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Ross and Yasui operations for complex biventricular repair in infants with critical left ventricular outflow tract obstruction☆

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Abstract

Objective: To define the outcomes following Ross and Yasui procedures for complex biventricular repair of critical left ventricular outflow tract obstruction (LVOTO). **Methods:** Of 1217 neonates presenting with critical LVOTO enrolled in the Congenital Heart Surgeons Society studies (1994–2008), 52 underwent the Ross or Yasui procedure and their outcomes were investigated using univariate and multivariable parametric models. **Results:** ROSS ($N = 39$): The Ross procedure (median age 87 days) was rarely the primary intervention (5/39, 13%). A significant number of cases were performed to treat iatrogenic aortic regurgitation after other previous interventions (25/39, 64%). Co-existing functional morphological defects were also common: 72% had preoperative evidence of mitral dysfunction, moderate-to-severe left ventricular dysfunction or endocardial fibroelastosis. Emergency iatrogenic aortic regurgitation ($P = 0.005$) and co-existing abnormalities (mitral stenosis, $P = 0.02$; mitral regurgitation, $P = 0.05$; LV dysfunction, $P = 0.03$) were strong determinants of death. Severe postoperative ventricular dysfunction or need for extracorporeal membrane oxygenation (ECMO) conferred negligible survival. Younger age was associated with disproportionately worse late outcome (5-year survival $44 \pm 10\%$ for neonates vs $76 \pm 8\%$ for age >3 months, $P = 0.0013$). However, mitral and left ventricular dysfunction and emergency presentation were significantly more common in the younger age groups. Infants less than 3 months of age without co-existing abnormalities had acceptable late survival ($\approx 75 \pm 20\%$). YASUI ($N = 13$): Yasui repair (median age 22 days) was usually the primary intervention (nine of 13) but occasionally followed Norwood palliation (four of 13). None was an emergency. All had a ventricular septal defect. Survival was $69 \pm 13\%$ at 10 years, which is not significantly different from other biventricular repair strategies in neonates. Aortic atresia was associated with better survival than stenosis ($90 \pm 12\%$ vs $30 \pm 14\%$ at 3 years, $P = 0.039$). None reverted to univentricular physiology later. **Conclusions:** Case selection is key for complex biventricular repair and the importance of appropriate case selection is exaggerated at young ages. All available options should be considered before pursuing the Ross operation in the presence of co-existing functional morphological abnormalities or emergent iatrogenic aortic regurgitation. However, both the Ross and Yasui operations in children (including neonates and young infants) with favourable functional morphology offer good survival, at least matching that of other biventricular repair strategies.

Keywords: Ross operation; Yasui operation; Left ventricular outflow tract obstruction; Neonate

1. Introduction

The degree of left ventricular hypoplasia and co-existing functional morphology typically determines whether neonates with critical left ventricular outflow tract obstruction (LVOTO) are managed with univentricular palliation, biventricular repair or cardiac transplantation. Based on an intuitive perception of superior long-term functional status, a clinical bias exists towards favouring biventricular strategies in borderline cases [1]. Biventricular repair strategies predominantly include balloon aortic valvotomy, surgical valvuloplasty and, occasionally, allograft aortic valve replacement. More recently, complex repair strategies have emerged, which include the Ross and Yasui procedures [2–9].

The Ross procedure was originally described in young adults as an alterative to bioprosthetic, mechanical or allograft aortic valve replacement [10]. A pulmonary autograft is harvested and translocated to the aortic position, and the right ventricular outflow tract (RVOT) is

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then reconstructed using a valved conduit. Ross procedures have since been described in young children and even neonates with LVOTO [3,11]. In this scenario, an annular enlargement procedure is frequently necessary. The most common approach is to undertake an aortoventriculoplasty anteriorly to create an infundibular ventricular septal defect that is subsequently patched with the autograft (the Ross—Konno procedure) [3,6].

The Yasui operation was originally described as a strategy to repair neonates with aortic atresia with a ventricular septal defect [12] — a patient subset in whom left ventricular function and size is often adequate to support a systemic circulation. The left ventricular outflow tract is routed to the native pulmonary valve through an intra-cardiac baffle arising from the ventricular septal defect. The two great arteries are then associated through a Damus—Kaye—Stanzel anastamosis. Pulmonary blood flow is provided by a right ventricular—pulmonary artery valved conduit (the Rastelli operation).

Both Ross and Yasui procedures for children born with critical LVOTO are rare and outcomes with these strategies are therefore unclear. The Congenital Heart Surgeons' Society (CHSS) Data Centre has enrolled two large diagnostic inception cohorts of children who presented as neonates with critical LVOTO (including both aortic stenosis and atresia). We identified all children within these cohorts who underwent the Ross or Yasui operation at some point during their follow-up, and investigated their outcomes. The aims were to (1) define outcomes (survival and surgical re-intervention) and (2) identify patient-specific features that influence survival. Ultimately, our goal is to improve clinical decision making for neonates and infants with critical LVOTO.

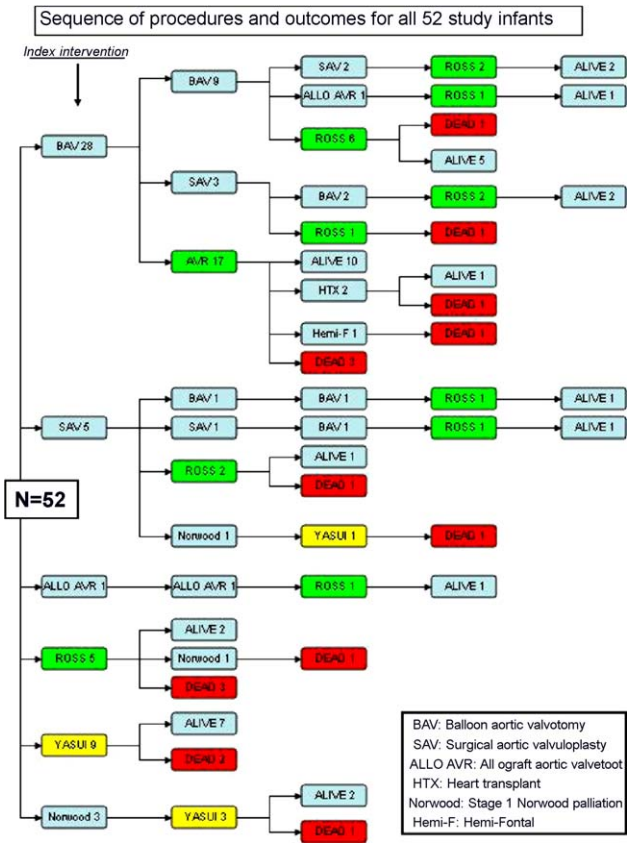

Fig. 1. Sequence and nature of interventions directed towards the left ventricular outflow tract stenosis in neonates born with critical LVOTO enrolled with the Congenital Heart Surgeons' Society 1994—2007 who ultimately received either Ross or Yasui operations at some point during follow-up (N = 52).

