for patients with CABG versus 2/10 for patients with PCI, $p = 0.64$). In contrast, the intervention was performed on a single vessel (left anterior descending artery) in 9 patients in the PCI group, versus 3 in the CABG group, $p = 0.006$. Thus, patients with CABG were more likely to have complete revascularization at time of procedure, compared to patients with PCI where only severe lesions were addressed (7/11 vs 1/10, $p = 0.02$). In patients with single-vessel intervention on the left anterior descending artery, 5/12 (42 %) had complete occlusion of the right coronary artery (4/9 patients with PCI vs 1/3 patients with CABG, $p = 0.80$). The type of intervention differed significantly according to the reporting center, with some centers favouring CABG over PCI, $p = 0.008$ (Table 4).

Arterial grafts using the internal thoracic artery were primarily adopted for all patients with CABG, whereas 4 (36 %) patients required additional venous grafts using the saphenous vein due to multiple vessel disease. Venous grafts were not used on the LAD. For patients with PCI, 1 patient had an unsuccessful attempt due to failure to cross the lesion, with no further intervention. Stent implantation was performed for 8 patients, combined with thrombus aspiration and in situ thrombolysis in 1 patient, rotational ablation in 1 patient and the CROSSER® technique in another [11]. In addition, 1 patient had rotational ablation without stent implantation.

Reintervention

During the 5.3 ± 5.8 years of follow-up after first intervention, 6 patients required reintervention, all after PCI (6/10 vs 0/11, $p = 0.004$) (Fig. 2). Half of the reinterventions occurred in the first year following initial intervention. Reinterventions followed cardiac events in 2/6 (33 %) patients and were based on angiographic findings for 4/6 (67 %) patients. All reinterventions were on the same vessel, for in-stent restenosis in 4/6 (67 %) and stenosis at different site in 2/6 (33 %). All reinterventions were with PCI (stent implantation in 5 patients, thromboaspiration with balloon dilatation in 1 patient), and 2 patients needed a third intervention with CABG (Fig. 1). Incidence of reintervention was similar for patients with and without signs of ischemia at time of procedure (5/14 vs 1/7, $p = 0.61$). There was a tendency for more reintervention in patients with incomplete

Table 3 Patients' characteristics at intervention according to intervention

Patients' characteristics at intervention	CABG ($n = 11$)	PCI ($n = 10$)	Medical treatment ($n = 1$)	p value*
Age at 1st intervention (years)				0.14
Mean ± SD	8.3 ± 3.9	11.3 ± 4.9	0.8	
Median [range]	11.1 [5.4–22.1]	7.6 [2.6–14.1]	0.8	
Time from diagnosis (years)	5.6 ± 4.1	6.5 ± 4.7	0.1	0.64
Cardiac event leading to intervention *n* (%)	4 (36)	2 (20)	1 (100)	0.64
Multivessel intervention *n* (%)	8 (73)	2 (20)	1 (100)	0.006
Complete revascularization	7 (64)	1 (10)	1 (100)	0.02
Follow-up post-intervention (years)	4.0 ± 3.2	3.5 ± 2.8	25.4	0.73

* CABG versus PCI

CABG coronary artery bypass grafting, *PCI* percutaneous coronary intervention

Table 4 Patients' characteristics at intervention according to center

Patients' characteristics at intervention	Center 1 ($n = 2$)	Center 2 ($n = 1$)	Center 3 ($n = 9$)	Center 4 ($n = 8$)	Center 5 ($n = 2$)	p value
Type intervention n (%)						0.008
CABG	1 (50)	1 (100)	7 (78)	0 (0)	2 (100)	
PCI	1 (50)	0 (0)	2 (22)	7 (78)	0 (0)	
Systemic thrombolysis	0 (0)	0 (0)	0 (0)	1 (12)	0 (0)	
Age at 1st intervention (years)					0.96	
Mean ± SD	7.4 ± 2.0	7.52	9.4 ± 3.9	10.1 ± 6.6	8.5 ± 6.2	
Median [range]	7.4 [6.0–8.8]	7.52	10.6 [2.6–14.1]	9.5 [0.8–22.1]	8.5 [4.1–13.0]	
Time from diagnosis (years)	6.4 ± 1.1	7.3	4.4 ± 3.6	6.5 ± 5.5	7.3 ± 7.6	0.86
Cardiac event leading to intervention n (%)	1 (50)	1 (100)	6 (67)	6 (75)	1 (50)	0.87
Multivessel intervention n (%)	1 (50)	1 (100)	5 (56)	3 (38)	1 (50)	0.81
Follow-up post-intervention (years)	7.3 ± 4.6	3.7	2.9 ± 2.4	3.9 ± 3.1	–	0.32

