Balloon Angioplasty for the Distal Anastomotic Stenosis

Ino et al. suggested the main mechanism of balloon dilatation for a stenotic PA was due to non-stretch mechanisms such as tearing, flap formation, or dissection [16]. The same mechanism may apply if a RV-PA shunt is anastomosed to the native PA without patch augmentation on the central branch PA. In our series, a large ePTFE cuff was pre-anastomosed to the RV-PA shunt. Therefore, there is a large area of ePTFE at the distal anastomosis, which may have made BA more amenable on this particular lesion. In other words, the balloon may have stretched mainly the ePTFE graft and cuff rather than actual native PAs.

Balloon Angioplasty for Proximal Anastomotic Stenosis

Given the nature of the proximal anastomosis, where the shunt takes off with a sharp angle from the small right ventriculotomy, the proximal anastomosis was a common stenotic site in our series (95%). Potential mechanisms include a kinking of the shunt in the AP direction, muscle growth at the ventriculotomy or fibromuscular proliferation into the shunt. We speculated that BA might not be effective at dilating in the AP direction due to the structural kinking; however, our results showed that BA dilated the shunt in the lateral direction rather than in the AP direction.

Balloon Angioplasty for In-Stent Stenosis

The majority (7/11, 63%) of in-stent stenosis in this series was "intentional," created by a hemoclip placed at the time of stage I palliation to control pulmonary blood flow. Progression of desaturation was expected for those patients and therefore more meticulous follow-up was implemented. We believe that this strategy represents an effective means to manipulate the amount of pulmonary blood flow through the RV-PA shunt, thereby preventing sudden circulatory collapse due to pulmonary overcirculation in the immediate postoperative period. The mechanism of stenosis in the remaining 4 patients was not related to hemoclip placement, and may be due to tissue proliferation associated with the procedure and/or minor kinking of the shunt. BA was also effective for this lesion partly because of the nature of ePTFE since the material itself is expandable by pressure [17].

Balloon Angioplasty vs. Stent Placement

A large number of reports suggest stent placement efficacious for stenotic RV-PA shunts following stage I palliation [6,7,11–14]. Re-intervention rates after stent placement are low. Potential disadvantages of stent placement include: distortion of the branch PA bifurcation, erosion of the anastomotic sites, in-stent stenosis and complications related to stent removal at the time of the next operation. None of these potential complications became an issue using a BA-alone strategy. If BA is not effective to improve the internal diameter and/or arterial saturation, stent placement or early surgical intervention can be considered as the future options.

Balloon Angioplasty Following Stage I palliation

Even though a substantial body of evidence shows that early stage II palliation can be safely performed as early as the age of 3 months [18], we still believe that the physiology of cavopulmonary connection can be achieved in the safest manner when the pulmonary vasculature is fully matured. In addition, it is possible that a stenotic RV-PA shunt does not supply sufficient pulmonary blood flow to facilitate normal growth of peripheral pulmonary vasculature, leaving premature lung vasculature with or without a vulnerable pulmonary vascular resistance. Therefore, we think that gaining an additional 2–3 months by BA could be beneficial. All 17 patients underwent a BDG at the standard time and had favorable postoperative clinical outcomes.

Balloon Angioplasty for RV-PA shunt as an Additional Pulmonary Blood Source

We have a rather unique surgical strategy, where a RV-PA shunt is left in place at the time of a BDG, serving as an additional pulmonary blood source. This shunt may be beneficial in terms of facilitating further native PA growth and potentially preventing development of arteriovenous fistula by providing hepatic factors. However, we do recognize that the presence of an additional pulmonary blood source following stage II palliation is controversial. Our limited experience (two patients) showed that BA for RV-PA shunt stenosis following BDG was effective and also in patients who were awaiting biventricular repair [19].

Study Limitation

The major limitations of this study are due to the retrospective non-randomized nature of the patient cohort. Since our institutional policy has been consistent during the study period, there is no comparison group. Lastly, there were no follow-up angiograms to document the medium-term results of BA. Our measure of success comes from immediate post-operative angiographic results and clinical outcomes.

CONCLUSIONS

The BA-alone strategy for stenotic RV-PA shunts in severely desaturated patients was effective in all three shunt portions. Premature surgery was avoided and all patients underwent elective operations at an appropriate age with good clinical outcomes. This strategy can be considered effective to minimize shunt-related premature surgical intervention.

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ORIGINAL ARTICLE

Repair of Ebstein's anomaly in neonates and small infants: impact of right ventricular exclusion and its indications†

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Abstract

OBJECTIVES: In cases of severe Ebstein's anomaly, it is essential to determine whether biventricular repair (BVR) or single-ventricle palliation is feasible. Since 1999, in our institution, we have used the novel technique comprising tricuspid valve (TV) closure and right ventricular and right atrial (RV/RA) exclusion to reduce the deleterious effects of an enlarged RV in patients with severe Ebstein's anomaly. However, in cases with good RV function, primary BVR is performed. In the present study, we describe our surgical strategy in the treatment of severely symptomatic neonates with Ebstein's anomaly.

METHODS: From June 1999 to October 2011, 12 neonates with a severely symptomatic Ebstein's anomaly underwent surgical repair. The mean age at the first operation was 29 ± 25 (range, 5–92) days; and the mean body weight was 2.8 ± 0.5 (range, 2.0–4.1) kg. The associated anomalies included pulmonary atresia with an intact ventricular septum in 7, critical pulmonary stenosis in 1, ventricular septal defect in 3 and coarctation of the aorta in 1 patient. The mean cardio-thoracic ratio (CTR) was 80 ± 14% (range, 57–98%). Preoperatively, 9 patients had grade IV tricuspid regurgitation (TR), as detected by echocardiography, and 6 required ventilator support.

RESULTS: Five patients underwent primary BVR. Seven patients underwent staged palliation using a modified Blalock-Taussig shunt (BT shunt) with/without RV/RA exclusion. There was 1 case each of hospital death and late death. The median follow-up duration in the present study was 6.5 years. Among the 8 patients who underwent TV repair, postoperative TR was trivial or mild in 6 patients, moderate in 1 and absent in 1. After surgery, the mean CTR and serum B-type natriuretic peptide levels decreased to 59 ± 14% (range, 45–70%) and 46 ± 28 (range, 12–83) pg/dl, respectively.

CONCLUSIONS: Critically ill neonates with Ebstein's anomaly can be successfully treated using RV/RA exclusion combined with a modified BT shunt in cases where RV function is poor. However, in cases of good RV function, we recommend the use of primary BVR.

Keywords: Ebstein's anomaly • Neonate • Cardiac surgery • Right ventricular exclusion

INTRODUCTION

Management of a neonate with symptomatic Ebstein's anomaly is a very challenging situation for paediatric cardiologists and paediatric cardio-thoracic surgeons, as these patients tend to have a higher risk of early mortality compared with neonates with hypoplastic left heart syndrome, even in institutions with the most experienced surgeons [1, 2]. Tricuspid valve (TV) repair for symptomatic neonatal Ebstein's anomaly is reportedly an extremely high-risk procedure with a high early mortality rate. TV repair outcomes in patients with Ebstein's anomaly and right ventricular (RV) outflow obstruction are particularly poor. In 1991, Starnes *et al.* [3] introduced an innovative surgical treatment for severe neonatal Ebstein's anomaly, referred to as the Starnes operation. This procedure involved the univentricularization of the heart by TV closure using a fenestrated patch and a modified Blalock-Taussig shunt (BT shunt). Acceptable survival rates have been reported for neonates or early infants with Ebstein's anomaly who underwent the Starnes operation. Since 1998, in our institution, we have used a novel technique comprising TV closure and free wall resection of the RV and right atrium (RV/RA exclusion) to create a single left ventricle (LV) in patients with isolated RV dysfunction to reduce the deleterious effects of an enlarged RV [4]. We have applied this technique since 1999 to patients with severe Ebstein's anomaly.

Appropriate patient selection and determination of which patients should be treated with a univentricular or biventricular approach have been problematic, since accurately estimating RV function is difficult despite the development of diagnostic procedures, including echocardiography and magnetic resonance imaging. Some doctors state that all neonates with symptomatic Ebstein's anomaly and pulmonary obstruction should undergo the Starnes operation, which has been accepted in most institutions worldwide. However, in our institution, an effort has always been

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made to preserve the biventricular physiology in neonates or early infants with symptomatic Ebstein's anomaly since the introduction of the Starnes' concept. A functioning RV should be able to generate a pressure difference between the RV and RA in the systolic phase and, thus, cause some antegrade main pulmonary arterial (PA) flow. We believe that the presence of the trans-TV systolic pressure difference of >30 mmHg, an antegrade main pulmonary blood flow and a good non-atrialized RV morphology are indicators of a positive potential for restoring RV function. Thus, biventricular repair (BVR) at the time of the first surgical intervention in patients with these preoperative findings should still be considered. Here, we aimed to describe the outcomes of symptomatic neonatal Ebstein's anomaly achieved in this institution and to determine whether our treatment strategy could be beneficial for avoiding the future establishment of Fontan circulation in these patients.

