Pulmonary arteriovenous malformations in children after the Kawashima procedure: Risk factors and midterm outcome

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ABSTRACT

Background : **Pulmonary arteriovenous malformations (PAVMs) are the major cause of progressive cyanosis in patients palliated with bidirectional cavopulmonary connection (BCPC). The aim of our study is to analyze the occurrence of PAVMs in patients after Kawashima procedure, to study the effect of total cavopulmonary connection (TCPC) on PAVMs, to evaluate the effect of axillary arteriovenous fistula (AAVF) creation on PAVMs, and to study the risk factors for PAVMs.**

Methods : **In this retrospective cohort study, all patients with left isomerism and azygous continuation of an interrupted inferior vena cava who underwent Kawashima procedure from July 2001 to December 2017 were included.**

Results : **Twenty-six patients after Kawashima procedure were included in our study. PAVMs were diagnosed in 12 patients (46%). Five of these 12 patients underwent TCPC with complete resolution of hypoxemia. Three patients underwent AAVF creation, 2 had complete resolution, while 1 had partial resolution of hypoxemia. Fourteen patients (54%) did not develop PAVMs. Nakata index below 267 mm^2/m^2 and McGoon ratio below 1.9 predicted the development of PAVMs with high sensitivity and specificity.**

Conclusions : **PAVMs represent a serious complication in patients who undergo Kawashima procedure. Small size of pulmonary arteries is an important risk factor for the development of PAVMs. Resolution of hypoxemia after TCPC completion supports the hepatic factor hypothesis. Early TCPC completion in these patients may help to avoid the development of PAVMs by restoring the hepatic factor. Resolution of hypoxemia after AAVF creation may support the lack of pulsatile flow hypothesis.**

Keywords : Arteriovenous malformation, congenital heart disease, Kawashima procedure, left isomerism, single ventricle

INTRODUCTION

Children with functionally single ventricle are usually palliated following a staged clinical pathway which ends with a total cavopulmonary connection (TCPC) leaving the single ventricle as a systemic pump while the systemic

Access this article online

Quick Response Code:

Website: www.annalspc.com

DOI: 10.4103/apc.APC_144_19

How to cite this article: Alibrahim IJ, Mohammed MH, Kabbani MS, Jijeh AM, Tamimi OR, Alghamdi AA, *et al*. Pulmonary arteriovenous malformations in children after the Kawashima procedure: Risk factors and midterm outcome. Ann Pediatr Card 2021;14:10-7.

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Submitted: 29-Sep-2019 **Revised:** 05-Dec-2019 **Accepted:** 05-Aug-2020 **Published:** 17-Sep-2020

venous circulation bypasses the heart to go directly to the lungs.[1-6] Bidirectional superior cavopulmonary connection (BCPC) is a commonly performed procedure as a transitional stage in single-ventricle surgical palliation.[1-6] It involves creating an anastomosis between the superior vena cava (SVC) and the pulmonary artery (PA) during infancy, while the completion of TCPC by connecting the inferior vena cava (IVC) and hepatic veins to the pulmonary circulation is left until few years of age.[1,4-6] BCPC provides an excellent transitional palliation with lower morbidity and mortality when compared to one-stage TCPC.[1] The durability of the BCPC becomes significantly limited in patients who develop pulmonary arteriovenous malformations (PAVMs).[1-6] These malformations consist of direct communication between the pulmonary arteries and pulmonary veins that result in direct shunting of the de-oxygenated blood without going through the capillaries for the gas exchange in the pulmonary alveoli. This usually results in severe hypoxia and decreased exercise tolerance in patients with BCPC.[1]

In 1984, Kawashima *et al.* described their initial experience with a modified BCPC in patients with interrupted IVC and azygous continuation into SVC.[7] The operation results in the drainage of all the systemic venous circulation to the lungs except the hepatic venous blood flow which enters the heart directly. This procedure could be considered as the ultimate palliative operation in some patients.[2,4-6] In comparison to patients who undergo regular BCPC, a significant percentage of patients who undergo Kawashima procedure may develop PAVMs in the subsequent years.[1-6]