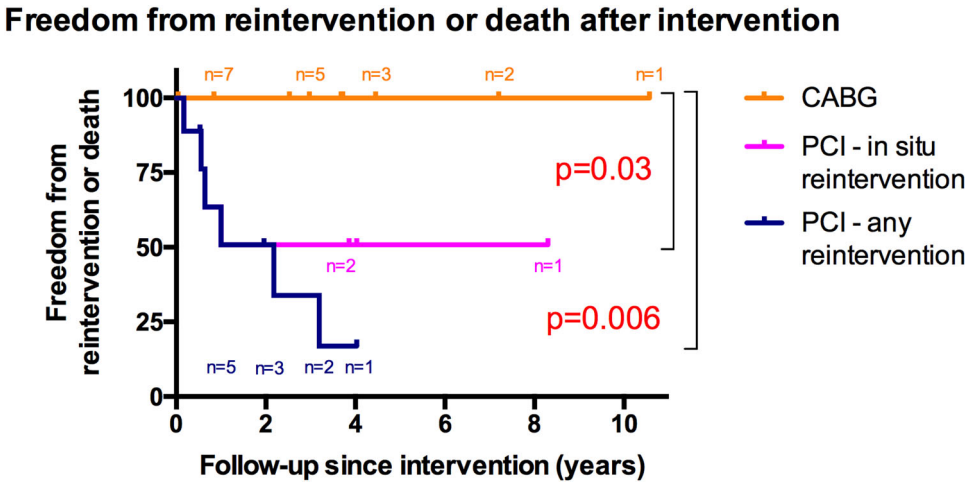

Fig. 2 Kaplan–Meir survival curve for freedom from reintervention or death on follow-up

revascularization; however, this did not reach statistical significance (6/13 vs 1/9, $p = 0.09$).

Patients' Outcome After Intervention

After last procedure, 16 (76 %) were tested for the presence of reversible ischemia or fixed perfusion defect (10 (91 %) patients after CABG and 6 (60 %) patients after PCI), either as part of routine screening or following symptoms suggestive of ischemia. Reversible ischemia was documented in 9 (56 %) patients, higher proportion after CABG than PCI (8/10 (80 %) vs 1/6 (17 %) patients, $p = 0.04$) (Fig. 3). There was no decrease in the number of patient with ischemia after last intervention ($p = 0.66$ for CABG, $p = 0.10$ for PCI) (Fig. 3). Also, 4/15 (27 %) patients had fixed perfusion defects on nuclear scan, no difference between CABG and PCI ($p = 0.60$).

Medical treatment post-intervention was similar between patients with CABG and PCI. More patients had statins after the procedure, compared to before (12/22 vs 5/22 patients, $p = 0.02$) (Table 2). During follow-up, 6 (27 %) patients sustained a cardiac event, consisting of chest pain in 2 (33 %) patients, dyspnea in 1 (17 %), syncope in 1 (17 %) and cardiac arrests in 2 (33 %). Of the 2 patients who had cardiac arrest, one died and one was successfully resuscitated and underwent CABG with defibrillator installation. The incidence of cardiac event post-PCI was similar between CABG and PCI (4/10 vs 1/11, $p = 0.11$).