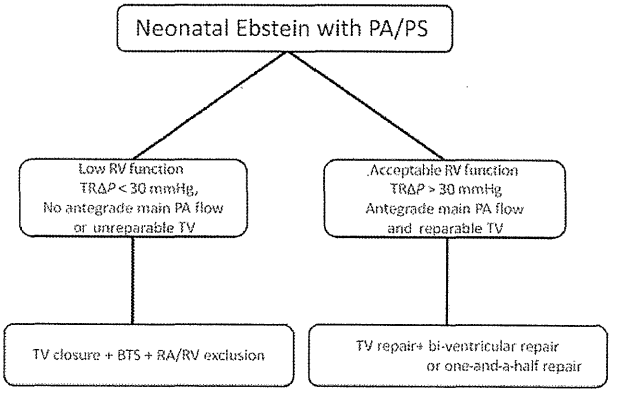

Figure 1: The management of symptomatic patients with neonatal Ebstein's anomaly at Okayama University Hospital. If the patient has a pressure difference of >30 mmHg in the systolic phase between the RV and the RA and a repairable TV, a biventricular or one-and-a-half repair is performed. In other cases, the patient undergoes TV closure with BT shunt application.

PATIENTS AND METHODS

Study subjects

We retrospectively reviewed the medical and surgical records of neonates with symptomatic Ebstein's anomaly who required surgical intervention in the neonatal or early infant period in Okayama University Hospital between June 1999 and November 2010.

Data collection and measurements

This study was approved by the Institutional Research Ethics Board at Okayama University Hospital, and patient consent was waived. Data collected from the medical records included patient demographics, cardiac diagnosis, clinical condition, previous procedures, operative data as well as postoperative and follow-up clinical status, including catheter and echocardiographic data. The pressure difference between the RV and RA was determined by the Doppler flow velocity of the tricuspid regurgitation (TR) as follows: $PG = 4 \times v2$ (PG: pressure gradient between the RV and RA; v: velocity of the TR flow as measured by echocardiography).

Selection of patient management

Our basic strategy is shown in Fig. 1. If a patient could be managed with oral medication, no surgical treatment was performed in the neonatal or early infant period. These patients were considered candidates for BVR. If patients could not be managed with oral medication, an early surgical intervention was indicated. The patients were considered as candidates for BVR or one-and-a-half repair when a trans-TV systolic pressure difference of >30 mmHg was observed on echocardiography and TV repair was possible. In these cases, TV repair and RV outflow reconstruction with/without a modified BT shunt were performed as an initial operation. If the patient was a suitable candidate, a one-stage BVR was performed. When the pressure difference was <30 mmHg or TV repair was not feasible, the patients were considered as suitable candidates for the Fontan operation. In these cases, a TV closure with fenestration, RV/RA exclusion and application of a modified BT shunt were performed as an initial operation.

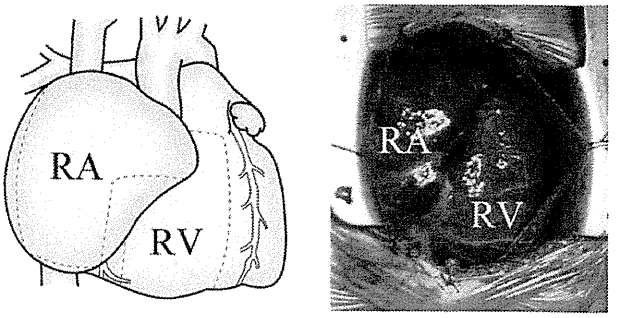

Figure 2: Total RV and RA exclusion of neonatal Ebstein's anomaly. The RV and RA are excluded along the dotted lines suggested here. RA: right atrium. RV: right ventricle.

Surgical procedures

If the patients needed a modified BT shunt with/without a pulmonary valvotomy and had good arterial oxygen saturation, the operation was performed without cardiopulmonary bypass (CPB). The BT shunt was created either from the innominate artery to the right PA or from the left subclavian artery to the left PA via a thoracotomy, using a 4-mm extended polytetrafluoroethylene (ePTFE) graft. A PA valvotomy was performed with clamping of the main PA.

If patients required CPB, the operation was performed using a conventional continuous flow CPB with moderate hypothermia (24–34°C) via a standard median sternotomy. CPB was established with bicaval drainages or an RA single venous drainage with an ascending aortic return. If needed, the RA was opened, and intracardiac repair was performed. The TV repair technique was selected according to the surgeon's preference.

The exclusion of the RV free wall was performed as previously described [4]. The TV was closed with a fenestrated ePTFE patch (the fenestration was created with a 3- or 4-mm puncher) or autologous TV tissue (Figs 2 and 3). When the TV was closed with autologous TV tissue, a small hole was left as a fenestration (a 3- or 4-mm Hegar dilator could be passed through it).

In cases of one-stage BVR, all associated cardiovascular anomalies were corrected, including closure of a ventricular septal defect (VSD) with a Dacron sauvage or ePTFE patch using 6-0 pledgeted

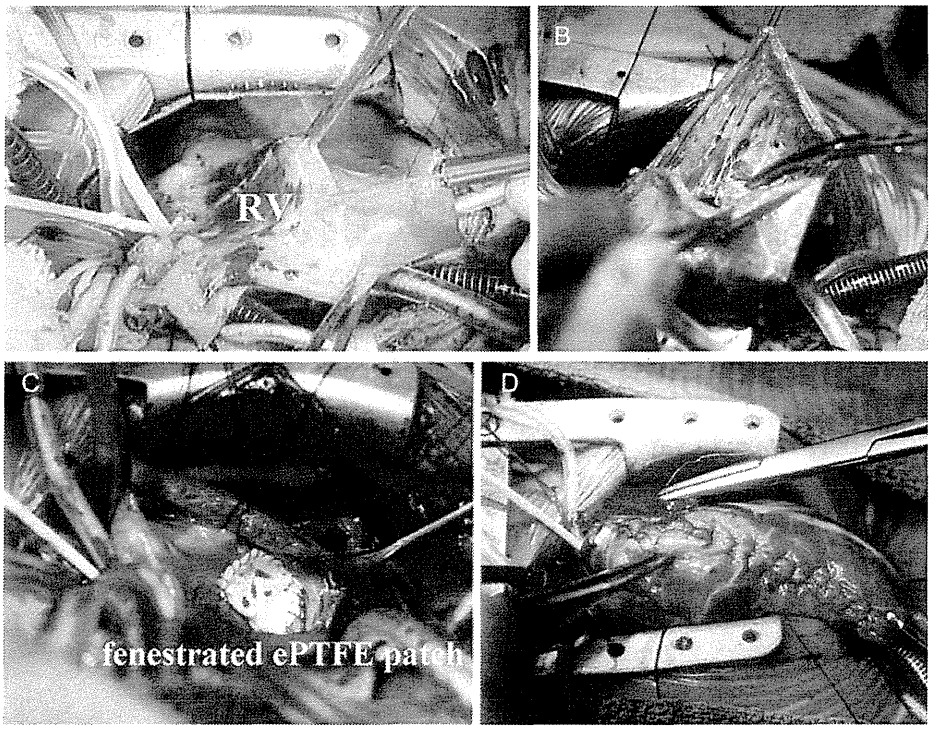

Figure 3: Images of an RV exclusion procedure. A 14-day old patient with an Ebstein's anomaly; the patient's body weight was 2.0 kg (Patient 12). (**A**) A paper-thin RV free wall. (**B**) The RV free wall was excised to reduce the size of the RV cavity. (**C**) The TV was closed with a fenestrated ePTFE patch. The blood in the coronary sinus was drained into the RA. (**D**) The RV free wall was closed directly, and a modified BT shunt was placed. BT shunt: Blalock-Taussig shunt. ePTFE graft: polytetrafluoroethylene graft. RV: right ventricle.

polypropylene sutures; closure of an atrial septal defect (ASD) or a patent foramen ovale (PFO), with 6-0 polypropylene running sutures; and repair of coarctation of the aorta (CoA), in an extended end-to-end fashion using 8-0 polypropylene running sutures.

Data analysis

Data are expressed as the mean ± SD or the median and range as appropriate. The Kaplan–Meier method was used to determine the estimated patient survival.

RESULTS

Patient characteristics

Twelve symptomatic neonates with Ebstein's anomaly were treated at our institute between June 1999 and November 2010. The mean gestational age was 38 ± 3 (range, 32–41) weeks. The mean birth body weight was 2.85 ± 0.46 (range, 2.29–3.56) kg. The mean cardio-thoracic ratio (CTR) on chest radiography was 80 ± 14% (range, 57–98%). Seven patients were born by normal delivery and 5 were delivered by Caesarean section. Table 1 summarizes the patient characteristics. According to Carpentier's classification of the Ebstein's anomaly, we noted that 2 patients were type A, 5 were type B and 5 were type C. TR was mild in 2 (17%) patients, moderate in 1 (8%) and severe in 9 (75%). True pulmonary atresia was observed in 7 patients, functional atresia in 1 and severe pulmonary stenosis in 1. These 9 patients received prostaglandin E1 infusions for maintaining pulmonary blood flow after birth. For 3 patients, the estimated trans-TV systolic pressure difference between the RV and RA by echocardiography was <20 mmHg. One patient had severe myocardial calcification that was detected after the first operation by a computerized tomography scan. The associated extracardiac anomalies included Down syndrome in 2 patients, anal atresia in 1, idiopathic chylous ascites in 1, hypertrophy of the adrenal glands in 1 and calcification of the kidney in 1.