2. Methods

Two separate cohorts of neonates presenting with critical LVOTO have been enrolled with the Congenital Heart Surgeons' Society. The first cohort enrolled 990 neonates from 29 member institutions between 1994 and 2001. The second enrolled 227 neonates from 15 member institutions between 2005 and 2008. To the best of our knowledge, patients represent all neonates diagnosed with critical LVOTO at the participating institutions during the study periods. In this investigation, we explored outcomes in the 52 children who ultimately received either a Ross or Yasui operation (complex biventricular repair) at some point during their follow-up (Fig. 1). Ethics board approval and individual parental consent for follow-up was obtained. Patient data were accrued and managed as previously described [1]. The CHSS data centre staff contacted patients and their families annually.

Critical neonatal LVOTO was defined as stenosis occurring at any level from the sub-valvar region to the innominate artery with or without left ventricular hypoplasia, such that the systemic circulation was ductal dependent. Infants with aortic atresia were included as the most extreme form of LVOTO. A total of 1217 therefore met the inclusion criteria of critical LVOTO with atrioventricular and ventriculoarterial concordant connections, aortic arch continuity and admission within 30 days of birth (as a surrogate for the critical nature of the lesion).

Outcomes were characterised separately for the Ross and Yasui operations because the aim was not to compare one procedure against the other. A comparative analysis was not the intent because any one given child may not be a candidate for both procedures: children without a ventricular septal defect are unable to undergo a Yasui operation, and conversely, children with aortic atresia are unlikely to be considered candidates for a Ross operation. Separate parametric models for time-related outcome were generated using multi-phase hazard domain techniques [13]. For events other than death (i.e., re-intervention), competing risks methodology [14] was employed to account for patients who died and were therefore no longer at risk of the event occurring. Competing risks involves censoring patients when they reach mutually exclusive end states other than the one in question. Risk factors for outcomes were then identified by undertaking univariate or multivariable risk—hazard analyses using the parametric models.

Variables for risk—hazard analyses were abstracted from reports. Transformations to improve linear calibration of continuous variables were explored. Missing values were imputed with the mean for that variable. During risk—hazard analysis, variables with excessive (>75%) missing values were suppressed to avoid over-determination. Because of the small study population, both univariate and multivariable risk—hazard analyses were undertaken. Variable selection

was undertaken by automated forward stepwise regression with entry threshold $P \leq 0.1$, retention threshold $P < .05$. Final selection was then guided by bootstrap re-sampling ($N = 1000$); reliability was considered as inclusion of variables (or their clusters) in $\geq$50% of re-samples. All statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics included comparisons of unpaired proportions using Fisher's exact test and comparisons of unpaired means using Student's *t*-test. Threshold for significance was considered $P < 0.05$. Survival is presented as estimate $\pm$ standard error.

3. Results

3.1. Cohort characteristics

A total of 1217 neonates with critical LVOTO were enrolled into the Congenital Heart Surgeons' Society cohorts between 1994 and 2008. Of this total denominator, the Ross operation was undertaken in 39 (3%) and Yasui operation was undertaken in 13 (1%). Therefore, the complex biventricular repair approach was ultimately pursued in 4% of all enrollees with the CHSS Data Centre critical LVOTO studies.

3.1.1. Ross operation ($N = 39$)

3.1.1.1. Indications. The Ross operation was performed at median age 87 days (range 1 day to 11.4 years). Overall, at the time of surgery, 12 (33%) were neonates, 20 (51%) were age <3 months and 33 (85%) were age <3 years. All had a primary diagnosis of critical aortic stenosis, and three had co-existing ventricular septal defects.

The majority (34/39, 81%) had received prior interventions to the left ventricular outflow tract (secondary Ross operations), often multiple. The nature and sequence of prior interventions for these 34 infants is shown in Fig. 1, and included balloon aortic valvuloplasty, surgical valvuloplasty or previous allograft aortic valve replacement.

The five primary Ross operations were all undertaken specifically to address the critical LVOTO in the first week of life. By contrast, in the 34 children who underwent a secondary Ross operation, the clinical indication for surgery was iatrogenic aortic regurgitation in 10 (29%), residual aortic stenosis in nine (26%) and mixed stenosis and regurgitation in 15 (44%). Because none of the children had important aortic regurgitation at the time of initial diagnosis, 25 of the total 39 patients actually underwent the Ross operation to manage iatrogenic aortic regurgitation rather than the original problem of LVOTO. Amongst those with iatrogenic regurgitation, four were considered emergency or salvage interventions (all after balloon aortic valvotomy). Three of these four had experienced cardiac arrest within the 24 h preceding surgery.

Because all primary Ross operations were undertaken at age <30 days, lesions associated with young age (patent ductus arteriosus and patent foramen ovale) were significantly more common in the five children who underwent primary Ross operation (Table 1). In addition, indexed aortic annular dimensions were significantly smaller in primary Ross recipients versus those undergoing Ross as a secondary operation ($P = 0.004$). Functional morphology was otherwise similar between primary versus secondary Ross operations — including prevalence of mitral regurgitation or stenosis, ventricular function, tricuspid valve function and presence of endocardial fibroelastosis (Table 1).

Table 1
Functional morphology at the time of Ross operation in neonates with critical LVOTO ($N = 39$).

