Rapid two-stage Starnes approach in high-risk neonates with Ebstein anomaly

Toshihide Asou, Motoyoshi Kawataki, Yuko Takeda, Hidetsugu Asai, Tsuyoshi Tachibana, Katsuaki Toyoshima, Ki-Sung Kim, and Hideaki Ueda

Abstract

OBJECTIVES: The purpose of this study is to review the short- and long-term outcomes of high-risk neonates with Ebstein anomaly treated with a newly developed rapid 2-stage Starnes procedure, which is aimed at reducing the size of the enlarged right side of the heart.

METHODS: Fifty-two foetuses with Ebstein anomaly were analysed in this study and divided into 2 groups. The control group comprised 25 foetuses, referred to us before 2008, and the study group was composed of 27 foetuses, referred to us after 2009. The right atrial area index was defined as high risk when it was >1.5. We applied our management approach to 6 high-risk neonates in the study group. This approach consisted of reducing the size of the right side of the heart through a 2-stage process: (i) right atrial plication without the use of a bypass and (ii) a Starnes procedure. Cox proportional hazards models were used to evaluate the effects of our management approach on the survival rates of the neonates.

†These authors contributed equally to this study.

© The Author(s) 2020. Published by Oxford University Press on behalf of the European Association for Cardio-Thoracic Surgery.
RESULTS: The mean follow-up period was 7.5 ± 3.3 years. All 6 high-risk neonates in the study group survived. The overall hazard ratio was 0.12 (95% confidence interval of 0.03–0.43) in the study group as compared with the control group ($P = 0.0007$). A Fontan operation was completed in all but 1 case, with the remaining case awaiting a Fontan operation.

CONCLUSIONS: We suggest that a rapid 2-stage Starnes approach can be effective in the treatment of high-risk neonates with Ebstein anomaly.

Keywords: Ebstein anomaly · Neonate · Foetus · Right ventricle exclusion · Volume reduction

INTRODUCTION

The rate of survival of neonates with Ebstein anomaly continues to increase with the improvement in conservative management and the development of novel surgical management approaches. During the 1990s, neonatal mortality ranged from 56% to 85% [1–6]. Today, these outcomes have improved and mortality rates range from 19% to 36% [7–14], as deduced from a review of recent articles. Nevertheless, this is a high mortality rate and the treatment of neonatal Ebstein anomaly continues to be a challenge. To elucidate a solution to this issue, we have focused on high-risk neonates in this study. Among very high-risk foetuses, there may be no survivors. Using the criteria for high-risk neonates proposed by McElhinney of a right atrium (RA) area index score >1.0, 1 study reported only 2 survivors out of 23 high-risk foetuses [7]. Andrew developed a prognostic score (SAS score) in which 5 variables were combined and weighted to obtain a best-guide prognosis [8]; of 12 foetuses in the high-risk category, none survived. Barre et al. [9] also reported 2 survivors and 12 non-survivors triaged by SAS score as high risk. Elzein et al. [14] performed surgical interventions in 5 neonates with a circular shunt, which was considered to be a high-risk variable, and 2 of them survived. Although the selection criteria were different, of 54 neonates associated with high risk, only 8 neonates (14.8%) survived more than 30 days of life [1, 7–11, 14]. Therefore, our target for rescue surgery was a group of patients with high-risk factors who exhibited extreme signs of the disease. Previously, we reported a novel surgical strategy, a rapid 2-stage Starnes procedure [10]. This was a rescue surgery performed within 24 h after birth, triaged based on the foetal echocardiographic findings. Due to this success, we have applied our newly developed procedure to 5 other high-risk neonates. We used an RA area index of >1.5 as a selection criterion for the triage of neonates with high risks [1, 2, 7]. The purpose of this study was to assess the short- and long-term outcomes in these 6 neonates with a severe form of Ebstein anomaly.

PATIENTS AND METHODS

The Institutional Review Board of the Kanagawa Children’s Medical Center Research Ethics Board approved this study (ID: 107-7) on 11 May 2018 and waived the need for patient consent. The medical records of the patients and their mothers were reviewed. We obtained echocardiographic data from a review of stored images whenever possible.

Study design

Celermajer et al. [1, 2] developed the RA area index and demonstrated it as a significant predictor to death when >1.5. RA area index was obtained by calculation using echocardiographic measurements (Fig. 1). Twenty-five foetuses with Ebstein anomaly were referred to us before 2008. We divided them into 2 groups depending on the RA area index, <1.5 vs >1.5, and analysed the Kaplan–Meier survival (Fig. 2). A significant difference existed between the 2 curves, with a hazard ratio of 7.56 ($P = 0.0034$). Considering these poor survival outcomes, we defined the foetuses with RA index >1.5 as a high-risk group. Abrupt decline in survival in the high-risk group was prominent, with foetuses dying in utero or immediately after birth. Since 2009, therefore, the strategy of the treatment of neonatal Ebstein anomaly changed from conservative to planned aggressive. A flow diagram depicting the perinatal outcomes in 52 foetuses including 25 before 2008 (control) and 27 after 2009 (study) is shown in Fig. 3.