Surgical data

All patients underwent open heart surgery in the neonatal stage (7 patients) or in early infancy (5 patients). Six (50%) patients required mechanical respiratory ventilator support preoperatively. At the initial operation, the mean age, body weight and body surface area were 29 ± 25 (range, 5–92) days, 2.81 ± 0.54 (range, 2.04–4.05) kg and 0.18 ± 0.02 (range, 0.15–0.22) m^2, respectively.

Five patients, aged 5–92 days, underwent a one-stage BVR (Patients 1–5 in Table 1). The TV repair methods for these 5 patients were Hardy's procedure in 2, Carpentier's procedure in 1, Cone's reconstruction in 1 and plasties of the septal and posterior leaflet in 1 patient with a dysplastic anterior leaflet (Fig. 4). The associated procedures included patch closure of a VSD in 3 patients, direct closure of an ASD or PFO in 4, semiclosure of an ASD in 1, repair of CoA in 1, and RV outflow reconstruction with pulmonary valvotomy and RV outflow muscle resection in 2.

The remaining 7 patients received a modified BT shunt with an ePTFE graft as palliative treatment via a median sternotomy

Table 1: Summary of the cardiac conditions and outcomes

No.	Carpentier's classification	Associated cardiovascular anomaly	TR	RVOTO	RV systolic function	1st Op	RV ex	Final status	Outcome
1	A	CoA, VSD, ASD	Trivial	No	Normal contraction with VSD	BVR	No	BVR	Alive
2	B	VSD, ASD, PDA, PAPVD	Severe	No	Normal contraction with VSD	BVR	No	BVR	Alive
3	B	VSD, ASD,	Severe	No	PG = 48 mmHg	BVR	No	BVR	Alive
4	B	Severe PS, PDA, ASD, PLSVC	Severe	PS	PG = 43 mmHg	BVR	No	BVR	Alive
5	C	PA/IVS, PDA, PFO	Severe	PA	PG = 53 mmHg	BVR	No	BVR	Alive
6	B	PA/IVS, PDA, PFO	Severe	PA	Mild plastering	BTS	No	BVR	Alive
7	B	PA/IVS, PDA, PFO	Severe	PA	No data	BTS	No	BTS	Dead
8	C	HypoRV, PFO, PS (small PV with normal leaflets)	Trivial	PS	Obvious antegrade mPA flow	BTS	No	1 + 1/2	Alive
9	C	PA/IVS, PDA, PFO	Severe	PA	PG = 4 mmHg	BTS	Yes	TCPC	Dead
10	A	PA/IVS, PDA, PFO	Moderate	PA	PG = 185 mmHg	BTS	No	BVR	Alive
11	C	PA/IVS, PDA, PFO	Severe	PA	PG = 9 mmHg	BTS	Yes	BDG	Alive
12	C	PA/IVS, PDA, ASD	Severe	PA	PG = 15 mmHg	BTS	Yes	BTS	Alive

ASD: atrial septal defect; BDG: bidirectional Glenn operation; BTS: Blalock-Taussig shunt; BVR: biventricular repair; CoA: coarctation of the aorta; hypoRV: hypoplastic right ventricle; PA: pulmonary atresia; PA/IVS: pulmonary atresia with an intact ventricular septum; PAPVD: partial anomalous pulmonary venous drainage; PDA: patent ductus arteriosus; PG: pressure gradient; PFO: patent foramen ovale; PLSVC: persistent left superior veno cava; PS: pulmonary stenosis; PV: pulmonary valve; RV ex: total right ventricular exclusion; RVOTO: right ventricular outflow tract obstruction; sys.: systolic; TCPC: total cavopulmonary connection; TR: tricuspid regurgitation; VSD: ventricular septal defect; 1st Op: first-stage operation.

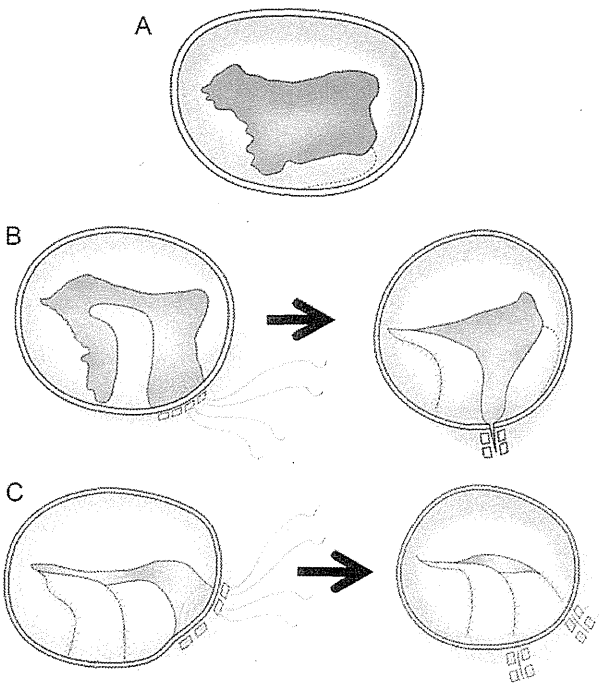

Figure 4: TV plasty with dysplastic septal and posterior leaflets and a non-sail-like anterior leaflet in Patient 4. (A) The septal and posterior leaflets were severely dysplastic. The anterior leaflet was also mildly dysplastic and lacked sufficient area for monocuspization. The fused or dysplastic chordae of the septal leaflet were divided to create a free area for the septal leaflet. The created free septal leaflet was subsequently partially cut off from the annulus (dotted line). (B) The created free leaflet was rotated counterclockwise and sutured to the leaflet. Thereafter, an annuloplasty using pledgeted polypropylene sutures was performed. The posterior leaflet was then partially cut off from the annulus (dotted line). (C) The free leaflet was rotated counterclockwise and sutured, and an annuloplasty using pledgeted polypropylene sutures was consequently performed.

(5 patients) or a thoracotomy (2 patients) at the age of 7–50 days. The diameter of the ePTFE graft used was 3.0 mm in 2 patients, 3.5 mm in 2 and 4.0 mm in 3. CPB was established in 4 of the 7 patients. The associated procedures consisted of RV/RA exclusion in 3 patients, plication of the RA in 1, creation of an ASD in 1, closure of the TV using autologous TV tissue with fenestration in 2 and TV with a fenestrated ePTFE patch in 1.

Postoperative outcomes

Figure 5 illustrates the patient flow chart about the selected surgical technique and the outcomes. Four of the 12 patients were believed to have low RV function and were considered as Fontan candidates. However, the other 8 patients were estimated to have acceptable RV function and were considered as suitable candidates for BVR or one-and-a-half repair.

One case of early death occurred because of sepsis (Patient 7 in Table 1). This patient's age at the first intervention was 43 days; he was born at a gestational age of 41 weeks and had a body weight of 2.62 kg at birth. Moreover, he had true pulmonary atresia with an intact ventricular septum (PA-IVS), a PFO and severe TR. He was found to have a CTR of 98%, as indicated by chest radiography. Prostaglandin E1 was administered immediately after birth to open the arterial duct. He had a persistently increased white blood cell count and C-reactive protein (CRP) level before the operation. However, because he had heart failure due to high PA flow and because the increase in the white blood cell count and CRP level was very mild, the patient underwent application of a 3-mm modified BT shunt, ligation of the arterial duct and plication of the RA via a median sternotomy. TV repair was not performed because of the risk of postoperative deterioration due to infection resulting from CPB. However, this patient experienced septic shock in the early postoperative period and died on the seventh postoperative day.

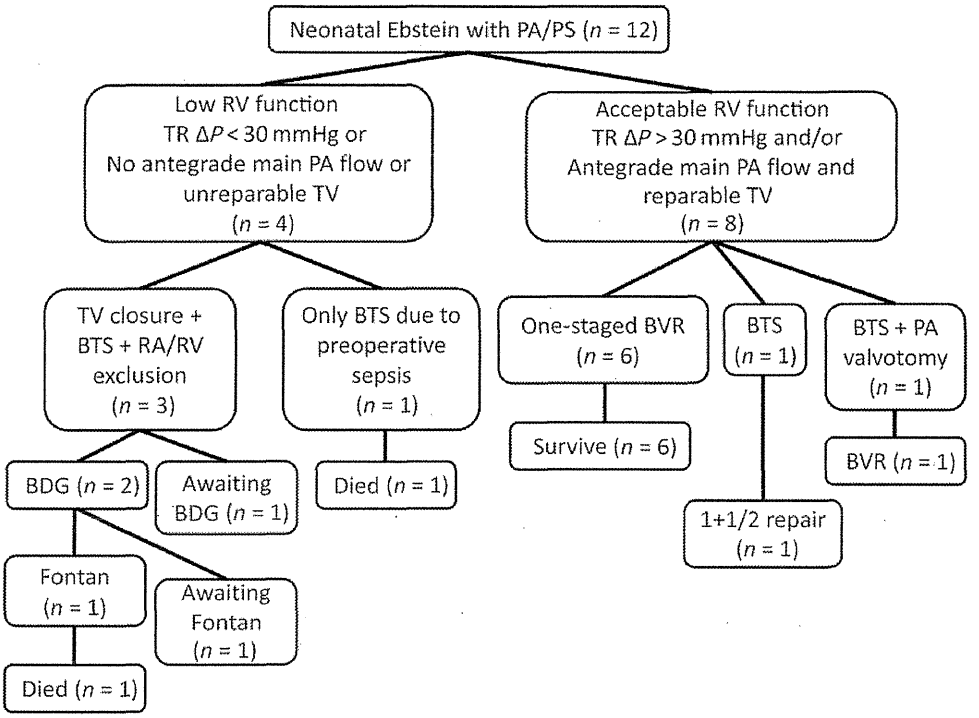

Figure 5: Flow chart of patients. The presence of a trans-TV systolic pressure difference of >30 mmHg and antegrade main pulmonary blood flow are considered important indicators for good RV function. Patients were considered as candidates for the Fontan operation when the pressure difference was <30 mmHg or the TV was not reparable. Four of the 12 patients were considered as Fontan candidates in the present study. The other 8 patients were considered as candidates for BVR or one-and-a-half repair. All the patients with good RV function survived for a long duration. Among the Fontan candidates, 1 case of early death was noted, whereas 1 suddenly died 3 years after the Fontan operation.

