Outcomes following the Kawashima procedure for single-ventricle palliation in left atrial isomerism

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Abstract

OBJECTIVES: Patients with left atrial isomerism and interrupted inferior vena cava palliated with a superior cavopulmonary connection or Kawashima procedure (KP) have a high incidence of developing pulmonary arteriovenous malformations. The necessity for hepatic vein redirection (HVR) and its timing remains a controversy. We aimed to assess the clinical outcome of patients with left atrial isomerism following a KP. The main end points were death, requirement for HVR and the impact of HVR on oxygen saturation.

METHODS: Retrospective review of 21 patients with a diagnosis of left atrial isomerism, interruption of the inferior vena cava and single-ventricle physiology managed with a KP at a single centre between January 1990 and March 2010.

RESULTS: Twenty-one patients had a KP, with 12 subsequently undergoing HVR. There was relatively a constant monthly decrement in the proportion of patients who were free from death or HVR up until 60 months following the KP, with a dramatic increase in the hazard after this time. The Cox proportional hazards regression model demonstrated a reduced early risk for HVR or death in patients who underwent pulmonary artery banding versus arterial shunt as the primary procedure (hazard ratio: 0.10; P = 0.01), and an increased risk with bilateral superior vena cavae (SVCs) (hazard ratio: 3.4; P = 0.04) and age at KP (hazard ratio: 1.02 per month increase in age at KP; P = 0.02). HVR mortality was relatively high with 3 of 12 patients dying in the early postoperative period with profound cyanosis. The timing of HVR after the KP did not influence the postoperative rate of increase in oxygen saturation.

CONCLUSION: These findings confirm that the majority of patients who undergo a KP will require HVR. Patients who are older at the time of the KP or having an initial arterial shunt or bilateral SVCs are at higher risk of HVR or death. The relatively high mortality at HVR was characterized by severe postoperative cyanosis.

Keywords: Isomerism • Kawashima • Hepatic vein redirection • Interrupted inferior vena cava • Pulmonary arteriovenous malformations

INTRODUCTION

Patients with a disturbance of laterality (heterotaxy syndromes and isomerism of the left or right atrial appendages) may present with a wide variety of cardiac malformations such as anomalies of all cardiac segments including venous connections, the atrioventricular junction and the outflow tracts [1, 2]. The complexity of the cardiac malformations often results in single-ventricle physiology managed by a staged surgical palliation. Interruption of the inferior vena cava (IVC) with azygous or hemiazygous continuation above the diaphragm is particularly characteristic of isomerism of the left atrial appendages or left atrial isomerism (LAI) [3].

LAI is a rare condition with an incidence of 1–4 in 100,000 live births [4, 5]. In patients with LAI and interruption of the IVC, the surgical creation of a superior cavopulmonary connection or a Kawashima procedure (KP) results in the diversion of all systemic venous return, except the hepatic venous return, to the pulmonary vascular bed [6]. The development of pulmonary arteriovenous malformations (PAVMs) in patients after establishing a superior cavopulmonary connection is a well-known complication. A particularly high incidence of PAVMs has been reported after the KP [7–9], which may be due to the absence of hepatic venous flow or lack of an unidentified ‘hepatic factor’ in the pulmonary circulation [7, 10, 11]. Whatever the mechanism may be, surgical redirection of the hepatic veins to the pulmonary vascular bed has been advocated to resolve PAVMs and to improve oxygen saturation [10–13].

There is a paucity of data on the incidence of oxygen desaturation due to PAVMs following the Kawashima operation and the optimal timing of hepatic vein redirection (HVR). It is controversial whether HVR should be undertaken only for patients who develop significant oxygen desaturation or whether this
should be regarded as a more ‘routine’ part of the single-ventricle palliation and undertaken by all patients.

We report on a group of patients with LAI, single-ventricle physiology and an interrupted IVC from a single institution over a period of 20 years. Our primary aims were to report on the clinical course of patients following a KP, particularly the requirement for HVR, and on the impact of HVR on oxygen saturation. In addition, we sought to determine which factors might predict the necessity for, or timing of, HVR. During the follow-up period, there was no institutional policy of ‘routine’ redirection of the hepatic veins following a Kawashima operation.

MATERIALS AND METHODS

Patients and methods

Patients with a diagnosis of LAI, interruption of the IVC and single-ventricle physiology managed with a KP between January 1990 and March 2010 were included. Data sources were: patient case records, operation notes and departmental computerized database (Heartsuite, Systeria Ltd, Glasgow, UK). Demographic data, cardiac morphology, type and date of surgical procedures and relevant clinical information such as oxygen saturation were recorded. Confirmation of the cardiac anatomy was based on the reports of cardiac ultrasound, magnetic resonance imaging (MRI), cardiac catheterization and surgical findings.