Previous studies showed indirect, but compelling, clinical evidence that two major etiologic hypotheses may contribute to the development of PAVMs: the hepatic factor hypothesis and the loss of pulsatile pulmonary blood flow hypothesis.[1] The hepatic factor hypothesis postulates that lack of the hepatic venous effluent which carries an unidentified factor (the hepatic factor) to the pulmonary arteries results in the development of the PAVMs. This can be seen in patients who have interruption of the hepatic flow to the lung such as Kawashima patients or in patients with liver failure where the flow is not interrupted but the hepatic factor synthesis is disturbed.[1-6] The lack of pulsatile flow hypothesis postulates that patients with BCPC or TCPC are at risk of developing PAVMs due to the lack of arterial pulsatility in their pulmonary arteries blood flow.[1] Creation of axillary arteriovenous fistula (AAVF) has been shown to improve the pulmonary flow pulsatility and hence reduce the risk of PAVMs.[8]

It is not yet clear which proportion of patients with Kawashima circulation will ultimately develop PAVMs and need TCPC. The aim of our study was to analyze the occurrence of PAVMs in patients who were palliated with Kawashima procedure, to study the effect of TCPC on PAVMs (hepatic factor hypothesis), to evaluate the effect of AAVF creation on PAVMs (lack of pulsatile flow hypothesis), and to explore the possible risk factors for developing PAVMs.

METHODS

In this retrospective cohort study, all patients with functionally single ventricle and left isomerism with interrupted IVC and azygous continuation who underwent Kawashima procedure at our cardiac center between July 2001 and December 2017 were included. The medical charts, echocardiograms, and cardiac catheterization data were reviewed. Some of the patients who underwent Kawashima procedure developed PAVMs and were managed by either AAVF creation or TCPC completion. We divided the patients into two groups: PAVM group and non-PAVM group. We have studied the following variables: gender, weight, age at Kawashima procedure, diagnosis categories (unbalanced atrioventricular septal defect [AVSD] versus others), ventricular morphology, and presence of bilateral SVC versus single right or left SVC. The previous and concomitant cardiac procedures were reviewed. The echocardiographic findings (cardiac function, atrioventricular [AV] valve regurgitation, systemic outflow obstruction, and presence of pulmonary forward flow [PFF]) before and after Kawashima procedure were reviewed. The cardiac catheterization data before Kawashima and TCPC procedure were reviewed as well.

The diagnosis of PAVMs was suspected if there is a progressive reduction of resting systemic arterial oxygen saturation without any evidence of parenchymal lung disease or in the presence of arterial oxygen saturation of 80% or less in room air during cardiac catheterization. The diagnosis was confirmed by positive contrast echocardiogram where agitated saline is injected and the bubble contrast was traced by echocardiography. The appearance of dense bubble contrast in the pulmonary venous atrium and systemic ventricle within five cardiac cycles after the bubbles reach the PA indicates lack of passage of the bubbles through the pulmonary capillary bed and therefore indicates the presence of PAVMs.[9,10] The diagnosis can also be confirmed during cardiac catheterization by the following: pulmonary angiogram where PAVMs are shown as dilated and tortuous vessels that extend far into the periphery of the lung, evidence of right to left shunting demonstrated by the rapid appearance of contrast in the pulmonary veins during pulmonary arterial angiogram, and pulmonary venous saturation <94% in the absence of parenchymal lung disease.[4]

Patients with PAVMs were treated with either TCPC completion or by creation of AAVF if they were not

suitable for TCPC completion. Resolution of hypoxemia was considered as partial if there is 10% increase or more in the oxygen saturations at least 6 months after TCPC completion or AAVF creation. The resolution of hypoxemia was considered to be complete if the oxygen saturation was 90% or above in room air at least 6 months after TCPC completion or AAVF creation. Regression of PAVMs was considered to be complete when they were no longer demonstrated by pulmonary angiography or the bubble contrast echocardiographic study was negative. The regression was considered to be partial when the PAVMs were getting less but still existed in pulmonary angiograms.