The follow-up period of the 11 early survivors was 6.7 ± 4.6 (range, 0.4–12.2) years. There was 1 case of late death (Patient 9 in Table 1). This patient's age at the first surgical intervention was 50 days; he was born at the gestational age of 40 weeks and had a body weight of 3.15 kg at birth. He had PA-IVS (true pulmonary atresia), a PFO and severe TR. Prostaglandin E1 was administered immediately after birth to open the arterial duct. The trans-TV systolic pressure difference was only 4 mmHg, as detected by echocardiography. Based on these findings, the patient was considered as a Fontan candidate. The application of a 4-mm modified BT shunt with exclusion of the RV and RA free walls, closure of the TV with a fenestration, creation of an ASD and ligation of the arterial duct were performed. He had no serious complications postoperatively and was clinically well. He underwent a bidirectional Glenn (BDG) procedure at the age of 8 months and total cavopulmonary connection (TCPC) at the age of 5 years. His main heart rhythm after the TCPC was a junctional rhythm, but he appeared clinically well. However, he suddenly died probably due to a fatal arrhythmia 3 years after the Fontan operation. The actual estimated survival for all patients was 91% at 1 year and 73% at 10 years.

In the 3 patients who underwent RV/RA exclusion, the paradoxical interventricular septal motion, which was present in all these patients preoperatively, was completely normalized. Postoperatively, the marked left ventricular compression due to RV volume overload at end-diastole was improved, and the LV shape at end-diastole was almost circular in the short-axis view—the D-shaped LV observed at end-diastole preoperatively changed to a circular shape postoperatively. Moreover, a small, banana-shaped RV cavity was observed without thrombosis.

Among the 7 patients who underwent a palliative operation, 2 underwent BVR, 1 underwent a one-and-a-half repair, 1 underwent a Fontan operation and 1 underwent a BDG operation. Thus, the final cardiac status of the early survivors was as follows: underwent BVR, underwent one-and-a-half repair, underwent Fontan operation, awaiting Fontan operation and awaiting BDG in 7 (58%), 1 (8%), 1 (8%), 1 (8%) and 1 patient (8%), respectively. Three of the 7 patients who underwent BVR had true pulmonary atresia.

Of the 10 late survivors, 3 patients experienced significant complications. One patient had severe cardiac failure due to a severe myocardial calcification of unknown origin, is currently under treatment and has not been discharged, 1 required home oxygenation therapy after the BDG and 1 required haemolytic therapy due to thrombo-embolism of the artificial pulmonary valve.

The latest examination of the TR in the eight early survivors who underwent TV repair showed that the condition was not present in 1 patient, trivial to mild in 6 and moderate in 1. The latest CTR was 59 ± 9% (range, 45–70%). The serum B-type natriuretic peptide level of the late survivors at a follow-up period of >1 year ($n = 7$) was 46 ± 28 (range, 12–83) pg/ml.

DISCUSSION

Management of a neonatal symptomatic Ebstein's anomaly is extremely challenging, even in institutions with highly experienced surgeons, and is also controversial. Shinkawa *et al.* [5] reported that the overall survival rate estimated for all neonates undergoing surgical intervention was 66.7% at 1 year, 62.2% at 5 and 10 years and 51.9% at 15 years. Knott-Craig *et al.* [6] reported on a series of 22

symptomatic neonates and young infants who underwent BVR, and observed a 73% hospital survival rate. In our current report, 12 patients underwent surgical intervention with a hospital mortality rate of 8.3%. Five of these 12 patients were neonates. All of these neonates are currently alive, and 3 of the 5 neonates were clinically well for >2 years after their first operation. Our results seem to be comparable with or perhaps an improvement over those of these previous reports.

In the present study, a very high rate of successful BVR and one-and-a-half repair with excellent survival was achieved in this patient population. One of the key factors for achieving successful repair in both cases is an estimation of the potential for RV function. Our current policy is that the possibility of BVR should not be excluded at the time of the initial operation in cases where echocardiography indicates a preserved RV function. In the present report, the presence of a trans-TV systolic pressure difference of >30 mmHg, an antegrade main pulmonary blood flow and a good non-atrialized RV morphology were considered as indicators of good RV function. If the patient had pulmonary atresia and a very small trans-TV systolic pressure difference, BVR or one-and-a-half repair was not considered to be feasible, as we believe that no potential for good RV function was present. TV closure and RV/RA exclusion or RV exclusion with RA plication has been selected in Okayama University Hospital for such patients. In other cases where one of the above-mentioned indicators is present and the TV is repairable, we perform a one-stage BVR or TV repair with a BT shunt and the creation of an RV outflow tract as an initial operation.

The feasibility of TV repair is another important factor for performing BVR or one-and-a-half repair. However, it is largely dependent on the surgeon's skill. If a patient has a sail-like anterior leaflet, a conventional tricuspid repair such as Carpentier's repair or Danielson's repair is feasible. However, in other cases, it may not be feasible to repair the TV in such a manner. In the present study, 2 patients had a dysplastic anterior leaflet. One patient (having a mildly dysplastic anterior leaflet) underwent a Cone's operation, whereas the other patient (having a moderately dysplastic anterior leaflet) underwent extensions of the septal and posterior tricuspid leaflets. The postoperative TRs were mild after the operations in both of these patients. Although these operations require a substantial amount of skill, attempting them is valuable because of the outcomes that can be achieved.

A severely enlarged RV compresses the LV and causes abnormal motion of the interventricular septum, which can affect LV function. We have used the total RV/RA exclusion procedure in adults with isolated congestive right heart failure since 1998 and have applied this procedure to patients with severe Ebstein's anomaly since 1999 [4, 7, 8]. This procedure is composed of the resection of the RV free wall, resection or plication of the RA and a cavopulmonary connection or application of a systemic–pulmonary shunt. This procedure increases the volume at end-diastole, restores the cylindrical shape and improves contractile function of the surgically created single LV [7]. The resultant increase in systemic output leads to rapid improvements in the patient's' postoperative condition. The Starnes operation is a simpler procedure and can achieve a comparable effect with regard to LV function improvement when compared with our modified technique, along with normalization of paradoxical interventricular septum motion. However, we believe that a remnant large RV can affect the LV function and have a greater thrombogenic effect when compared with a smaller RV. Further detailed evaluation of postoperative LV function and incidence of postoperative thrombo-embolic events is required to compare postoperative LV function between Starnes operation and our modification. Furthermore, significant lung compression due to an extremely enlarged RA and RV has been reported to be an important risk factor in the survival of neonates with Ebstein's anomaly. Therefore, we believe that RV/RA exclusion is beneficial for postoperative respiratory function and can thus improve postoperative survival [9]. Kajihara *et al.* [10] reported a case of successful management using a 'rapid two-stage Starnes procedure' in neonates with severe Ebstein's anomaly. This group performed main PA ligation, plication of the RA and RV wall, application of a BT shunt and PDA ligation without CPB as an initial operation on the day of birth in order to achieve early lung expansion and improvement in LV function. They subsequently performed Starnes operation using CPB at the age of 12 days. In this previous report, the concept of achieving an early reduction of the enlarged RV and RA to improve LV function and lung function is similar to that in the present study. However, compared with their procedure, the present procedure requires fewer suture lines on the RV than RV plication and requires only 1 surgical intervention. However, the advantages of their surgical strategy include the possibility of reduction of the RV and RA volume while avoiding the risk associated with CPB in the very early neonatal period. Further investigation is required to elucidate the advantages and disadvantages of each surgical strategy for the treatment of neonates with severe Ebstein's anomaly who are not suitable for BVR.

If a patient has a low PA resistance, good LV function and sufficient RV function to handle venous blood volume from the inferior vena cava, the use of one-and-a-half repair could yield good mid-to-long-term results without the occurrence of typical Fontan complications, such as protein-losing enteropathy and congestive liver dysfunction [11]. Therefore, one-and-a-half repair is currently one of the choices for definitive repair at our institution.

The major limitation of this study is the small number of patients. All patients were treated with the same strategy in the present study. Therefore, we were unable to perform comparisons between patients who underwent an RV exclusion procedure and those who did not undergo this procedure for verifying the effect of the RV exclusion procedure on postoperative LV function. Thus, further accumulation of surgical experiences and investigation on the real benefits of RV/RA exclusion are required.