	Primary Ross ($N = 5$)		Secondary Ross ($N = 34$)		*P*
	N	% or range	*N*	% or range	
Clinical indication for Ross					
Aortic stenosis alone	5	100	9	26	0.16
Aortic regurgitation alone	0	0	10	29	<0.0001
Mixed stenosis/regurgitation	0	0	15	44	<0.0001
Emergency presentation	0	0	4	12	0.56
Morphology					
Aortic annular *Z*-score	−8.3	−10.6 to −6.1	−4.7	−5.6 to −3.8	0.004
Aortic valve morphology					0.17
Unicuspid	2	40	3	9	—
Bicuspid	1	20	18	53	—
Tricuspid	1	20	2	6	—
Mitral stenosis	0	0	2	6	0.58
Mitral regurgitation	3	60	12	35	0.36
Tricuspid regurgitation	1	20	3	9	0.48
Left ventricular dysfunction					0.28
None	3	60	25	74	—
Mild	1	20	3	9	—
Moderate	0	0	5	15	—
Severe	1	20	1	3	—
Patent foramen ovale	5	100	12	35	0.016
Patent ductus arteriosus	5	100	9	26	0.004
Endocardial fibroelastosis	2	40	15	44	0.39
Ventricular septal defect	2	40	1	3	0.024

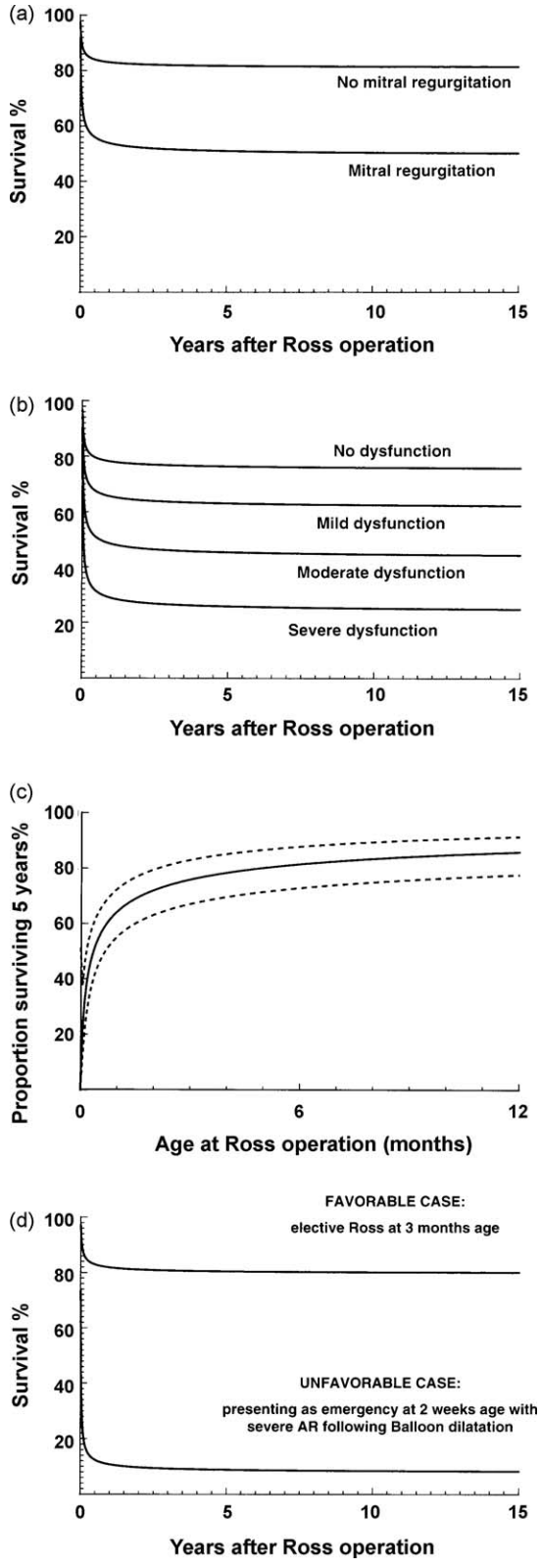

Fig. 2. Survival after Ross operation ($N = 39$). Survival was $74 \pm 7\%$, $67 \pm 8\%$ and $67 \pm 8\%$ at 1, 5 and 7 years, respectively. Survival plots have then been stratified by: (a) presence of important (at least moderate) regurgitation prior to Ross, or (b) grade of left ventricular dysfunction prior to Ross. Stratified plots were generated from univariate parametric models. (c) Nomogram demonstrating the relationship between age at the time of Ross operation and survival. The relationship was non-linear and young ages were associated with disproportionately worse survival at 5 years, especially for infants aged <3 months. Five-year survival was: $44 \pm 10\%$, $64 \pm 8\%$, $76 \pm 7\%$, $86 \pm 7\%$ and $93 \pm 7\%$ for children aged 7 days, 30 days, 90 days, 1 year and 5 years at the time of Ross operation, respectively. (d) Risk-adjusted survival after Ross operation, stratified according to either unfavourable risk-profile or favourable risk-profile. Plots were generated from multivariable parametric models. *Lines* represent parametric determinants of continuous point estimated. *Dashed lines* enclose 70% confidence intervals.

The prevalence of co-existing functional and morphologic cardiac abnormalities was high in children undergoing the Ross procedure (Table 1). Important mitral regurgitation was present in as many as 16 (41%), mitral stenosis in two and tricuspid regurgitation in four. One child underwent Ross operation in the presence of mild-to-moderate native pulmonary regurgitation (and did not survive). Left ventricular impairment was present in over a quarter ($N = 11$, 28%), at least moderate in seven (18%) and severe in three. In addition, endocardial fibroelastosis, a known risk factor for biventricular repair in critical LVOTO, was present in 16/39 (41%). In fact, as many as 28 of the 39 (72%) Ross recipients had preoperative evidence of (1) important (moderate or worse) mitral valvular dysfunction, (2) moderate or severe left ventricular dysfunction or (3) endocardial fibroelastosis.

In summary, Ross operation was rarely a primary management strategy for critical LVOTO. Instead, children had typically undergone prior interventions. In almost two-thirds, iatrogenic aortic regurgitation was present, which had precipitated cardiac arrest in four. Furthermore, important concomitant functional and morphological defects were common.

3.1.1.2. Operative details. Surgical details at the time of the Ross operation are shown in Table 2. The median cardiopulmonary bypass duration was approximately 3 h, ranging from as little as 80 min, up to in excess of 4.5 h. Neither cardiopulmonary bypass nor myocardial ischaemic durations were different for primary versus secondary Ross operations. The pulmonary autograft offered an age- and sex-matched neo-aortic valve with median *Z*-score of +1.2. Konno aortoventriculoplasty was performed in the majority ($N = 26$, 67%). Pulmonary allograft was the predominant conduit choice for the right ventricular outflow tract, although bovine jugular venous conduit (Contegra^{TM}) was used in four. Concomitant procedures were common: 18 (46%) undergoing at least arch reconstruction, coarctation repair, mitral valve repair or endocardial fibroelastosis resection.

3.1.1.3. Survival. Deaths occurred in 12 children (31%), including two on the operating table. A large early hazard for death was present after the Ross operation: >80% of all deaths occurred within 2 months. Estimated survival was $74 \pm 7\%$ and $67 \pm 8\%$ at 1 and 10 years, respectively.