All of the patients who underwent TCPC completion had extracardiac nonfenestrated Fontan procedure. The anastomosis was completed between hepatic vein and right PA near the main PA ensuring bidirectional equal flow in both PA branches. The flow in the confluence was confirmed by intraoperative transesophageal Doppler echocardiography with no signs of obstruction in the pulmonary blood flow. For the patients who underwent AAVF creation, the fistula was created to augment the pulmonary blood flow. For the patients who underwent AAVF creation, the fistula was created to augment the pulmonary blood flow and to improve the oxygen saturation in severely hypoxemic patients. A side-to-side anastomosis was constructed between the axillary artery and the axillary vein with ligation of the axillary vein distally to yield a functional side-to-end arteriovenous anastomosis. Our current regimen for postoperative anticoagulation after Kawashima procedure includes warfarin for 6–12 months then aspirin continuously. Early death was defined as death in the hospital or death within 30 days of discharge, while all other deaths were considered as late death.

Statistical analysis

Data were expressed as numbers and percentages for categorical variables and as mean ± standard deviation for continuous variables. Data that did not fit a normal distribution were expressed as median and interquartile range (IQR). Continuous variables were compared using paired Student's *t*-tests and categorical variables were compared using Chi-square tests or Fisher's exact test appropriately. Cutoff values were obtained from the receiver operating characteristic curve, where we chose the point of the best sensitivity and specificity. $P < 0.05$ was considered statistically significant. The statistical analysis was performed using SPSS for Windows, version 16.0 Chicago, SPSS Inc.

RESULTS

During the study period, 419 patients underwent BCPC procedure and 237 patients underwent TCPC completion as palliation for single-ventricle physiology in our institution. Twenty-six patients out of 419 (6%) underwent Kawashima procedure, and the median follow-up period was 4.8 years (IQR: 2.6–6.9 years). Fourteen patients (54%) were females. At Kawashima procedure, the median age was 13.5 months (IQR: 7.7–26 months) and the mean weight was 9 ± 3 kg. The single systemic ventricle had right ventricular morphology in 15 patients (57%), left ventricular morphology in 9 patients (35%), and undetermined ventricular morphology in 2 patients (8%). Fourteen patients (54%) had unbalanced AVSD. Ten patients (38%) had bilateral SVC and 16 patients (62%) had unilateral SVC (8 patients had right SVC and 8 patients had left SVC). No patient had hemodynamic, echocardiographic, or angiographic findings at cardiac catheterization that indicated the presence of clinically significant PAVMs before Kawashima procedure. The mean preoperative oxygen saturation was 76% ± 5%. Sixteen patients (62%) underwent palliative procedures before Kawashima procedure [Table 1]. Fifteen patients underwent 19 concomitant cardiac procedures during Kawashima operation [Table 1]. Diagnostic cardiac catheterization was performed in 18 patients before Kawashima procedure [Table 2], while eight patients underwent Kawashima procedure based on other diagnostic modalities.

Table 1: Other cardiac procedures before or during Kawashima procedure

Previous cardiac procedures	Number of patients
Right or left Blalock–Taussig shunt	8
Patent ductus arteriosus stenting	3
PA banding	2
Central shunt	2
Permanent pacemaker implantation	1
Concomitant cardiac procedure	**Number of procedures**
PA plasty	8
PA banding	4
Common AV valve repair	4
Tightening of PA banding	1
Right superior vena cave ligation	1
Ventricular septal defect enlargement	1

AV: Arteriovenous, PA: Pulmonary artery

Table: 2. Pre Kawashima cardiac catheterization findings

Cardiac catheterization findings	PAVM (*n*=9)	Non-PAVM (*n*=9)	*P*
Mean PA pressure (mmHg)	13.6±3	13±3.5	0.67
PA saturation (%)	72±8	73±9	0.9
Aortic O2 saturation (%)	79±5	78±7	0.8
Superior vena cave saturation (%)	62±8	58±8	0.3
QP: QS	0.7±0.2	0.9±0.5	0.26
Indexed pulmonary vascular resistance (wood unit/m^2)	1.5±0.9 (*n*=5)	1.7±0.2 (*n*=3)	0.76
Nakata index (mm^2/BSA)	238±94	385±94	0.01
McGoon ratio	1.5±0.3	2.1±0.5	0.03
Hemoglobin (g/dl)	11±6	12±4	0.7

n: Number of patients, PAVM: Pulmonary arteriovenous malformation, QP/QS: Pulmonary to systemic flow ratio, BSA: Body surface area, PA: Pulmonary artery