CONCLUSIONS

Critically ill neonates and small infants with Ebstein's anomaly and poor RV function can be successfully treated by RV/RA exclusion or RV exclusion with RA plication in addition to BT shunt application. However, in cases with good RV function, primary BVR is advocated. Our management strategy for neonates with symptomatic Ebstein's anomalies was beneficial for avoiding a future establishment of Fontan circulation. Cone reconstruction and reconstruction of the septal and posterior leaflets were good options for increasing the likelihood of successful TV repair.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

***Dr O. Ghez** (London, UK)*: Your study reflects very well the challenging management of children with this malformation. Clearly the treatment must be tailored to each individual patient, as you showed very well in your 12 patients, who all had different operations. You emphasize in your manuscript that even though the procedure of RV exclusion, which you already described, provides excellent haemodynamic results for univentricular palliation, some children can be saved towards a biventricular repair in this selected group of symptomatic neonates. Your criteria for primary repair are a well functioning right ventricle, which is not so easy to assess, as you showed, and a repairable tricuspid valve, about which maybe you could elaborate a bit more. With your strategy, you achieved excellent results in these 12 patients, with only one early death and one late death. I noticed, however, that three of your patients did not go into this route of either RV exclusion or biventricular repair immediately. Three of those had a BT shunt and then eventually two of those went to a biventricular repair and one to a one and a half ventricular repair.

Regarding the first operation, can I ask you to clarify your indications for performing a systemic to pulmonary artery shunt, either isolated or associated with an RVOT opening? This is not very clear in the manuscript. In other words, when would you stage a repair in these patients? This is my first question.

And the last question, you used several techniques for tricuspid valve repair in the four patients in whom it was performed. One of those had a cone repair. Is it now your treatment of choice?

Dr Sano: In response to your first question, the indication for the modified BT shunt alone is in the patients who have less than moderate tricuspid regurgitation, and also the patients with a CTR less than 80%, as well as in the patients where their future indication is possibly biventricular repair.

The indication for the modified BT shunt with RV outflow tract reconstruction, is in the patients who have rather good RV function and also the patients who may be candidates for future biventricular repair. If the patients have very bad RV function or a very thin RV wall, regurgitation increases from the pulmonary artery to the RV if pulmonary valvotomy or RV outflow tract reconstruction is performed. Finally, the RV distends and these patients do not do well.

Indications for RV/RA exclusion is in patients who have a huge CTR, >90%, severe tricuspid regurgitation and poor RV function. It is not always easy to evaluate the RV function in the neonatal period, so one of these patients achieved a one and a half ventricular repair later on. For patients in the initial palliation group, the second stage operation should be done at around six to 12 months, if possible, certainly at older than three months, because a bidirectional Glenn procedure can be done.

Your final question relates to my recent preference for tricuspid valve repair. I now do more cone operations in older patients, and I am very happy with the results. Recently, I tried to use the cone operation in the neonate. I did only one cone operation in my university, and I did another one in the other unit.

***Dr J. Amato** (Chicago, IL, USA)*: I just wanted to pinpoint the one patient in whom you had the plication. I am a little surprised, because I had a little bit more in my series, but what was your technique for the plication and what did you do with the valve adjacent to that plication?

Dr Sano: In that particular patient it was a little bit dangerous to repair under cardiopulmonary bypass, so I did a shunt, and a suture to the right atrium to make the right atrium small.

Dr Amato: Did you have to do anything to that leaflet of the valve in the plication?

Dr Sano: No. In the second stage I did. In the first stage I did a BT shunt and an RV plication to the surface without using bypass.

***Dr M. Wojtalik** (Poznan, Poland)*: According to your presentation, after right ventricular resection you close the tricuspid valve. Do you think it is always necessary in all cases for such an operation?

Dr Sano: I presented the abnormal interventricular septal motion (IVS) at the STS meeting. The IVS motion is abnormal in these patients because the huge dilated RV compresses the LV. However, the abnormal motion disappears after surgery because the dilated RV becomes small. I showed the video of the patient with more than 400% of normal size RV. In the patient whose RV is 200 or 250% of normal and in whom the IVS motion is not paradoxical, RV exclusion is not performed. It is not always necessary to do RV/RA exclusion. Only the patients who had a huge dilated RV which compressed the LV were selected for RV exclusion. Soon after the operation the LV becomes bigger, because IVS shifts to the RV side and LV shape returns to normal, therefore LV stroke volume increases and ejection fraction improves.

Dr Wojtalik: But after exclusion do you always close the tricuspid valve?

Dr Sano: Most of these patients had severe tricuspid regurgitation, a huge RV, and a very thin RV wall, so I did exclude the RV/RA. But some of the patients who had a 200–300% of normal size RV with rather good RV function, had plication or exclusion of RA and repair of the tricuspid valve without exclusion of the RV.

pinching between the PA and the aorta was observed. The right coronary button was then anastomosed to the graft. A position in the right sinus in an area just above the level of the commissures seemed most natural, and this location was chosen for the anastomosis (Fig 2E), which was performed in a running fashion.

Next, to create neosinuses of Valsalva, figure-of-eight sutures were placed in the graft near the equivalent of the sinotubular junction. The graft was then shortened and beveled. A running anastomosis was then performed between the graft and the residual ascending aorta. Air was removed from the heart, the cross-clamp was removed, and the heart was allowed to reperfuse.

The patient was weaned from cardiopulmonary bypass, protamine was administered, and cannulas were removed. Transesophageal echocardiography demonstrated excellent aortic valve function. There was complete resolution of the previously existing mild aortic regurgitation and no aortic stenosis. Flow through both main coronary arteries could be seen on transesophageal echocardiography. There was normal left ventricular function. Chest tubes were placed, and the sternum was closed in a standard fashion. The patient did well postoperatively and was discharged to home on postoperative day 6. He was doing well with no evidence of aortic insuffiency at most recent follow-up.

Comment

Several technical factors contributed to the excellent outcome in this case. Valve-sparing aortic root replacement requires extensive circumferential dissection of the aortic root. An anomalous coronary could potentially be injured if its presence has not been diagnosed preoperatively. Here, the anomalous LMCA was dissected out early in the operation, and its course was defined, preventing injury.

During valve-sparing aortic root replacement, the PA is not typically dissected away from the aorta at the commissure between the left and right sinuses of Valsalva. Inasmuch as these structures are usually very adherent at this location, dissection here may result in injury. Rather than dissecting the two apart, a notch is often created in the graft used for valve-sparing aortic root replacement at the corresponding location. However, because of the course of the anomalous LMCA between the aorta and PA in this case, dissection of this region was mandatory to mobilize and freely translocate the LMCA. This dissection was completed without injury to the PA or aorta at the commissure.

Ensuring proper length and spatial orientation of the newly translocated LMCA was critical to the success of this operation. Dissection of the LMCA as far as possible under the PA and onto the surface of the left ventricle allowed for as much mobility as possible. An appropriate location for the anastomosis of the LMCA to the graft was chosen by identifying a position where the artery appeared to lie naturally without any evidence of kinking. This location appeared to be just to the right of the commissure near the level of the annulus. To appropriately gauge the length of the LMCA, an orifice was first created in the graft at the chosen location, and the artery was actually brought through this site and trimmed to the correct length before the anastomosis was performed. After the anastomosis was complete, cardioplegia was administered through a catheter in the root to distend the root and confirm the excellent geometry of the newly translocated LMCA.

In this case, cardioplegia was successfully administered by a multimodality approach. Initial cardioplegia was administered through the aortic root in an antegrade fashion. Antegrade cardioplegia was also administered directly through the single coronary ostium, and retrograde cardioplegia was given intermittently through the coronary sinus. This strategy yielded excellent myocardial protection, as evidenced by the good biventricular function observed after cardiopulmonary bypass in this complex operation.

Recent data demonstrate that valve-sparing aortic root replacement can be performed safely and with good results in several high-risk settings, including aortic dissection, severe aortic insufficiency, and reoperative cardiac surgical procedures [4]. To our knowledge, this is the first case of a valve-sparing aortic root procedure in conjunction with anatomic correction of a major coronary anomaly. The outcome of this case provides evidence that valve-sparing aortic root replacement can be effectively performed in this complex scenario.

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FEATURE ARTICLES

The Effect of Pulmonary Root Translocation on the Left Ventricular Outflow Tract

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We report the effect of pulmonary root translocation on the left ventricular outflow tract. A double switch operation with pulmonary root translocation was

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performed in a 6-year-old boy whose diagnosis was dextrocardia, congenitally corrected transposition of the great arteries, ventricular septal defect, and pulmonary stenosis. Postoperative magnetic resonance imaging showed more natural left ventricular outflow than preoperatively (19 mm vs 22 mm in length between the top of the interventricular septum and the aortic valve). This technique does not require coronary transfer and enables preservation of the aortic root structure. The long-term results, including left ventricular outflow tract morphology, should be evaluated.

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A length more than 80% of the normal left ventricular diastolic dimension between the top of the interventricular septum and the aortic valve is a risk factor for mortality and left ventricular outflow (LVOT) obstruction in Rastelli-type operations for transposition of the great arteries (TGA) and ventricular septal defect (VSD) [1, 2]. There are several treatment options for TGA/VSD with pulmonary stenosis (PS), or even with congenitally corrected TGA. Among them, pulmonary root translocation (PRT) is a new approach for anatomic repair of transposition complexes with VSD and PS [3]. Acceptable growth of the right ventricular outflow tract after this procedure has also been reported [4]. We report here the morphologic effect of PRT on LVOT obstruction for congenitally corrected TGA, VSD, and PS.