Discussion

This is the first report of 22 KD cases who underwent CA intervention during childhood or early adulthood in Canada. This represents the first series from western

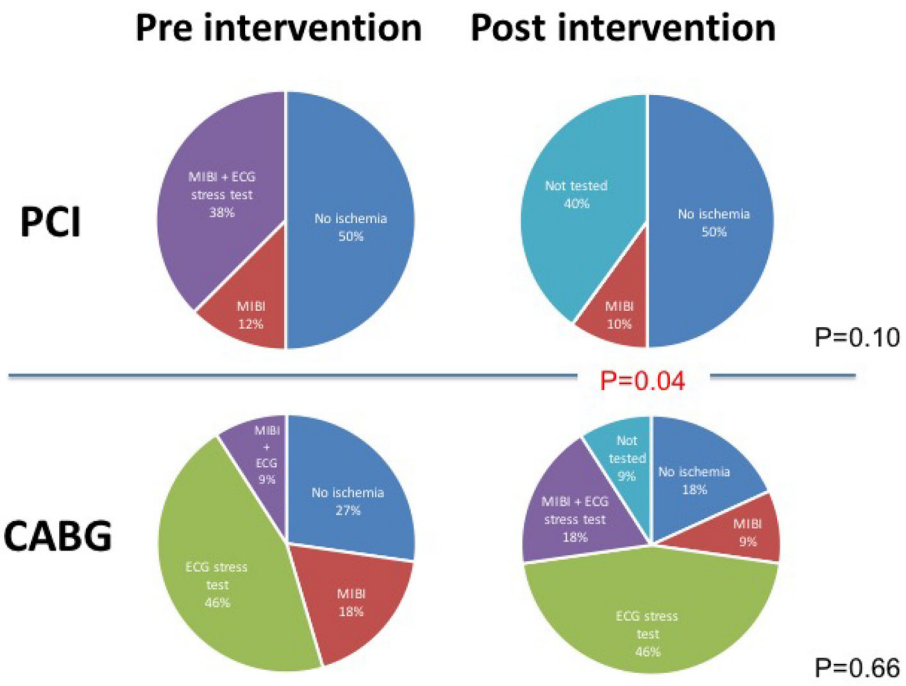

Fig. 3 Presence of ischemia before and after intervention according to procedure

countries compared to Japan where a growing experience is being reported [5–10]. There is a marked difference in choice of intervention between centers in our series. Intervention was performed following a cardiac event in one-third of patients, and only two-thirds of patients had signs of ischemia before the procedure. Patients with CABG were younger at KD onset and were more likely to have multivessel intervention and complete revascularization, which led to a lower incidence of reintervention compared to PCI. Nevertheless, more patients with CABG had signs of ischemia after last intervention, but the rates of cardiac symptoms were similar between both groups.

Most of the decisions in interventions after KD are based on expert's opinion, and centers' experience, due to the lack of official recommendations. Opinions are mostly extrapolated from experiences in adults with atherosclerotic coronary disease and to some extent on recent Japanese experience. Although the pathophysiology differs between KD and atherosclerotic heart disease, interventions have the same goals to relieve ischemic symptoms and lower the risk of myocardial ischemia, infarction and sudden cardiac death. However, the aneurysmal lesions in KD and the higher intensity of CA calcification [10] impose selective decision making as opposed to simple extrapolation from the adult experience.

In 2001, the Japanese Ministry of Health suggested the presence of ischemic symptoms or ischemia on stress testing as indications for intervention [12]. Due to the risk of sudden cardiac death, they also recommended to consider intervention for patients with >75 % stenosis of the left anterior descending artery. In our Canadian series, up to one-third of patients with no signs of ischemia were offered intervention, similar to other reported series [8–10]. Interestingly, KD patients with no signs of ischemia at time of CABG had higher rates of reintervention, probably due to competitive flow through their native coronary arteries [8]. This is in agreement with the most recent guidelines in adults with atherosclerotic heart disease that discourage interventions in patients with no signs of ischemia [13]. These findings were not replicated in our study, although limited by statistical power due to small sample size. The optimal timing of CA intervention following KD seems to be an important factor based on a retrospective study from Japan [14]. Accordingly, patients operated on sooner (3.8 ± 0.8 years) following KD onset were less likely to exhibit ventricular dysfunction (8 vs 100 %, $p < 0.001$) or myocardial infarction before the procedure (8 vs 67 %, $p = 0.04$) than those operated on later (13.9 ± 1.6 years). Postoperative freedom from cardiac events was likely to be advantageous in early intervention without reaching statistical significance (100 vs 67 %, respectively, $p = 0.08$). Although there are no actual data on ischemic or subischemic events in that series, earlier intervention in these patients seemed more favorable.