Twelve out of 26 patients (46%) developed PAVMs. The diagnosis of PAVMs was confirmed by cardiac catheterization in all of the 12 patients. Four patients had contrast echocardiographic studies, and all were positive. Five patients had TCPC completion with complete resolution of hypoxemia 6 months after TCPC completion. One of them had cardiac catheterization after TCPC completion due to signs of failing Fontan which showed complete regression of PAVMs, and this patient is still alive. Three patients out of 12 underwent AAVF creation after 32 ± 19 months of Kawashima procedure due to deep cyanosis with oxygen saturation around 65%. Two of them had complete resolution of hypoxemia 6 months after AAVF creation. This was confirmed by cardiac catheterization in one of these patients. The third patient had partial resolution of hypoxemia after AAVF creation and that was confirmed by cardiac catheterization [Figure 1]. AAVF creation was chosen in these patients because they were not suitable for Fontan, one patient was severely hypoxic with small weight (9.3 kg), the second one was severely hypoxic with moderate AV valve regurgitation, and the third one was severely hypoxic with polycythemia, which required blood extraction. The rest of the patients (4/12) who developed PAVMS are still waiting for TCPC completion. Fourteen out of 26 patients (54%) did not show evidence of PAVMs. Four of them had TCPC completion, while 10 patients are still waiting for this procedure [Figure 2]. The duration between Kawashima and TCPC was 61 ± 38 months in the PAVM group and 51 ± 17 in the non-PAVM group ($P = 0.63$).

Thirteen patients had systemic to pulmonary shunt (Blalock–Taussig shunt, central shunt, or patent ductus arteriosus stenting) before Kawashima procedure. Seven out of 13 patients (54%) had PAVMs. While 5 out of the other 13 patients (who had no systemic to pulmonary shunt, 38%) developed PAVMs ($P = 0.43$), all of these modified procedures were removed at the time of Kawashima procedure.

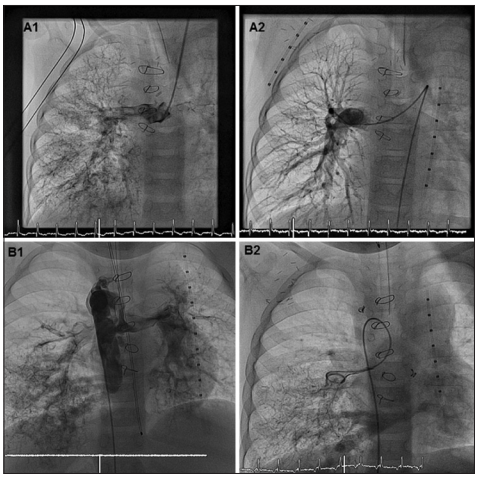

Figure 1: Pulmonary angiograms demonstrating pulmonary arteriovenous malformations before (A1 and B1) and after (A2 and B2) axillary arteriovenous fistula creation. Note the complete regression of pulmonary arteriovenous malformations in A and partial regression in B after axillary arteriovenous fistula creation

We have analyzed all of the variables for the risk factor of developing PAVMs, and the only variable that carried statistical significance was the size of pulmonary arteries. Nakata index and McGoon ratio were lower in the PAVM group ($P = 0.01$ and 0.03, respectively). Nakata index below 267 mm^2/m^2 predicted the development of PAVMs (sensitivity and specificity = 71% and 100%, respectively). McGoon ratio below 1.9 predicted the development of PAVMs (sensitivity and specificity = 85% and 80%, respectively) [Table 2 and Figure 3b].

The mean PA pressure was similar in both the groups [$P = 0.67$, Table 2]. However, we were able to calculate the indexed pulmonary vascular resistance in eight patients (5 in the PAVM group and 3 in the non-PAVM group) with no significant difference ($P = 0.76$).

We performed PA banding in six patients. Four patients underwent banding at the time of Kawashima procedure while two had PA banding before the procedure (one of them underwent tightening of previous PA banding during Kawashima procedure while the other had transection of the PA). This resulted in five patients with PA banding during follow-up. They had some PFF to maintain pulsatility in the pulmonary arteries. Two out of the five patients developed PAVMs. Cardiac catheterization showed no pulsatility in the pulmonary blood flow in one of these patients. Three patients did not develop PAVMs, one of them underwent cardiac catheterization which showed good pulsatility in the pulmonary arteries.