A 6-year-old boy was referred to our unit as a candidate for a double switch operation. His diagnosis of dextrocardia, congenitally corrected TGA, VSD, and PS was made just after birth. Situs was solitus. The right-sided ventricle was the morphologic left ventricle, which was connected to the pulmonary artery. The left ventricle was the morphologic right ventricle, which was connected to the aorta. A right modified Blalock-Taussig shunt was performed 13 months later because of severe cyanosis. The most recent cardiac catheter study performed at 5 years of age showed that the pulmonary arteries were well grown. Volumetry showed that the morphologic left ventricular end-diastolic volume was 189% of normal, and the morphologic right ventricular end diastolic volume was 176%. The pressure gradient across the right ventricular outflow tract was 54 mm Hg. Echocardiography showed that the annular size of the pulmonary valve was 65% of normal, and the leaflet showed doming. Magnetic resonance imaging (MRI) showed that the length between the top of the interventricular septum and the aortic valve was 22 mm, which was 69% of the normal left ventricular diastolic dimension by echocardiography.

An operation was performed with bicaval drainage and ascending aortic return. A right modified Blalock-Taussig shunt was closed and divided. After aortic cross-clamping and cardioplegia infusion, the right atrium was opened and the left heart was vented through the patent foramen ovale. Right ventriculotomy was performed. Then, the pulmonary root was removed carefully. A direct suture closure of the defect of the pulmonary root showed significant aortic valve insufficiency; therefore, the defect was closed with a 10-mm diameter circle 0.4-mm polytetrafluoroethylene (PTFE) sheet (W.L. Gore & Associates, Inc., Newark, DE). The VSD was closed with a longitudinally opened 16-mm PTFE tube graft to connect the morphologic left ventricle to the aortic valve via the right atrium and right ventriculotomy. The left atrium was then opened just beneath the interatrial groove, and the interatrial septum was incised. The Senning procedure was performed in the usual fashion. The autologous pulmonary root was transferred to the left side of the aorta. The pulmonary root was too short for direct anastomosis with the right ventriculotomy. The pulmonary valve leaflet seemed to be stenotic, so the pulmonary valve was resected and the valve annulus was opened. A 16-mm expanded PTFE valved conduit and patch with bulging sinuses were used to interpose between the right ventriculotomy and the pulmonary root [5]. Intraoperative transesophageal echocardiography showed good competency of the aortic valve and the 16-mm expanded PTFE valved conduit. No significant pressure gradient across both vena cavae was detected at manometry.

Postoperative MRI showed a more natural LVOT, 19 mm long, between the top of the interventricular

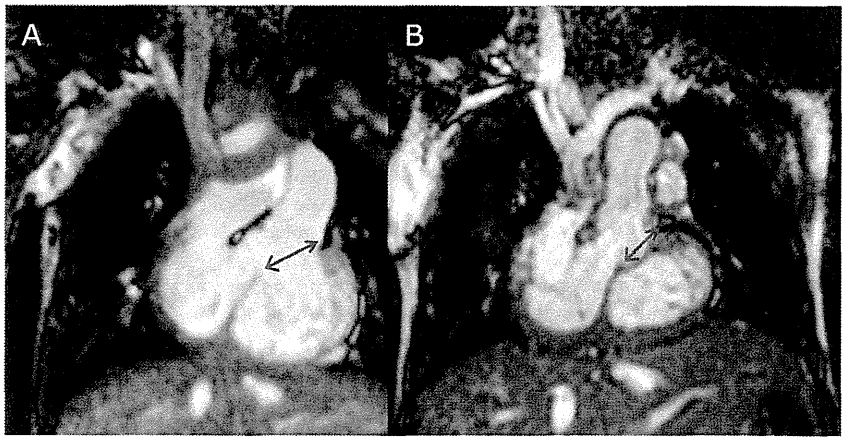

Fig 1. (A) Preoperative and (B) postoperative magnetic resonance imaging showing left ventricular outflow tract morphology. The length between the top of the interventricular septum and the aortic valve was 22 mm preoperatively and 19 mm postoperatively, as denoted by arrows in (A) and (B), respectively.

septum and the aortic valve, compared with the preoperative MRI of 22 mm (Fig 1). Postoperative electric cardiography showed normal sinus rhythm. Postoperative echocardiography showed that the flow velocity across right ventricular outflow tract was 3.0 m/s. One year and 4 months later, an echocardiogram showed that the velocities across the right and left ventricular outflow tracts were 2.1 and 2.0 m/s, respectively. Aortic valve regurgitation was not significant during follow-up.

Comment

As reported by Dearani and colleagues [6], LVOT stenosis is a major morbidity in Rastelli-type repair for TGA/PS at long-term follow-up. PRT for TGA/VSD with PS could be an adjunct to avoid this postoperative morbidity. As shown by MRI in our case, a more natural LVOT was obtained by the use of PRT because of the parallel transfer of the aortic root, even with the double switch operation. The advantages of this operation include no requirement for coronary transfer. This technique also enables preservation of the aortic root structure and avoids the risk of aortic root dilatation caused by the incision around it. The risk of reintervention for right ventricular outflow tract stenosis is also diminished if an autologous pulmonary valve structure is preserved. The indications for how this technique should be applied to the TGA/VSD complex need to be determined; a pulmonary root that is too small is not an indication. Then, the PRT technique does not accommodate LVOT, especially at less than 50% of the normal diameter of the pulmonary valve. Moreover, an excessively large pulmonary root is a concern. PRT for a pulmonary root that is too large could cause kinking of the coronary arteries or aortic valve deformity because of excessive parallel transfer of aortic root. We attempted to use proper supplements for the defect of the pulmonary root to avoid these disadvantages. Careful attention should be paid during removal not to injure the pulmonary valve. An incision should be placed just around the pulmonary annulus to avoid injury of the pulmonary valve and other surrounding tissues. The main pulmonary artery should be opened to confirm the pulmonary valve annulus during removal.

It is unknown whether the length between the top of the interventricular septum and the aortic valve will become shorter (a straighter LVOT) in the future. Further examinations should be performed at long-term follow-up to investigate the morphology of LVOT after PRT.

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Bridge Use of Endovascular Repair and Delayed Open Operation for Infected Aneurysm of Aortic Arch

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We present the first clinical report of the successful treatment of an infected thoracic aortic arch aneurysm with the use of endovascular repair as a bridge to second-stage open operation. A 70-year-old patient underwent urgent endovascular repair through the right femoral approach because of a diagnosis of sepsis and impending rupture of an infected thoracic aortic arch aneurysm. After 2 weeks of medical treatment, we successfully performed explantation of the stent graft, wide debridement of the surrounding tissue, and in-situ replacement using a rifampicin-bonded four-branched prosthetic graft with omental flap.

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Infected aortic aneurysm is rare and remains challenging to treat. The standard treatment is an open surgical procedure, including wide debridement of the infected aorta and surrounding tissue, in-situ or extraanatomic reconstruction, and long-term antibiotic therapy. Recently, several reports have described acceptable short-term results of endovascular repair for infected aortic aneurysms [1, 2]. However, its role remains controversial because persistent infection is always a concern. Endovascular repair for infected aortic aneurysm should be considered as a bridge to improve a patient's condition during the wait for an open operation. However, few publications have described the use of this strategy. We describe the first clinical report of

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Thoughts and Progress

Effects of Atrial Natriuretic Peptide After Prolonged Hypothermic Storage of the Isolated Rat Heart

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Abstract: Primary graft failure (PGF) caused by ischemia-reperfusion injury (IRI) is the strongest determinant of perioperative mortality after heart transplantation. Atrial natriuretic peptide (ANP) has been found to reduce the IRI of cardiomyocytes and may be beneficial in alleviating PGF after heart transplantation, although there is a lack of evidence to support this issue. The purpose of this study was to investigate the cardioprotective effects of ANP after prolonged hypothermic storage. For this purpose, an isolated working-heart rat model was used. After the preparation, the hearts were arrested with and stored in an extracellular-based cardioplegic solution at 3–4°C for 6 h and followed by 25 min of reperfusion. The hearts were divided into four groups ($n = 7$ in each group) according to the timing of ANP administration: Group 1 (in perfusate before storage), Group 2 (in cardioplegia), Group 3 (in reperfusate), and control (no administration of ANP). Left ventricular functional recovery and the incidence of ventricular fibrillation (VF) were compared. ANP administration at the time of reperfusion improved the percent recovery of left ventricular developed pressure (control, 45.5 ± 10.2; Group 1, 47.4 ± 8.8; Group 2, 45.3 ± 12 vs. Group 3, 76.3 ± 7; $P < 0.05$) and maximum first derivative of the left ventricular pressure (control, 47.9 ± 8.7; Group 1, 46.7 ± 8.8; Group 2, 49.6 ± 10.8 vs. Group 3, 76.6 ± 7.5; $P < 0.05$). The incidence of VF after reperfusion did not differ significantly among these four groups (71.4, 85.7, 57.1, and 85.7% in Groups 1, 2, 3, and control, respectively). This result suggests that the administration of ANP at the time of reperfusion may have the potential to decrease the incidence of PGF after heart transplantation. **Key Words:** Atrial natriuretic peptide—Hypothermic storage—Myocardial reperfusion injury—Primary graft failure.