Patient management

All patients were managed at a single tertiary congenital heart disease centre and operated on by one of two surgeons (D.A. and C.A.). Following the KP, patients were regularly monitored for signs of desaturation by pulse oximetry. If there was evidence of decreasing oxygen saturation, saline contrast echocardiography was used as an initial test for PAVMs or veno-venous collateral vessels. If this study was positive, further investigation was undertaken with MRI and/or cardiac catheterization with a view to occluding veno-venous collateral vessels. If PAVMs were confirmed, then HVR was undertaken with the aim of improving oxygen saturation. Thus, HVR was used selectively to improve oxygen saturation; there was no policy of ‘routine’ redirection of the hepatic veins during the study period. All HVRs were performed as part of an intracardiac lateral tunnel total cavopulmonary connection.

Data analysis

Death or need for HVR was the primary outcome measure. Deaths were classified as ‘early’ if they occurred within 30 days of a surgical procedure and as ‘late’ if they occurred after 30 days. The impact of number of superior vena cavae (SVCs), pre-Kawashima pulmonary blood flow (shunt versus pulmonary artery banding) and the impact of age at Kawashima were analysed. The change in oxygen saturation following HVR and the impact of time since Kawashima on this response were measured.

Statistical analysis

Intergroup comparisons were carried out via Student’s t-test. Patient survival over time was demonstrated using Kaplan–Meier plots. Factors related to death and need for HVR were quantified via Cox’s proportional hazards regression. Changes in oxygen saturation after HVR were modelled via generalized estimating equations, using fractional polynomials to account for nonlinear trajectories. All analyses were performed with Stata v11 (StataCorp, College Station, TX, USA).

Ethical approval

The study was registered and approved by our institution. Patient or parental consent was not deemed necessary due to the retrospective, anonymized nature of the study.

RESULTS

Baseline demographics

In the study period, 24 patients were diagnosed with LAI and single-ventricle physiology. Their clinical course is summarized in Fig. 1. Twenty-one patients (11 males) were palliated with the KP at a median age of 14 months (range 1–156). The cardiac anatomy of these 21 patients is summarized in Table 1. Twelve patients had HVR at a median age of 93.5 months (range 11–143). The HVR was performed at a median time interval of 58.5 months (range 6–119) from the KP. Five patients had veno-venous collaterals identified prior to HVR. Of these, three patients had device occlusion of the larger collaterals performed prior to HVR. One patient underwent a late biventricular repair at the age of 10 and was therefore excluded from further analysis.
Mortality

Mortality data are summarized in Fig. 1. Among the 21 patients who underwent a KP, there was one early postoperative death and one late death prior to HVR. The early death occurred 2 days after KP due to arrhythmias and deterioration of cardiac function. The late death occurred 5 months after Kawashima due to arrhythmias.

Twelve patients proceeded to HVR. There were four deaths following HVR; three were early deaths. One patient died more than 10 years after HVR from a subarachnoid haemorrhage. The early deaths are described here. Patient A developed early desaturation due to proven PAVMs following Kawashima, with saturation of 70% in supplemental oxygen. Following HVR, the patient was unable to wean from cardiopulmonary bypass due to profound desaturation and died in the theatre. Patient B was on oxygen therapy with saturation of 60% prior to HVR. This patient died 10 days after HVR following postoperative renal failure, liver failure and cerebral oedema. Patient C developed multiple significant PAVMs and had saturation of 73% at the time of HVR. Postoperatively, the patient experienced severe hypoxia, metabolic acidosis and multiple cardiac arrests. The patient died 2 days after surgery from a multiorgan failure.

Risk factors for hepatic vein redirection

Fig. 2 shows the Kaplan-Meier plot for freedom from death or HVR following Kawashima, demonstrating a sharp increase in risk (hazard) after 60 months. Significant risk factors for death or need for HVR on multivariable analysis (Table 2) included: age at Kawashima (hazard ratio: 1.02 per month increase in age at Kawashima; \( P = 0.02 \)) and mechanism of pulmonary blood flow prior to Kawashima. The latter finding demonstrated a benefit when pulmonary blood flow was restricted by pulmonary artery banding, compared with augmentation by insertion of a Blalock-Taussig shunt (hazard ratio: 0.10; \( P = 0.01 \), Fig. 3). Arterial oxygenation after Kawashima did not influence death or need for HVR. There was an increased risk in the presence of bilateral SVCs (hazard ratio: 3.4; \( P = 0.04 \), Fig. 4).