Several morphological, clinical, and perioperative features were associated with poor survival (Table 3) in univariate analysis. Unfavourable morphological features included mitral valve disease, left ventricular impairment, patent ductus arteriosus and patent foramen ovale and longer cardiopulmonary bypass duration (Fig. 2). The pre- and postoperative clinical condition was an especially strong determinant of outcome. Emergency or salvage operation in the face of iatrogenic aortic regurgitation was associated

with <20% survival at 1 year. Similarly, the need for postoperative extracorporeal membrane oxygenation (ECMO) was associated with very poor prognosis (<5% late survival).

3.1.1.4. Ross operation in young age groups. Younger patient age at the time of the Ross operation was an important determinant of outcome. The relationship was non-linear, and infants aged <3 months exhibited disproportionately poor survival (Fig. 2c). Therefore, for all neonates ($N = 12$), actuarial survival was less than 50% beyond 1 year. By contrast, survival in infants aged >3 months was approximately 80%.

Because the neonatal Ross operation is an emerging management strategy for neonates with critical LVOTO, we explored the age variable further. Younger patient age – particularly <3 months – was associated with several other unfavourable features, including emergency presentation with iatrogenic regurgitation ($P = 0.04$), higher grade of left ventricular dysfunction ($P = 0.03$) and co-existing arch hypoplasia ($P = 0.01$) (Table 4). In addition, infants <3 months age had significantly longer cardiopulmonary bypass durations than of children age >3 months (214 vs 149 min, $P = 0.0002$). Therefore, young patient age may instead represent a surrogate for technical and morphological complexity rather than an independent risk.

Because young patient age may amplify the operative risks associated with other morphological features, possible important interactions were sought (Table 3). Particular at-risk patient subgroups appeared to be neonates with iatrogenic aortic regurgitation, infants <3 months age with associated functional/morphological abnormalities and infants <3 months age requiring concomitant procedures at the time of the Ross operation. For example, infants <3 months age with co-existing defects exhibited 39 ± 13% 5-year survival versus 75 ± 22% for those without co-existing defects.

In summary, therefore, it is the constellation of features for a given patient that will instead determine survival, rather than young patient age *per se* (Fig. 2d). Several features were notably unassociated with worse survival. These included the Ross operation as the index procedure versus non-index procedure, the need for annular enlargement and older versus more recent era.

Table 2
Operative features at the time of Ross operation in children with critical LVOTO ($N = 39$).

Variable	N	% or range
Age at operation (days)	87	1 day to 11.3 years
Weight (kg)	4.5	2.5–40
CPB duration (min)	180	81–288
Myocardial ischemia duration (min)	124	62–108
Circulatory arrest	7	18
Konno annular enlargement	26	67
Arch/coarctation repair	9	23
Endocardial fibroelastosis resection	8	21
Mitral valve repair	6	15
Postoperative extracorporeal membrane oxygenation	4 (3 died)	10
Death	12	31
Death in operating room	2	5
Re-operation	10	26

Table 3
Patient-specific features associated with increased risk of time-related death ($N = 39$, 12 deaths).

Feature	Parameter estimate	P value
A. Univariate analysis		
Preoperative risk factors for death		
Mitral stenosis	+1.76	0.02
Mitral regurgitation	+1.20	0.05
Higher grade of left ventricular dysfunction	+0.54	0.03
Patent ductus arteriosus	+2.17	0.003
Patent foramen ovale	+2.14	0.01
Ventricular septal defect	+1.63	0.03
Emergency presentation	+1.85	0.005
Intra-operative risk factors for death		
Younger operative age[a]	−0.43	0.001
Smaller operative weight[b]	+19.0	0.0009
Aortic arch augmentation/reconstruction	+1.38	0.008
Longer cardiopulmonary bypass duration[c]	+0.0004	0.002
Longer myocardial ischaemic duration[c]	+0.0005	0.05
PFO left open as 'pop valve'	+1.16	0.05
Postoperative risk factors for death		
Higher grade of postoperative left ventricular dysfunction	+0.94	<0.0001
Postoperative extracorporeal membrane oxygenation	+2.73	<0.0001
B. Multivariable analysis		
Emergency presentation with iatrogenic aortic regurgitation	+1.60	0.01
Younger operative age[a]	−0.43	0.002
C. Interactions		
Neonatal age[a] iatrogenic regurgitation	+1.48	0.01
Neonatal age[a] co-existing morphologic defects	+1.60	0.005
Neonatal age[a] concomitant surgical procedures	+1.21	0.04
Age <3 months[a] co-existing morphologic defects	+1.80	0.007
Age <3 months[a] concomitant surgical procedures	+1.50	0.01

The intercept for the multivariable model in B is 0.49. PFO, patent foramen ovale.
[a] Entered as logarithmic transformation to improve linear calibration.
[b] Entered as the inverse-squared transformation to improve linear calibration.

3.1.2. Yasui operation ($N = 13$)

3.1.2.1. Indications. The Yasui operation was performed at median age 22 days (range 3 days to 1.5 years). At the time of surgery, eight (62%) were neonates, and four of the remaining five were under 1 year of age. The primary diagnosis was aortic atresia in eight (62%) and critical aortic stenosis in five (38%). All had ventricular septal defects.

For most ($N = 9$; 69%) children, Yasui operation was the index intervention to the left ventricular outflow tract. In the remaining four, the Yasui operation was undertaken following prior univentricular palliation through the Norwood operation (Fig. 1). All Yasui operations were elective procedures, with no emergency presentations.

Although arch hypoplasia and/or aortic coarctation were common ($N = 8$, 62%), other co-existing valvar or functional abnormalities were infrequent (Table 5). None had preoperative evidence of endocardial fibroelastosis. In summary, therefore, Yasui operation was typically a planned, elective, primary biventricular management strategy for young infants

Table 4
Differences in pre- and perioperative features between Ross recipients <3 months age and recipients >3 months age.

	Age <3 months (*N* = 20)		Age >3 months (*N* = 19)		*P*
	N	% or range	*N*	% or range	
Preoperative features					
Mitral regurgitation	13	65	3	16	0.002
Patent ductus arteriosus	14	70	1	5	<0.0001
Patent foramen ovale	15	75	3	16	0.0002
Impaired left ventricular function	10	50	1	5	0.018
Emergency presentation	4	20	0	0	0.04
Operative features					
Cardiopulmonary bypass duration (min)	191	82–288	158	81–212	0.0002
Circulatory arrest	6	30	1	5	0.04
Konno modification	17	85	9	47	0.01
Arch reconstruction	6	30	1	5	0.04
PFO left open as 'pop valve'	9	45	0	0	0.0009
Postoperative extracorporeal membrane oxygenation	4	20	0	0	0.03

PFO, patent foramen ovale.

and neonates without associated morphological and functional abnormalities.