Nine out of 26 patients had PFF: 4/9 with severe pulmonary stenosis (PS) which was not eliminated at the time of Kawashima procedure and 5/9 underwent PA banding, 3 (33%) of those who had PFF developed PAVMs. While 17/26 had no PFF, 9/17 had pulmonary atresia and 8/17 had PFF elimination at the time of Kawashima procedure, 9 (53%) of those who had no PFF developed PAVMs [Table 3].

We had 3 late deaths: two in the PAVM group while waiting for TCPC completion: the first one occurred in a 4-year-old female child who had left isomerism, interrupted IVC with azygous continuation, unbalanced AVSD with a dominant left ventricle, common atrium, and single right SVC. She underwent Kawashima procedure, common AV valve repair, and PA banding at the age of 8 months. She died at another institution with no clear record of the cause of death. The second death occurred in a 4-year-old child. She had left isomerism, interrupted IVC with azygous continuation, unbalanced AVSD with undetermined ventricular morphology, transposition of great arteries, severe PS, and single left SVC. She underwent central shunt then Kawashima

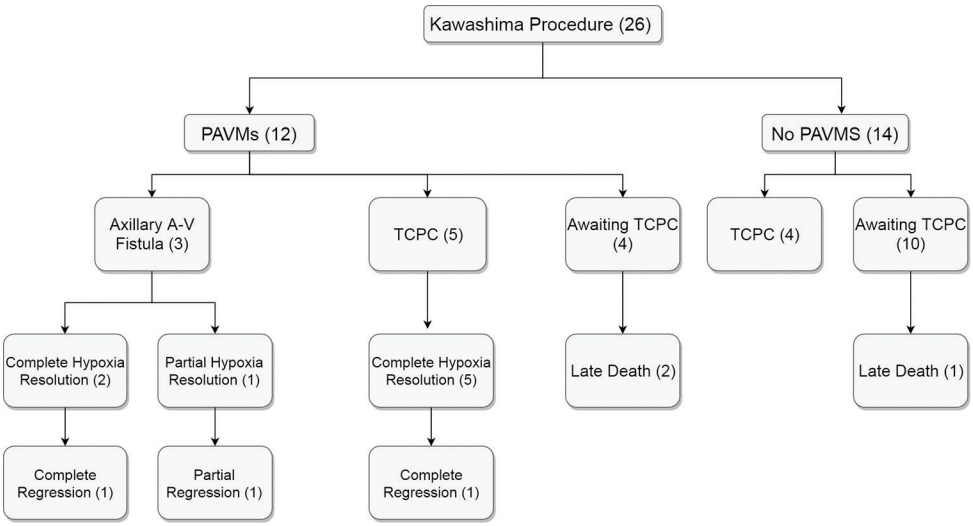

Figure 2: Outcome of patients after Kawashima procedure

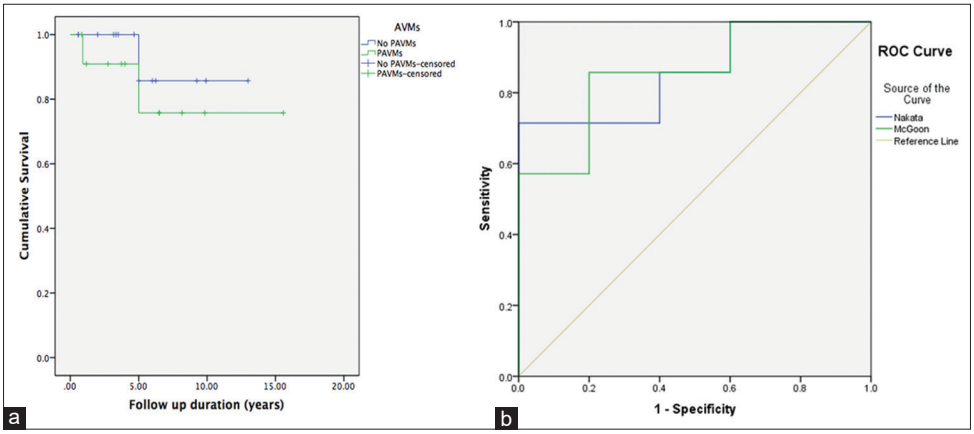

Figure 3: (a) Overall survival estimated by the Kaplan–Meier method (survival at 5 years in no pulmonary arteriovenous malformation group: 86% and survival at 5 years in pulmonary arteriovenous malformation group: 76%). (b) Receiver operating characteristic curve for Nakata index and McGoon ratio