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Primary graft failure (PGF) is the strongest determinant of perioperative mortality after heart transplantation, and is responsible for up to 42% of perioperative deaths (1). Acute ischemia-reperfusion injury (IRI) with myocardial stunning has been proposed to be a predominant factor in the development of PGF (2). Most donor hearts are stored in a cold preservation solution and transported on ice. Hypothermic storage slows but does not completely arrest cellular metabolism. Consequently, progressive ischemic injury is an inevitable consequence of prolonged storage.

IRI involves damage to cardiomyocytes, vascular smooth muscle, and endothelial cells. When cardiomyocytes are reoxygenated after a prolonged period of energy depletion, severe cytosolic calcium overload and reactivation of energy production result in deleterious hypercontracture, which leads to cell disruption in tissue (3). Recent experimental studies have demonstrated that reoxygenation-induced hypercontracture can be prevented if the contractile apparatus is temporarily blocked during the initial phase of reoxygenation to reestablish normal cytosolic calcium control (4).

Myocardial guanosine 3′, 5′-cyclic monophosphate (cGMP), which reduces the calcium sensitivity of myofilaments (5), is reduced in myocardial cells after prolonged ischemia (6). The stimulation of cGMP synthesis at the time of reoxygenation has an inhibitory contractile effect in reperfused myocardium, and is able to prevent reoxygenation-induced hypercontracture in isolated cardiomyocytes (7), isolated hearts (6), and in situ hearts (8).

Atrial natriuretic peptide (ANP) is known to stimulate the synthesis of the particulate guanylate cyclase, causing a consequent increase in cGMP synthesis. Thus, it is able to protect the myocardium against IRI and can preserve myocardial function.

Based on these findings, it seems likely that ANP could be beneficial in ameliorating PGF in a transplanted heart. Although there is evidence that ANP can have a cardioprotective effect in acute myocardial infarction (9–11) or cardiac surgery (12), its potential role in heart transplantation has not yet been investigated. Therefore, we investigated the ability of ANP to improve the functional recovery of isolated working rat hearts after prolonged

hypothermic storage in an extracellular-based cardioplegic solution.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats were used in the present study. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the US National Institutes of Health (National Institutes of Health publication no. 85–23, revised 1996). The experimental protocol was approved by the Experimental Animals Committee of the Okayama University School of Medicine.

Isolated rat heart model

The composition of the modified Krebs–Henseleit bicarbonate buffer (KHB) used for organ perfusion was as follows (in mM): NaCl, 118.0; $NaHCO_3$, 25.0; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KCl, 4.7; KH_2PO_4, 1.2; and glucose, 11. The pH was 7.4. The KHB was bubbled with 95% oxygen and 5% carbon dioxide gas at 38.0°C to maintain an aortic partial oxygen pressure of >400 mm Hg. It was filtered through a cellulose acetate membrane (pore size 0.45 μm) to remove any particulate contaminants.

The composition of the extracellular-based cardioplegic solution was as follows (in mM): Na^+, 142.0; K^+, 18.5; Mg^{2+}, 18.5; Ca^{2+}, 1.1; HCO_3^-, 1.9; and glucose, 11.1.

We modified and used an isolated, perfused, rat heart apparatus that was previously described by Fujii and associates (13). This circuit was designed to work in two interchangeable conditions, namely the unloaded and loaded modes. In the unloaded mode, the hearts were perfused through the aorta at a pressure of 80 cmH_2O and continued to beat without external work. In the loaded mode, the hearts were perfused in the same fashion, but beat against external force. These hearts were not paced and the coronary effluent was discarded.

The rats were anesthetized with an intraperitoneal injection of pentobarbital (50 mg/kg), and heparin (100 IU/100 g body weight) was injected into the exposed right femoral vein. The hearts were quickly excised and immersed in cold (4°C) modified KHB, and Langendorff perfusion was established. The aorta was cannulated within 1 min after the excision. The pulmonary artery was incised to facilitate coronary drainage. The heart was then perfused in a retrograde manner under the perfusion conditions of the unloaded mode at 38.0°C for 10 min. Subsequently, the changes in heart rate (HR), left ventricular developed pressure (LVDP), and the first derivative of LV pressure (dp/dt max) were monitored under the loaded mode with commercially available software (PowerLab, ADInstruments, Sydney, New South Wales, Australia) using an intraventricular balloon inserted through the mitral annulus that was inflated with distilled water. During the pressure measurement, the left ventricular end-diastolic pressure was maintained at 4 mm Hg using the intraventricular balloon. The coronary flow (CF) was measured by direct collection of coronary effluent dripping from the heart for 1 min.

Study protocol

The study protocol is shown in Fig. 1. Hearts were perfused in the unloaded mode for 10 min followed by the loaded mode for 15 min. During the later interval, we measured the baseline value of HR, LVDP, and dp/dt max. The cardioplegic solution (at 3–4°C) was then infused into the coronary circulation for 1 min from a reservoir located 80 cm above the heart and the hearts were stored on ice (3–4°C) in 100 mL of the same cardioplegic solution for 6 h. At the end of this period, the hearts were remounted on the perfusion apparatus and reperfused in the unloaded mode for 10 min. The apparatus was then switched to the loaded mode and we recorded the aforementioned indices of cardiac function at 1, 5, 10, and 15 min. Data beyond 15 min were not recorded because we observed no further recovery beyond 15 min. The recovery of each parameter was expressed as a percentage of its prestorage value.

The CF and its cGMP concentration were also measured before storage, and at 1 and 15 min of the postreperfusion loaded mode.

The hearts were removed from the apparatus at the end of the experiment. They were heated to 70°C for 14 days, and were then weighed to

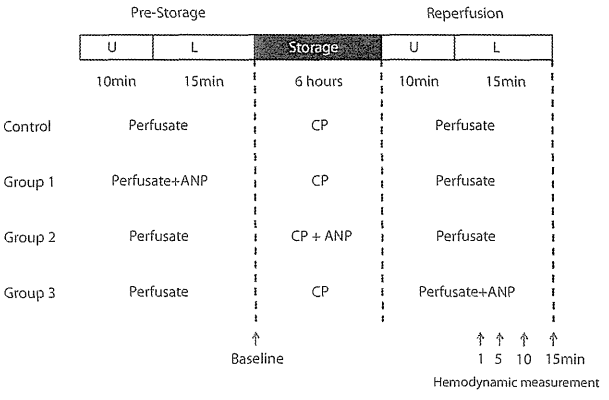

FIG. 1. Experimental protocol.

determine the dry weight of ventricular myocardium. The concentration of cGMP was determined by radioimmunoassay as previously described (14) and was expressed in pmol/g dry weight per min.

We also noted the incidence of ventricular fibrillation (VF) at the time of reperfusion.

The rats were divided into four groups ($n = 7$ in each group). The control hearts were perfused with KHB. To determine the optimal timing for ANP administration, we added alpha-human atrionatriuretic peptide (ANP; Sankyo-Daiichi, Tokyo, Japan) to the perfusate before storage (Group 1), to the cardioplegic solution (Group 2), or to the perfusate during reperfusion (Group 3), using a dose of 0.1 μM. It has been reported that administration of 0.1 μM ANP induces a threefold increase in cGMP release into the coronary effluent without any effect on cardiac function in the isolated rat heart (15).

Exclusion

At the first hemodynamic evaluation, hearts beating at a rate less than 250 beats/min were considered to have experienced myocardial damage during the preparation. These hearts were excluded from the study.

Statistical analysis

All data were expressed as mean ± standard deviation. The statistical analysis was performed using commercially available software (SPSS for Windows; SPSS Japan, Tokyo, Japan). Differences among multiple groups were determined using one-way analysis of variance followed by Scheffe's test. The incidence of VF among groups was compared using the chi-square test. A P value of <0.05 was regarded as statistically significant.

RESULTS

Preischemic data

Table 1 shows the body weight of the rats, HR, CF, dp/dt max, LVDP, and cGMP release in the coronary effluent during the preischemic loaded perfusion. There were no statistically significant differences in HR, CF, dp/dt max, and LVDP. Only Group 1 had a higher release of cGMP in the coronary drainage induced by the administration of ANP.

Postischemic cardiac functional recovery and changes in cGMP

The postischemic recovery of HR, dp/dt max, and LVDP was expressed as a percentage of the preischemic value; the results are listed in Fig. 2. The recovery of LVDP and dp/dt max was better in Group 3 than in the other groups (LVDP: control, 45.5 ± 10.2; Group 1, 47.4 ± 8.8; Group 2, 45.3 ± 12; vs. Group 3, 76.3 ± 7; $P < 0.05$. dp/dt max: control, 47.9 ± 8.7; Group 1, 46.7 ± 8.8; Group 2, 49.6 ± 10.8; vs. Group 3, 76.6 ± 7.5; $P < 0.05$). There was no difference in the recovery of HR (control, 82 ± 4.7; Group 1, 90.3 ± 7.4, Group 2, 87.8 ± 7.6; Group 3, 89 ± 11.2).

The cGMP release into the CF increased after ischemia only in Group 3 (control, 1.31 ± 0.23; Group 1, 1.35 ± 0.15; Group 2, 1.26 ± 0.28; vs. Group 3, 5.32 ± 1.63; $P < 0.05$). There was no difference in the postischemic recovery of CF (control, 79.7 ± 20.1; Group 1, 85.6 ± 9.5; Group 2, 78 ± 10.6; Group 3, 83.6 ± 11).

The postischemic cardiac functional recovery was closely related to the significantly increased cGMP release due to the infusion of ANP at the time of reperfusion.