3.1.2.2. Operative details. Operative details at the time of the Yasui operation are shown in Table 5. The median cardiopulmonary bypass duration was 2 h 40 min, but ranged from as little as 80 min, up to almost 4 h. No child underwent ventricular septal defect enlargement. One child had a residual septal defect postoperatively that did not require re-operation.

3.1.2.3. Survival. Deaths occurred in four children (30%). Survival was $77 \pm 12\%$ and $69 \pm 13\%$ at 1 and 10 years, respectively, the hazard being principally early. Using univariate analysis, the only patient-specific feature associated with poor survival was the patency of the aortic valve. Aortic atresia was associated with significantly better survival versus critical aortic stenosis (parameter estimate +2.4, $P = 0.04$). However, the statistical reliability of this finding is uncertain in this small cohort size. Survival was independent of patient age and whether the operation was primary or otherwise followed previous Norwood palliation.

Table 5
Patient-specific features of children who underwent Yasui operation for critical LVOTO (*N* = 13).

Feature	*N*	% or range
Aortic atresia	8	62
Aortic stenosis	5	38
Mitral stenosis	0	0
Mitral regurgitation	0	0
Aortic arch stenosis/coarctation	8	62
Atrial septal defect	8	62
Ventricular septal defect	13	100
Endocardial fibroelastosis	0	0
Left ventricular dysfunction (> moderate)	6	46
Patent ductus arteriosus	3	23
Emergency presentation	0	0
Age at operation (days)	22	3 days to 1.5 years
Weight at operation (kg 0)	3.3	2.8 days to 11.5 years
Cardiopulmonary bypass duration	139	82–217
Myocardial ischemic duration	83	43–134
Circulatory arrest	10	77
Pulmonary allograft to RVOT	5	38
Aortic allograft to RVOT	3	23
Residual ventricular septal defect	1	8
Postoperative extracorporeal membrane oxygenation	2	15
Died	4	31
Died in operating room	0	0
Re-operation	8	62

3.2. Re-operation

Because the Ross and Yasui operations both involve reconstruction of the right ventricular outflow tract, re-operations are anticipated. The time-related risk of re-operation was not different following either the Ross or Yasui procedure: 50% of survivors remained free from re-operation after 7 years, and almost a third after 10 years (Fig. 3). All

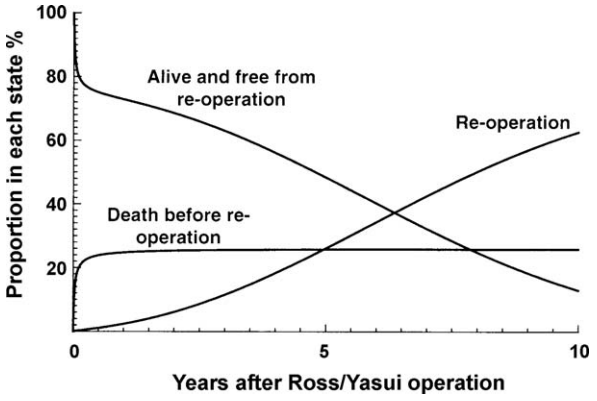

Fig. 3. Freedom from surgical re-intervention in children who underwent either Ross or Yasui operation (*N* = 52). The competing risks model demonstrates the time-related risk of patients assuming any of the mutually exclusive endstates after Ross operation of either: re-operation, death without re-operation. Children not in either of these endstates must therefore remain alive without re-intervention. Five years after Ross operation, $48 \pm 8\%$ remained alive and free from re-intervention, $26 \pm 5\%$ had died without re-intervention and $26 \pm \%$ had undergone re-intervention. By 7 years after Ross operation, more than half the survivors had undergone re-intervention. *Lines* represent parametric determinants of continuous point estimates.

nine re-operations in the Yasui recipients were for right ventricular–pulmonary artery conduit change. By contrast, re-operation following the Ross procedure ($N = 10$) was highly variable and included right ventricular–pulmonary artery conduit change ($N = 5$), neo-aortic valve replacement ($N = 1$), cardiac transplantation ($N = 2$) and reversion to single ventricle strategy ($N = 2$). Of all re-operations in Ross recipients, 40% indicated a failure of the complex biventricular repair strategy. Features associated with increased time-related risk of re-operation for both cohorts, included higher grade of tricuspid regurgitation at the time of diagnosis ($P = 0.0002$), higher grade of aortic stenosis at the time of diagnosis ($P = 0.047$) and smaller indexed dimension of the pulmonary autograft ($P = 0.047$).

4. Discussion

Complex biventricular repair can provide a good and definitive solution in children born with critical LVOTO. However, our investigation reveals that Ross operation undertaken in young children in the presence of unfavourable functional morphology is associated with poor survival. Survival is particularly poor for neonates and infants aged <3 months. These young patients commonly exhibit unfavourable co-existing features – including iatrogenic aortic regurgitation related to previous failed interventions. However, in children (including neonates and young infants) with favourable functional morphology, both Ross and Yasui procedures offer good survival comparable with other biventricular repair strategies [1,15]. Therefore, case selection is key for complex biventricular repair and its influence on outcome appears to be amplified at young ages.

In young infants with favourable morphology and older children, medium-term survival is good with the Ross operation ($\geq$70–85% at 5 years) [16,17]. In addition, selected centres have reported excellent results in the neonatal population [6,8]. We have reported 5- and 10-year survival with biventricular repair to be in the region of 70% for all neonates born with critical LVOTO [1]. Therefore, in summary, the Ross operation remains a useful strategy in infants with critical aortic stenosis. However, if case selection were to be improved, our data indicate that late survival for these complex repairs might exceed 80–90%.

In this series, children undergoing Ross operation were a heterogeneous group who frequently exhibited co-existing functional abnormalities. Mitral dysfunction – particularly important regurgitation – was especially common, in addition to left ventricular impairment and endocardial fibroelastosis. The latter features have both been previously identified as strong determinants of poor outcome following other biventricular repair strategies [1,18]. Therefore, the presence of these features should prompt caution before pursuing the Ross operation (and also other biventricular strategies). The association between cardiopulmonary bypass exposure and survival suggests that particular attention should be paid to co-existing lesions that are likely to increase technical complexity or necessitate concomitant procedures.

Ross operation in the first few months of life has emerged as a technically demanding primary management option for aortic stenosis [8]. Therefore, we were particularly interested in outcomes in this age group. Our data indicate that young patient age does appear to be an independent risk factor – as with many congenital operations (particularly biventricular repair [19]). However, in our series, the younger patients were also those with the highest prevalence of other high-risk features. For young infants with otherwise normal functional anatomy, late survival was approximately 75%, suggesting that the neonatal and infant Ross procedure is an appropriate strategy in these favourable subsets.