The impact of hepatic vein redirection on oxygen saturation

The impact of HVR on oxygen saturation is shown in Fig. 5. The steepest trajectory of improvement of oxygen saturation is observed in the first 4 months after HVR, after which the trajectory plateaus. Time between Kawashima and HVR did not influence the trajectory for improvement in saturation (interaction \( P = 0.221 \)). However, those patients whose time between the KP and HVR was more than 5 years had a trend towards lower saturation at the time of HVR (mean: −6.8; \( P = 0.07 \)).

DISCUSSION

The results we report confirm the high incidence of PAVMs in patients with interruption of the IVC undergoing single-ventricle
The risk of HVR or death increases particularly beyond 60 months after the KP. This finding is consistent with that of Brown et al. [8], who concluded that, in most patients with heterotaxy and interrupted IVC with azygous continuation, clinical evidence of PAVMs will develop after KP if patients are followed up long enough. The increased risk seen with age may not be solely a function of age, but may be correlated with increased duration of low oxygen saturation. However, our study was not suitably designed to make this distinction.

In our population, there was an increase in the hazard ratio for death or requirement for HVR in patients who had bilateral SVCs versus those with a single SVC. This trend was also noted by Brown et al. [8] who reported that the presence of bilateral SVCs was an independent predictor of the development of PAVMs.

We observed a reduced risk for death or HVR in patients with pulsatile pulmonary artery flow before the KP. Pulsatile blood flow has a role in promoting growth of the pulmonary arteries. Although maintaining pulsatile antegrade pulmonary artery flow after KP has been advocated [14], there has been no previous observation of the effect of pre-Kawashima haemodynamics on PAVM development. It is likely that there is a multifactorial interaction in the development of PAVMs [15-17]. This includes liver-derived angiogenic modulators and other locally active modulators within the lung such as nitric oxide and vascular endothelial growth factors (VEGFs), which are also seen in the systemic circulation. Mori et al. [18] demonstrated the presence of aortopulmonary collaterals in association with elevated serum VEGFs. These levels remained elevated despite improvements in saturation after Fontan completion, suggesting a stimulus other than hypoxia such as shear stress. Shear stress from pulsatile flow is an important modulator of the nitric oxide pathway and may have an effect on PAVM development and explain the relationship of non-pulsatile blood flow and the development of PAVMs observed in this study.

Transforming growth factor (TGF)-β signalling also has an important role in the development of PAVMs when studied in patients with hereditary haemorrhagic telangiectasia [19]. The TGF-β family signalling is affected by mutations implicated in disorders of left–right determination in heterotaxy. This may also explain the added susceptibility of patients with LAI to develop PAVMs.

We adopt a policy of preferring to leave antegrade pulmonary blood flow in patients in whom there is a sufficient degree of pulmonary stenosis at the time of the KP.

**Timing of the Kawashima procedure**

The impact of the age at the KP on the development of PAVMs yields conflicting results. In our study, for every 1 month of age increase at the time of Kawashima, the hazard ratio for death or HVR increased by 0.02. This suggests that we should consider performing the KP at a younger age. Previous work concluded that the KP can be performed safely at a young age (5–15 months) with good results [20]. However, Kutty et al. [21] reported a non-significant trend towards a lower age at the KP for patients with proven PAVMs compared with those without PAVMs. Furthermore, Nath et al. [20] found their incidence of PAVMs after the KP to be similar to other reports where the KP...
was performed at a later age. Thus, at present, it is not possible to reach firm conclusions on the optimal timing of the KP to minimize future development of PAVMs.

Clinical management

Whatever the pathogenesis of PAVMs may be, many reports confirm institutional preference for an ‘expectant’ course for patients following the KP resulting in HVR being undertaken when a significant reduction in systemic arterial oxygen saturation has occurred [8, 9]. Previous work has shown that in children after superior cavopulmonary connection without clinical or angiographic evidence of PAVMs, the same histological changes—such as increased expression of VEGFs and its receptor [22] and increased micro-vessel density—are observed in the lungs of children with clinically apparent PAVMs [23]. This suggests an early angiogenic stimulus in the lungs after cavopulmonary anastomosis and might advocate for earlier scheduling of HVR.