Table 3: Effect of the presence of pulmonary forward flow at the time of Kawashima procedure in the development of pulmonary arteriovenous malformation

	PAVMs (%)	No PAVMs (%)	Total
PFF	3 (33)	6 (67)	9
No PFF	9 (53)	8 (47)	17
Total	12	14	26 (P=0.59)

KP: Kawashima procedure, PAVMs: Pulmonary arteriovenous malformations, PFF: Pulmonary forward flow

procedure and common AV valve repair at the age of 5 months. This patient died due to septic shock at the age of 4 years. The third death was in the non-PAVM group while the patient was waiting for TCPC procedure. She was a 4-year-old child with left isomerism, interrupted IVC with azygous continuation, unbalanced AVSD with a dominant right ventricle, dextrocardia, small VSD, bilateral SVC, and mixed systemic and pulmonary venous connection into the common atrium. She underwent PA banding, right BCPC, and left Kawashima procedure at the age of 2.5 years. Subsequently, she had severely depressed ventricular function, severe common AV valve regurgitation, and systemic outflow obstruction. She underwent debanding and Damus–Kaye–Stansel procedure at the age of 3 years. Despite that, she continued to have severely depressed ventricular function and severe common AV valve regurgitation, and this resulted in intractable heart failure and death.

The 5-year survival was 86% in the non-PAVM group while it was 76% in the PAVM group [Figure 3a]. Significant AV valve regurgitation was observed in all of the three patients who died. This may indicate that AV valve regurgitation may have a deleterious effect on the outcome.

DISCUSSION

The main objective of terminal palliation of single-ventricle pathway is to divert the systemic venous return to the

lung. Although Kawashima procedure diverts most of the systemic venous return to the lung, the development of PAVMs remains a major complication of this procedure despite the good initial expectation.[1,3,4,6] After the completion of Kawashima procedure, patients are prone to develop PAVMs with a reported incidence ranging from 17% to 58%.[2-4] In our study, however, the occurrence of 46% of PAVMs after Kawashima procedure appears to be clearly in the higher range of the reported studies.

Small PA branch, indicated by low Nakata index and McGoon ratio before Kawashima procedure, was a predictor for developing PAVMs in our study with strong sensitivity and specificity. To the best of our knowledge, the relation between the size of pulmonary arteries and developing PAVMs has not been demonstrated in the literature previously. The theory behind the relation between small pulmonary arteries and PAVM development could be related to the hemodynamic effects of small pulmonary arteries on pulmonary vessel flow and resistance since it is known that as vessel diameter decreases, the resistance increases and blood flow decreases. In our study, there was no significant *P* value between both the groups for pulmonary blood flow and indexed pulmonary vascular resistance [Table 2], however, the theory behind this relation could be considered in further studies with larger number of cases.

Brown *et al.*[4] reported that the presence of bilateral SVCs was an independent predictor of the development of PAVMs. In contrast to that, in our study, bilateral SVC was seen in only one-third of the patients (38%) who developed PAVMs, while the majority had a single SVC.

There is some evidence that the absence of the hepatic factor may play an important role in the development of PAVMs. Patients with end-stage liver disease are prone to develop progressive cyanosis due to PAVMs.[11,12] Resolution of cyanosis is seen with restored liver function following liver transplantation.[12] McElhinney *et al.* have indicated that the development of unilateral PAVMs after TCPC completion is probably due to the unilateral streaming of the hepatic venous flow to one lung that results in the development of PAVMS in the other lung which is deprived of that hepatic venous flow. Revision of the TCPC connection to eliminate hepatic venous streaming was an effective surgical strategy to resolve the PAVMs in this setting.[13] The presence of PAVMs in the right lung devoid of hepatic venous flow following the classic BCPC supports this hypothesis as well.[14]

In patients with left isomerism and interrupted IVC who have undergone a Kawashima procedure, hepatic venous blood is diverted away from both lungs and they are at risk of developing bilateral PAVMs.[1] Multiple reports have indicated complete resolution of hypoxemia and PAVMs following the connection of the hepatic veins to the pulmonary arteries.[5,15] Our results are consistent with this theory as all of our patients who had PAVMs and underwent TCPC completion had complete clinical resolution of cyanosis. This was also confirmed by angiography which showed regression of PAVMs in those patients who underwent cardiac catheterization after TCPC. We recommend early TCPC completion in patients who underwent Kawashima procedure to avoid the development of PAVMs due to the longstanding deprivation of the hepatic factor.