Interestingly, the majority of children in this series underwent the Ross operation in face of moderate-to-severe iatrogenic aortic regurgitation after previous interventions. Of concern is that four of our cohort were emergencies and three had sustained a cardiac arrest in the preceding 24 h. Others have reported a similar high prevalence of iatrogenic aortic regurgitation in recipients of infant Ross operations and correspondingly high mortality in these children [20,21]. Our data question whether it is ever appropriate to pursue the Ross operation in the presence of emergency severe aortic regurgitation following balloon valvotomy, although we acknowledge few attractive alternative options exist. Donor organs for transplantation are unlikely to be available at short notice. A period of mechanical (ECMO) and/or inotropic support may result in brief improvement, but such improvements are unlikely to be sustained. One possible alternative may be allograft aortic valve replacement. Allografts in the aortic position are thought not to fare well in very young infants, and may be technically challenging to implant. However, in light of our experience, a difficult allograft aortic valve replacement with short durability may be a more appealing alternative to the Ross operation. Finally, anecdotal experience using a hybrid approach has been successfully employed as a bail-out option in this scenario. However this requires at least probe-patency of the ductus arteriosus [22]. The difficult conundrum of emergency iatrogenic aortic regurgitation also serves to emphasise the importance of initial decision management in neonates with critical LVOTO [1,19]. Pre-emptive identification of neonates at risk of early re-intervention after embarking on biventricular strategies will help prevent encountering this difficult scenario [1].

In contrast to children undergoing Ross operations, recipients of Yasui repairs appeared a more homogeneous clinical entity. Although of young age, most were scheduled for primary, elective repairs. These features are likely to account for both the favourable outcomes that we and others [9,23] report and the lack of important risk factors identified in this small experience. Aortic stenosis as a risk for poor survival is intriguing. We can offer no plausible explanation, and in such a small cohort, its reliability is questionable.

Surgical re-interventions in both the Ross and Yasui recipients are anticipated for stenosis of the RVOT conduit. However, the heterogeneity within our Ross cohort both in terms of substrate and outcome is again illustrated by the fact that half of all re-operations after Ross were for reasons unrelated to the RVOT conduit. Complete failure of the complex biventricular approach transpired in 40% of Ross recipients as evidenced by cardiac transplantation or reversion to univentricular physiology. This latter point serves to highlight the importance of decision tools that we

previously reported to aid the univentricular/biventricular conundrum at the time of presentation in borderline candidates [1].

Our use of the Congenital Heart Surgeons Society cohorts has allowed us to demonstrate that complex biventricular repair strategies are only rarely pursued in neonates with critical LVOTO (≈4%). A merit of such multi-institutional cohorts is that we can investigate lesions and operations that any one surgeon may only very occasionally encounter. Nevertheless, several limitations inherent to our analysis should be acknowledged. First, although this is the largest series of its kind, our study cohort remains small. Statistical power and reliability are therefore compromised, and we necessarily include univariate analyses rather than the more powerful risk-adjusted multivariable models. Second, there may be important institutional differences. Although individual institutions were explored as risk factors, numbers from some institutions were small. Finally, the most important limitation relates to its retrospective nature. The data pertain to past experiences — both good and bad — with these operations. Bad experiences in high-risk children should not tarnish otherwise favourable experiences in suitable candidates, but instead guide future decision management and improve results through better-informed case selection.

In summary, both the Ross and Yasui biventricular repair strategies for children with critical LVOTO are associated with good survival in favourable circumstances. Patients selected for the Ross operation are clinically heterogeneous, frequently affected by a broad range of co-existing functional morphological abnormalities. Iatrogenic problems from previous failed interventional strategies are common. The presence of mitral valvular regurgitation, left ventricular dysfunction, iatrogenic aortic insufficiency and emergency presentation are particularly associated with poor outcome and should therefore prompt re-evaluation of management options. Although young infants and neonates are higher risk, survival is likely to be acceptable in the presence of good functional morphology and where absence of co-existing defects permits expeditious repair. Therefore, case selection is key for complex biventricular repair and its influence on outcome appears to be amplified at young ages.