Whether HVR should be scheduled relatively early even in the absence of significant desaturation has remained a controversy [8]. During the course of our study, there was no rigid policy in place regarding the timing of HVR. Overall, the decision to proceed to HVR was based on the clinical measurement of oxygen saturation where levels <80% or a downward trend would prompt investigation with a view to HVR. Of the patients who came to HVR (n = 12), three (25%) died early following the surgery. The HVR procedures during our study were performed between 2002 and 2009. In the same time period, 100 other Fontan operations were performed at our centre, with an overall survival of 100% at 30 days and 98% at 1 year after surgery. Thus, our current management strategy for patients with LAI is associated with a high operative mortality compared with Fontan completion for other indications. The early postoperative deaths following HVR were all characterized by severe systemic desaturation compared with Fontan completion for other indications. The early postoperative deaths following HVR were all characterized by severe systemic desaturation which worsened postoperatively. Inhaled nitric oxide and sildenafil have been reported to improve saturation in the early postoperative phase of patients with PAVMs [24], but were ineffective in our patients. It is likely, therefore, that the preoperative management strategy resulted in an unfavourable condition for surgery.

Other centres have also reported high mortality in patients with LAI undergoing HVR. In a 28-year series of 163 patients with LAI, Gilljam et al. [25] reported 5 deaths among 10 patients undergoing HVR. Brown et al. [8] performed HVR after diagnosis of PAVMs which were diagnosed in 58% of patients at risk at a median time interval of 5 years after the KP. They reported only one early postoperative death complicated by desaturation and low cardiac output out of 10 HVRs. McElhinney et al. [9] reported 1 death out of 16 HVRs. However, centres who have operated earlier have reported low operative mortality. Nath et al. [20] reported one early death due to severe ventricular and AV valve dysfunction out of eight HVRs performed at an interval of 2.7 years (range 1.8-5.8) after KP. Kuttty et al. [21] reported no early operative mortality following 13 HVRs done at a median time interval of 2.61 years (range 0.61–7.35). We would now consider performing HVR before 60 months after Kawashima as a maximum with a very careful monitoring of saturation with a low threshold for redirection in the presence of a downward trend.

Transplantation is always considered, but our approach has typically been trying to redirect hepatic veins first. This is compounded by the relative lack of availability for cardiac transplantation for this population. It is hoped that with earlier HVR and improved outcomes, this should be less of an issue.

The impact of hepatic vein redirection on oxygen saturation

Our results show an improvement in levels of hypoxaemia in those who survive HVR with a particularly steep and fast improvement of the oxygen saturation in the first 4 months. Patients who had a longer interval between KP and HVR had lower saturation prior to HVR but showed a similar trend in terms of improvement of saturation following HVR. McElhinney et al. [9] demonstrated resolution of hypoxaemia in 11 of 15 surviving patients, with oxygen saturation increasing to 93% or over at a follow up of 2.8-10 years. The immediate improvement in saturation will be related to the elimination of the right to left shunt at the hepatic-atrial level following HVR. However, the continued increase in saturation thereafter is a reflection of improvement or resolution of pulmonary AVMs. Our results demonstrate that there is always a potential for improvement of oxygen saturation following HVR regardless of the interval from the KP although the patients with an interval of >5 years between KP and HVR had a lower overall saturation level than those operated on earlier. McElhinney et al. identified four non-responders in their group. Brown et al. [8] reported an increased risk of developing PAVMs after 2 years after KP and advocated early HVR as a consequence.

Our study is retrospective and has the limitations of any study of that nature. However, all databases were comprehensively reviewed and cross-referenced to maximize data collection.

CONCLUSION

The incidence of PAVMs after KP is high. Our data demonstrate a marked increase in necessity for HVR particularly beyond 60 months after the KP. Although there is an improvement in oxygen saturation regardless of the interval from the KP to HVR, there is a high mortality rate after HVR related to profound desaturation which may reflect an unduly conservative approach. Following this analysis, our unit preference is more inclined towards elective early HVR after KP in patients with LAI.

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EDITORIAL COMMENT

Kawashima procedure: can pulmonary arteriovenous malformations be avoided?

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Patients with heterotaxy syndrome, interruption of the inferior vena cava with azygous continuation and single-ventricle physiology are commonly palliated with a bidirectional cavopulmonary anastomosis (Kawashima procedure) which, in this anatomical setting, results in a ‘near complete’ Fontan circulation. The paper by A. Vollebregt and collaborators reports the outcome of Kawashima procedure in 21 patients with left atrial isomerism and interruption of the inferior vena cava [1]. The