Very few papers retrospectively compare outcomes after PCI and CABG in KD, and no randomized control study addresses this issue. According to the Japanese Ministry of Health guidelines, patients with severe left ventricular dysfunction, with multiple vessel lesions, ostial lesions and long segmental lesions should be considered for CABG

[12]. In retrospective reports, patients who underwent CABG were more likely to be younger at the time of procedure and to have multivessel disease [8]. Similarly, in our series, despite similar proportion of multivessel disease before intervention, more patients with CABG had multivessel intervention compared to PCI. The incidence of all-cause mortality and/or cardiac events during follow-up after intervention was similar between CABG and PCI; however, need for repeat vascularization for the target vessel was higher after PCI, consistent with other studies in pediatric patients with KD [8]. This could be explained by the practice to intervene only on severe lesions when PCI is chosen as opposed to CABG where both severe and less severe lesions are addressed during the same surgery. On the other hand, the main findings relative to the type of vascular graft in KD are the superiority of arterial graft patency (87 % [95 % CI 78–93]) compared to the saphenous vein (44 % [95 % CI 26–61]) at 20 years post-surgery on the one hand, and the advantage of arterial graft growth correspondent to somatic growth in children [5]. This probably explains the absence of reintervention following CABG in our series since the duration follow-up did not reach the reported 20 years from Japan. From the comparative perspective in adults with atherosclerotic disease, overall survival is similar with both approaches, but repeat revascularization is more commonly required after PCI than CABG (46 % after balloon dilatation, 40 % after stent implantation, 9.8 % after CABG, $p < 0.001$) [15]. Since this systematic review of the literature from 1996 to 2006, however, the introduction of drug-eluting stents has dramatically changed the outcome of coronary stenting with an obvious advantage over bare metal stents. Indeed, the introduction of drug-eluting stents brought a reduction of as much as 50–70 % in target lesion revascularization for in-stent restenosis [16] as well as a lower risk for death or MI with an adjusted Hazard Ratio 0.41–0.67 [17] compared to bare metal stents. A meta-analysis including 31 trials and 15,003 patients clearly demonstrated a significant reduction in repeat revascularization after PCI with a progressive decline in odds ratios (OR) from the pre-stent era (OR 7.0; 95 % CI 5.1–9.7; $p < 0.01$) to the bare metal stent era (OR 4.5; 95 % CI 3.6–5.5; $p < 0.01$) and to the drug-eluting stent era (OR 2.5; 95 % CI 1.8–3.4; $p < 0.01$) [18]. At the same time, the most recent comparison between CABG and drug-eluting stents showed a higher reintervention rate after PCI than CABG for both single- and multivessel disease ($p < 0.001$), as well as lower survival at 5 and 9 years for multivessel disease ($p < 0.001$) [19]. However, such a comparison in KD between CABG and drug-eluting stenting remains unclear.

There are limitations to this study inherent to the rarity of the disease on the one hand and to its retrospective nature on the other hand. The choice and indications for procedure were largely dependant on physician's and centers' preference. Also, protocols for stress testing were not uniform between centers, and nuclear perfusion scans were interpreted by different readers, limiting comparative conclusions on the presence of ischemia before and after procedure. The small number of patients, limited statistical power and due to the relatively short follow-up, long-term outcome could not be addressed. However, this is the largest Canada-based series reported up to now aside from Asia. With a high response rate, we think that this series represents current practice in Canada.

Conclusion

In this series, patients with CABG were more likely to have complete revascularization and thus required less reintervention. While PCI seems to have the advantage of better subsequent myocardial perfusion, uniform perfusion testing and interpretation are necessary in future studies to support such observation. However, PCI required more reintervention compared to CABG, both for initially addressed stenosis and new progressive lesions. In the absence of established guidelines, larger-scale studies are required to guide therapeutic approaches and better define the place of PCI in interventions after Kawasaki disease.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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