References

[1] Hickey EJ, Caldarone CA, Blackstone EH, Lofland GK, Yeh Jr T, Pizarro C, Tchervenkov CI, Pigula F, Overman DM, Jacobs ML, McCrindle BW. Critical left ventricular outflow tract obstruction: the disproportionate impact of biventricular repair in borderline cases. J Thorac Cardiovasc Surg 2007;134:1429—36 [Discussion 1436—1427].
[2] Daenen W, Gewillig M. Extended aortic root replacement with pulmonary autografts. Eur J Cardiothorac Surg 1993;7:42—6.
[3] Reddy VM, Rajasinghe HA, Teitel DF, Haas GS, Hanley FL. Aortoventriculoplasty with the pulmonary autograft: the "Ross—Konno" procedure. J Thorac Cardiovasc Surg 1996;111:158—65 [Discussion 165-157].
[4] Williams IA, Quaegebeur JM, Hsu DT, Gersony WM, Bourlon F, Mosca RS, Gersony DR, Solowiejczyk DE. Ross procedure in infants and toddlers followed into childhood. Circulation 2005;112:I390—5.
[5] Vida VL, Bottio T, Milanesi O, Reffo E, Biffanti R, Bonato R, Stellin G. Critical aortic stenosis in early infancy: surgical treatment for residual lesions after balloon dilation. Ann Thorac Surg 2005;79:47—51 [Discussion 51—42].
[6] Lacour-Gayet F, Sauer H, Ntalakoura K, Muller A, Razek V, Weil J, Haun C. Ross—Konno procedure in neonates: report of three patients. Ann Thorac Surg 2004;77:2223—5.
[7] Erez E, Tam VK, Kanter KR, Fyfe DA. Successful biventricular repair after initial Norwood operation for interrupted aortic arch with severe left ventricular outflow tract obstruction. Ann Thorac Surg 2001;71:1974—7.
[8] Ohye RG, Gomez CA, Ohye BJ, Goldberg CS, Bove EL. The Ross/Konno procedure in neonates and infants: intermediate-term survival and autograft function. Ann Thorac Surg 2001;72:823—30.
[9] Nathan M, Rimmer D, del Nido PJ, Mayer JE, Bacha EA, Shin A, Regan W, Gonzalez R, Pigula F. Aortic atresia or severe left ventricular outflow tract obstruction with ventricular septal defect: results of primary biventricular repair in neonates. Ann Thorac Surg 2006;82:2227—32.
[10] Ross DN. Replacement of aortic and mitral valves with a pulmonary autograft. Lancet 1967;2:956—8.
[11] Calhoon JH, Bolton JW. Ross/Konno procedure for critical aortic stenosis in infancy. Ann Thorac Surg 1995;60:S597—9.
[12] Yasui H, Kado H, Nakano E, Yonenaga K, Mitani A, Tomita Y, Iwao H, Yoshii K, Mizoguchi Y, Sunagawa H. Primary repair of interrupted aortic arch and severe aortic stenosis in neonates. J Thorac Cardiovasc Surg 1987;93:539—45.
[13] Blackstone EH, Naftel DC, Turner MEJ. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. J Am Stat Assoc 1986;81:615—24.
[14] Hickey EJ, McCrindle BW, Blackstone EH, Yeh Jr T, Pigula F, Clarke D, Tchervenkov CI, Hawkins J. Jugular venous valved conduit (Contegra) matches allograft performance in infant truncus arteriosus repair. Eur J Cardiothorac Surg 2008;33:890—8.
[15] McCrindle BW, Blackstone EH, Williams WG, Sittiwangkul R, Spray TL, Azakie A, Jonas RA. Are outcomes of surgical versus transcatheter balloon valvotomy equivalent in neonatal critical aortic stenosis? Circulation 2001;104:I152—8.
[16] Brown JW, Ruzmetov M, Vijay P, Rodefeld MD, Turrentine MW. The Ross—Konno procedure in children: outcomes, autograft and allograft function, and reoperations. Ann Thorac Surg 2006;82:1301—6.
[17] Hazekamp MG, Grotenhuis HB, Schoof PH, Rijlaarsdam ME, Ottenkamp J, Dion RA. Results of the Ross operation in a pediatric population. Eur J Cardiothorac Surg 2005;27:975—9.
[18] Colan SD, McElhinney DB, Crawford EC, Keane JF, Lock JE. Validation and re-evaluation of a discriminant model predicting anatomic suitability for biventricular repair in neonates with aortic stenosis. J Am Coll Cardiol 2006;47:1858—65.
[19] Lofland GK, McCrindle BW, Williams WG, Blackstone EH, Tchervenkov CI, Sittiwangkul R, Jonas RA. Critical aortic stenosis in the neonate: a multi-institutional study of management, outcomes, and risk factors. Congenital Heart Surgeons Society. J Thorac Cardiovasc Surg 2001;121:10—27.
[20] Pessotto R, Wells WJ, Baker CJ, Luna C, Starnes VA. Midterm results of the Ross procedure. Ann Thorac Surg 2001;71:S336—9.
[21] Kadner A, Raisky O, Degandt A, Tamisier D, Bonnet D, Sidi D, Vouhe PR. The Ross procedure in infants and young children. Ann Thorac Surg 2008;85:803—8.
[22] Pizarro C, Bhat MA, Derby CD, Radtke WA. Bailout after failed biventricular management of critical aortic stenosis: another application of the hybrid approach. Ann Thorac Surg 2009;87:e40—2.
[23] Pearl JM, Cripe LW. Manning PB Biventricular repair after Norwood palliation. Ann Thorac Surg 2003;75:132—6 [Discussion 136—137].

Appendix A. Conference discussion

Dr M. Hazekamp (*Leiden, The Netherlands*): It is important for pediatric cardiac surgeons to know that these things, however rare, occur and what the best way to treat them is.

But what you already stated yourself, it is clear there are two different groups in this study, one is the group where you go directly for a Norwood—Rastelli pathway or a Rastelli—Yasui operation because the aortic valve is either atretic or so small and there is a VSD, that there is no other option. And the second group consists of neonates where there is no VSD in the majority of cases and you try first try to spare the aortic valve, ballooning it or do a surgical valvotomy. And so it's different, two different groups that you describe, I think.

There is, of course, some overlap, gray zone, border zone, where you go either for a Ross—Konno operation or for Yasui operation. And I have several questions.

The first question would be what would be for you the *Z* score of the aortic valve to go directly for a Yasui-like operation or do it in one stage or in two stages? Would it be minus 4, minus 6, minus 8? There has been some data

reported in the literature, but did you find anything out of your study concerning that topic? That's the first question.

And the second question is, looking in retrospect to your Ross–Konno operation with the not very favourable results, especially in the neonatal group, was influenced by emergency procedures after failed balloon dilatation for aortic valve, but also by mitral valve problems, endocardial fibroelastosis and things like that. And we feel that in cases where the left ventricle, the mitral valve, are not perfectly complete or good, 100% good, sometimes it would be better to go directly for a monoventricular pathway. So looking in retrospect, would you also say that of some of your Ross–Konno patients?

Dr Hickey: You're absolutely right, this cohort represents two very different groups of patients and that became clear when we examined them. A VSD is obviously obligatory for undertaking a Yasui repair and yet not necessary for a Ross operation. And in converse, a Ross operation is not in practice undertaken on a patient without a patent aortic valve. Nevertheless, they are both grouped together as complex by ventricular approaches, which is why we investigated them in our study, but did not compare them head-to-head in any sort of statistical way.

You're right that there is a group, though, of patients who do sit in a gray zone who may be candidates for either a Ross or a Yasui operation: a patient with aortic stenosis and a VSD. In practice, our data is suggesting that if you're going to pursue a Ross operation in that scenario, then really the patient should be an ideal candidate without any degree of LV dysfunction, without any degree of mitral valve problems or arch problems, i.e., an absolutely favourable candidate. Because, if you get the decision wrong and you can't come off bypass or you end up in the first few days postoperatively in trouble, then that is a big problem to take down and revert to a single ventricle strategy.

In that scenario then, a Yasui, in that gray zone, may be a safer bet, because if you run into problems immediately afterwards, you can take down the Rastelli component and take out your baffle patch and easily revert to a single ventricle strategy. We did not have any experience though with patients who fell in that group and reverted from a Yasui back to a Norwood strategy.

As far as the aortic valve *Z* score is concerned for pursuing a Yasui operation, well, Yasui could be undertaken in either aortic atretics or stenotics. We didn't examine a *Z* score as a determinant of whether a primary Yasui should be undertaken or a secondary Yasui (after previous Norwood), so I don't have that information I'm afraid.

In terms of Ross–Konno operations, in the emergency scenario, yes, it was clear from our data that co-existing problems, particularly mitral valve and the left ventricular dysfunction, were strong determinants of bad outcome and emergency re-operations.

What are your other options in that scenario? Well, particularly for the neonate presenting as an emergency with aortic regurgitation after a balloon valvotomy, your options really are very limited, because cardiac transplantation is not likely to be an option given the fact you're not likely to find a donor at such short notice.