The lack of pulsatile flow hypothesis indicated that nonpulsatile flow to the lungs stimulated the development of PAVMs.[16] Nevertheless, a nonpulsatile flow as the sole etiologic factor suggested by this theory fails to explain PAVMs in patients with biventricular physiology and the hepatopulmonary syndrome in patients with liver cirrhosis.[11] Persistence of PAVMs has been reported after TCPC completion despite restoration of balanced hepatic venous flow. This may indicate that the loss of pulsatile flow could be an offending factor.[17] In our study, there was complete or partial resolution of hypoxia 6 months after AAVF creation supporting the theory of pulsatile flow as a possible offending factor in the development of PAVMs. In a recent study, Spearman *et al.*[18] reported that seven patients underwent arteriovenous fistula (AVF) creation for hypoxia after single-ventricle palliation and they concluded that AVF creation for such patients does not universally improve saturation. In contrast to that, in our study, all the patients who underwent AVF creation have either complete or partial resolution of hypoxemia.

AAVF creation appears to be a good alternative or bridging surgical option with low mortality and morbidity which can be offered to sick and deeply cyanosed patients who cannot proceed with TCPC completion. Hickey *et al.* concluded similarly that creation of arteriovenous fistula is a low-risk procedure and provides relief from severe cyanosis. It can remain an option in the decision-making for the management of rare patients with intractable cyanosis for whom TCPC completion and transplantation are unbearable.[19]

In our study, five patients underwent PA banding at the same time of Kawashima procedure to maintain some pulsatile flow to secure pulsatility in the pulmonary arteries and to provide the hepatic factor. Two of these patients developed PAVMs, one of them had lack of pulsatile pulmonary blood flow confirmed by cardiac catheterization. On the contrary, good pulsatility in pulmonary arteries was observed during cardiac catheterization in one of the three patients who did not develop PAVMs. This supports that the pulsatility of pulmonary blood flow that is maintained by PA banding or regained by AAVF creation may help to resolve PAVMs.

In our study, 9 out of 26 patients had PFF, 3 (33%) of them developed PAVMs. While 17/26 had no PFF, 9 (53%) of them developed PAVMs. Although statistically it was not significant, there was a tendency of developing PAVMs in patients with eliminated PFF versus those with persistent PFF (53% vs. 33% consecutively, $P = 0.56$).

Vollebregt *et al.*[3] showed high mortality after TCPC in patients with left isomerism, interrupted IVC, and azygous continuation and univentricular heart disease. They reported 12 patients who underwent TCPC after Kawashima procedure with 4 (33%) overall deaths, 3 were early deaths, and 1 patient died 10 years after TCPC due to a subarachnoid hemorrhage. In our study, we had 3 late deaths (12%) after Kawashima procedure and no mortality after TCPC in nine patients in both the PAVM and non-PAVM groups. There was no mortality after AAVF creation. However, this procedure was performed only in the last few years of our study period.

CONCLUSIONS

PAVMs represent a serious complication that is likely to develop in about half of the patients who undergo Kawashima procedure. Small size of pulmonary arteries is an important risk factor for the development of PAVMs. Resolution of hypoxemia after TCPC completion supports the hepatic factor hypothesis. Early TCPC completion in these patients may help to avoid the development of PAVMs by restoring the hepatic factor. Resolution of hypoxemia after AAVF creation may support the lack of pulsatile flow hypothesis. AAVF creation appears to be a good alternative or bridging surgical option with low mortality which can be offered to sick and deeply cyanosed patients.

Acknowledgment

We thank Prof. Talat. M. Yelbuz, MD, PhD, for his help during drafting, critical reading and revision of this manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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