Incidence of VF after reperfusion

The occurrence of VF after reperfusion was noted in six (85.7%), five (71.4%), six (85.7%), and four (57.1%) rats in the control group, Group 1, Group 2, and Group 3, respectively. There was no significant difference among these groups ($P = 0.552$).

DISCUSSION

The present study showed that the administration of ANP at the time of reperfusion elicited a significant improvement in the acute-phase postischemic recovery of left ventricular function after 6 h of hypothermic storage of the rat heart. This improvement

TABLE 1. *Preischemic data*

	BW(g)	LVDP (mm Hg)	dp/dt max (mm Hg/sec)	HR (beat/min)	CF (mL/min)	cGMP (pmol/dry weight/min)
Control	275 ± 21.5	132.2 ± 9.1	3811.4 ± 378.6	279.3 ± 19.7	9.5 ± 2	1.54 ± 0.25
Group 1	272.7 ± 18.9	127 ± 9.2	3879 ± 410	298 ± 21	10.1 ± 1.2	4.46 ± 0.98*
Group 2	282.3 ± 22.9	128.6 ± 6.5	3965.1 ± 530.9	290.7 ± 23.8	10.4 ± 1.4	1.45 ± 0.32
Group 3	272.9 ± 4.6	135.6 ± 9.3	3936.3 ± 549.3	291.7 ± 24.7	8.4 ± 1.2	1.42 ± 0.24

*$P < 0.05$ Group 1 versus control, Group 2, Group 3.

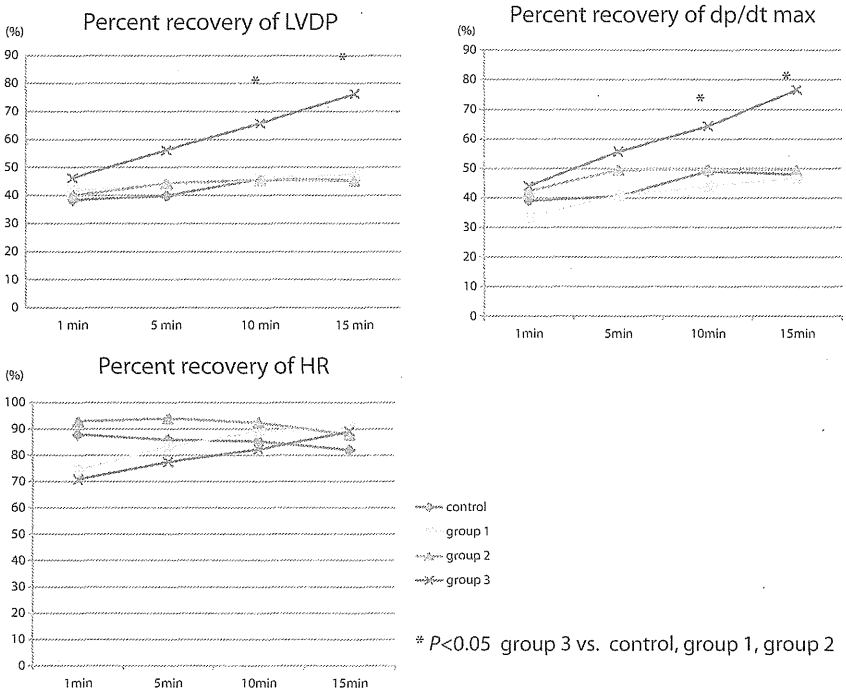

FIG. 2. The postischemic recovery of the first derivative of left ventricular pressure (dp/dt max), heart rate (HR), and left ventricular developed pressure (LVDP) is shown. The recovery of dp/dt max and LVDP was better in Group 3.

was attributed to the increased cGMP release triggered by ANP, as demonstrated by previous investigators (11,15). In contrast, the administration of ANP before ischemia or during cardioplegia was not associated with any significant improvement in the recovery of left ventricular function after reperfusion.

The timing of treatment aimed at increasing cGMP release for protection against hypoxia-reoxygenation or IRI has been controversial. Okawa and colleagues (16) reported that preischemic infusion of ANP elicits myoprotective effects during ischemia-reperfusion in isolated rat hearts. Agulló and colleagues (17) reported that L-arginine supplementation before hypoxia increases cGMP release during reoxygenation and improves functional recovery in isolated rat hearts subjected to 40 min of hypoxia. Recent ischemia-reperfusion studies (6,11) have demonstrated that urodilatin, a member of the natriuretic peptide family, improves functional recovery when administered at the time of reperfusion. Sangawa and colleagues (15) also reported that the administration of ANP at the time of reperfusion after 15 min of normothermic global ischemia improved postischemic recovery; however, no improvement was observed when ANP was administered before ischemia. All of these studies were performed under conditions of acute ischemic heart disease or resuscitation from sudden cardiac arrest; therefore, the ischemic times ranged from only 15 to 60 min.

Besides promoting the synthesis of cGMP, ANP also appears to have an additional cardioprotective effect against IRI in the myocardium. An experimental study has presented evidence for the presence of an independently functioning and local renin-angiotensin system in the heart (18). In an isolated perfused rat heart, angiotensin II was found to exacerbate ischemia-induced ventricular fibrillation and impaired cardiodynamics, whereas these effects were blocked by ANP (19). Morales et al. (20) reported that the direct blocking of the local renin-angiotensin system with angiotensin II receptor antagonists ameliorates myocardial stunning after global ischemia. Therefore, the functional antagonism of angiotensin II may underlie the protective effect of ANP against IRI.

Reperfusion-induced arrhythmia is one of the important factors for IRI. Several mechanisms are believed to be responsible for the development of reperfusion-induced arrhythmia. One of the important mechanisms is considered to be intercellular Ca^{2+} overload, caused by an involvement of H^+/Na^+ and Na^+/Ca^{2+} exchange (21,22). The effect of ANP on reperfusion-induced arrhythmia remains unclear. Takata et al. (23) reported that, in anesthetized dogs subjected to 30 min of left circumflex artery occlusion followed by 60 min of reperfusion, ANP infusion inhibited reperfusion-induced ventricular arrhythmias and preserved the high-energy phosphate content in the inner layer of the ischemic

myocardium. The authors suggested that the beneficial effects of ANP were probably due to its direct effects via cGMP as a stimulator of Na^+/Ca^{2+} exchange, leading to a reduction of intracellular Ca^{2+} overload. However, two other reports failed to detect any favorable effect on ventricular arrhythmias after coronary occlusion in dogs (9), or during reperfusion in the isolated rat heart after 30 min of regional ischemia (24). In the present study, the administration of ANP at the time of reperfusion did not prevent VF. However, as our findings indicated that ANP might reduce reperfusion-induced arrhythmia, we increased the number of rats to 13 in both the control group and Group 3, as a complementary study to determine whether or not a significant difference in the incidence of VF would be observed. We noted that 12 of 13 rats (92%) in the control group and 8 of 13 rats (62%) in Group 3 exhibited VF at the time of reperfusion. The incidence of VF tended to be lower in Group 3 than in the control group, but the difference was not statistically significant ($P = 0.062$). The reason for the disparity between the results of different studies regarding the beneficial effect of ANP on reperfusion-induced arrhythmias is unclear. Differences in the experimental protocol (i.e., the duration of the ischemic periods, the dose of ANP, or the extent of the ischemia) might have affected the results. We believe that further investigation is required to confirm the effect of ANP on reperfusion-induced arrhythmias.

Despite the improvements in the treatment of PGF, it is still associated with high morbidity and mortality (2), and is the most common cause of death within the first month after heart transplantation. It has been reported that a prolonged total graft ischemic time, which accelerates IRI, is one of the risk factors for PGF (25,26). But because of the shortage of donor hearts, the use of marginal hearts that have a prolonged ischemic time may increase the likelihood of PGF. Thus, investigation of the safe storage of donor hearts and the preservation of their ventricular function are becoming increasingly important. The excellent recovery of left ventricular function after 6 h of cold ischemic arrest in the present study indicates that ANP may have a preventive effect against PGF after heart transplantation.

Limitations of the model

There are several limitations to our study. First, we did not use the heart transplant model to evaluate the cardiac function of the rat heart. Therefore, it might be difficult to extrapolate the results directly to heart transplantation. Second, we did not confirm a cause and effect relationship between cGMP and postischemic recovery by using cGMP analogs and antagonists. However, previous studies using isolated rat heart models demonstrated that improved functional recovery, induced by the administration of the natriuretic peptide urodilatin during initial reperfusion after 40 min of ischemia, was reproduced by the cGMP analog 8-bromo-cGMP (6), and that reduction in lactate dehydrogenase release by urodilatin after 60 min of ischemia was abolished by adding the ANP receptor antagonist isatin (11). Third, we used an isolated perfused preparation. Although the preparations were denervated, direct cardiac responses can be studied independently of the systemic effects of ANP. Finally, we used a crystalloid solution in the perfusion circuit. Blood perfusion may induce different results from those of crystalloid perfusion (27). Because each blood component serves different roles during ischemia and reperfusion and might affect the results, we used a simple crystalloid solution in this study.

CONCLUSION

The administration of atrial natriuretic peptide at the time of reperfusion after prolonged hypothermic storage significantly improved left ventricular function after reperfusion, although it did not significantly reduce the incidence of ventricular fibrillation. ANP may be a beneficial adjunct to improve the ventricular function of a donor heart as a means of decreasing the incidence of primary graft failure during heart transplantation.

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