One option is an allograft aortic valve replacement, although allografts do not fare very well in neonates. But our data may suggest that actually an allograft AVR, although technically challenging, and with limited durability, may in fact be a better option than planning a technically complex Ross operation in a sick neonate, which is associated with very bad outcome.

Dr Hazekamp: I think it's more dependent on the state of the left ventricle and the mitral valve than on the LVOT. I mean, if there is endocardial fibroelastosis, if there are mitral valve problems, the *Z* score of the mitral valve is, let's say, minus 3, minus 4, we have seen in the past that when we actively pursue the Ross–Konno procedure that we now have several patients, years later, who ended up with a bad left ventricle diastolic dysfunction, pulmonary hypertension, and no option whatsoever, not even heart transplantation. So I think selection in that group should be very, very selective and very careful.

Dr Hickey: One of the merits of looking at our multi-institutional cohort with the CHSS is that we are looking at the entire denominator, or as close to the denominator as we can get, of all practice across several units. And this study is one of our final studies in a series of investigations looking at decision management in these infants. And I think it serves to emphasise that some of these patients that we're talking about we suspect have ended up down the wrong decision management paradigm way beyond the neonatal period. Our the series of investigations have emphasized repeatedly that it is the initial decision management in the first few days of life that is the key to optimising outcome. For example, 'trial' balloon valvotomies in the first few days of life is probably not the answer, because then you're at much higher risk of ending up in the scenario where you have a very sick child with torrential aortic regurgitation, with questionable LV function and some EFE, and to rescue a biventricular repair in that scenario is probably very, very challenging.***Dr Hazekamp***: I absolutely agree with you and that's the reason this series is so important.

Dr F. Lacour-Gayet (*Denver, Colorado, USA*): I have two comments and a question. It looks that the end point of your study is more or less to compare the Yasui operation to the Ross–Konno operation early in life, actually the Yasui are neonate and the Ross are not all neonate, only 12 out of 39.

I think that these indications are mutually exclusive in a way that you cannot compare these two operations. You can do a Ross for indication of Yasui, like an interrupted aortic arch with hypoplasia of the aortic annulus, but you cannot do a Yasui in a situation when there is no VSD or when there is an aortic regurgitation. So comparing the two techniques is comparing oranges and apples. It doesn't have sense to me. This is my first comment.

My second comment is that a lot of people are making the point that why do you do neonatal Ross in this patient? And a lot of people will tell you that it's not justified in regards if your results are not very good. So of course, they've not very good, but what else to do?

And we're facing some time terrible regurgitation following balloon valvuloplasty and this is the only way to save this patient. So I think that the fact that the mortality is high in this group of patients, bears, as you said, not very much other solution.

My question regards more the re-operation for the Yasui operation. We got information in Warsaw that it is a great number, a very high number, of restriction of the VSD flow in the Yasui operation and even some surgeons recommend today to enlarge the VSD at the time of the Yasui. Have you seen restriction of the VSD after the Yasui operation?

Dr Hickey: In fact, we haven't seen restriction of the Yasui baffle; none of the re-operations have been related to the baffle patch interestingly. In addition, none of the 13 Yasui patients required VSD enlargements at the time of their Yasui, which was a surprise to us. However, we acknowledge that VSD enlargement may be required in Yasui operations for other primary diagnoses.

In response to your other two points, I stress again that our intention was never to compare Yasui versus Ross. Some have suggested the Yasui is a sort of intra-cardiac Ross. It may be from a physiologic point of view, but it's not, it's totally different, and we did not want to compare head-to-head.

And finally, yes, I refer to my previous comments about emergency Ross in the presence of torrential AR. Yes, few other options are available. Again, I stress that our overall goal with our series of investigations into critical LVOTO is to try and improve the initial decision management and try and minimise the times that you end up in a scenario between a rock and a hard place with a young neonate with torrential aortic regurgitation.

Mr W. Brawn (*Birmingham, United Kingdom*): We have seen VSD stenosis or outflow tract stenosis after the Yasui operation, and it was very critical down to a few millimetres. So we have had concerns about that. More or less routinely we do enlarge the VSD and particularly where the VSD is not in a favourable position extending to the outflow tract beneath the pulmonary valve.

The second thing I'd like to comment on, and ask you to comment on, is that the degree of pulmonary hypertension in those patients who undergo biventricular palliation, seems to be very high and postpones a problem for them. Heart and lung transplant isn't a good option. And we've gone down the line in some of these, in a very few numbers, we've set up a double switch to reconvert the RV to the systemic circulation, which seems slightly mad, but the main purpose is to hopefully reduce the pulmonary hypertension so they are suitable for a heart transplant later on. It seems to be a viable option, but obviously is not a curative procedure.

Dr V. Hraska (*Sankt Augustin, Germany*): It was a very nice presentation confirming basically the conclusions from yesterday's postgraduate course that balloon angioplasty for critical aortic stenosis could be really dangerous. Surgeons are put to the very awkward position to deal with ruptured valves. Ross–Konno operation during newborn period, especially under these circumstances, is risky. So the solution is simply to take over the decision-making process in regards to critical aortic stenosis and to do it surgically. That's what I strongly believe, and I tried to deliver this message during yesterday's postgraduate course.

My question refers to the risk factor of Ross–Konno. Age less than 3 months was identified as a risk predictor. Is that right?

Dr Hickey: Yes.

Dr Hraska: Another point is the mitral valve problem. Patient born with the left ventricular outflow tract obstruction, not having a problem with the mitral valve, with time is getting a problem with the mitral valve because of progression of endocardial fibroelastosis. The right timing of operation

probably plays a crucial role. One has to be very careful in regards to development of endocardial fibroelastosis, which might be pretty quick after birth. Despite of successful Ross—Konno and resection of endocardial fibroelastosis, mitral valve regurgitation can become dominant afterwards.

Dr Hickey: I'll just be very brief.

The final example you are giving of a child who develops mitral valve regurgitation over time with EFE represents a slightly less severe scenario with LVOTO. All our neonates were critical and presenting in the first 30 days of life. But you've drawn attention to endocardial fibroelastosis, which amongst other risk factors, particularly LV dysfunction, has emerged time and time again in CHSS cohorts as a very strong determinant of bad outcome following attempted two ventricle repair. And yes, the decision management is way, at the moment, in favour biasing biventricular repair in borderline candidates typically through balloon valvotomy in the first few days of life. And yes, our data are repeatedly telling us that that is a risky procedure. Therefore, there are certain subgroups — particularly those with even mild EFE — who, with time, do badly and should probably be offered alternative strategies in the first few days of life.