Management approach during foetal life. A multidisciplinary team, which included obstetricians, neonatologists, paediatric cardiologists and paediatric cardiac surgeons, discussed a
plan for the management of the foetuses. After confirming the diagnosis, frequent follow-up foetal echocardiograms were performed to assess the progress of the disease. At the same time, we provided family counselling and obtained informed consent. To minimize the chance of not being able to perform the surgical intervention in the appropriate time frame, we planned for an elective Caesarean section at the gestational age of 38 weeks. Depending on the haemodynamic and metabolic instabilities of the newborn, the first stage of the procedure was performed within 24 h of birth.

Surgical approach

The main purpose of the rapid 2-stage approach is resuscitating the severely unstable high-risk neonates with Ebstein anomaly without the use of cardiopulmonary bypass as a first-stage procedure and delaying the risk of the major open heart surgery after stabilization of these patient’s physiology as a second-stage procedure.

First stage. The main goal of the first stage of the procedure for high-risk neonates with Ebstein anomaly is to stabilize haemodynamic and metabolic derangements in a minimally invasive manner without the use of a cardiopulmonary bypass [10]. Our surgical management strategy was associated with the concept that the enlarged right side of the heart compressed the left ventricle (LV), effectively limiting the filling of the LV. Consequently, the first stage of our management approach was aimed at reducing the right side of the heart as much as possible in a minimally invasive manner.

The first stage of the procedure consisted of the following steps: (i) ligation of the main pulmonary artery (PA) to abolish a circular shunt and noting the abrupt rise of systemic arterial pressure by 5–10 mmHg, (ii) plication or imbrications of the dilated right atrium, (iii) creation of a pulmonary blood flow source with a modified Blalock–Taussig shunt using a small-calibre graft (<3.0 mm in diameter, W. L. Gore & Associates, Inc., Flagstaff, Arizona, USA) interposed between the brachiocephalic artery and the PA or bilateral PA banding (exceptional) and (iv) ligation of the duct after modified Blalock–Taussig shunt. On the contrary, the duct was left open with an intravenous drip infusion of Prostaglandin when both PAs were banded. The first-stage palliative procedure was performed within 24 h of an elective Caesarean section.

Second stage (modified Starnes). Once the first stage of the procedure had stabilized the patient’s haemodynamics, we determined the appropriate timing for the second stage. This was done by observing the haemodynamic and metabolic changes...
via close follow-up of patients and frequent echocardiograms that focused on the paradoxical septal motion, which disappeared immediately after the first stage but reappeared within several hours or days. With the appearance of paradoxical septal motion, peripheral perfusion became poor; once this occurred, we decided to proceed to the second stage. With the standard cannulation for systemic perfusion and venous drainage, cardiopulmonary bypass was commenced and all procedures were performed with the heart beating. We used transoesophageal echocardiography in all 6 neonates but 1 to monitor cardiac function and detect microbubbles in the LV. Aortic venting was also used to remove air from the cardiac chambers. During the bypass, the RA was incised longitudinally and the right ventricle (RV) cavity was made smaller using the technique of internal RV exclusion described below. Then, a modified Starnes procedure [15–17] was performed to close the tricuspid valve using a glutaraldehyde (0.625%)-treated pericardial patch with a 3-mm fenestration. The RA incision was trimmed and closed.

Internal right ventricle exclusion technique. We did not perform the RV exclusion technique on our first patient [10]. The residual RV cavity was not particularly large but could have been problematic. Moving forwards, we applied a new ‘internal RV exclusion’ method to reduce the RV cavity as much as possible without being too invasive. Through the tricuspid valve, 2 pairs of pledgedt stitches were anchored to the interventricular septum at both the RV outflow and inflow tracts, and these stitches penetrated the RV free wall from inside to outside. These stitches were tied so that the RV free wall and the interventricular septum were approximated to each other (i.e. the interventricular septum and the RV free wall were held together as a thicker structure, becoming a part of the LV free wall). We believe that internal RV exclusion might be simpler and less invasive than the original procedure [15–17].

Statistical analysis
All statistical analyses were performed with EZR (version 1.41, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 2.6-1; The R Foundation for Statistical Computing, Vienna, Austria) [18, 19]. More precisely, it is a modified version of R Commander designed to add statistical functions frequently used in biostatistics. We generated Kaplan–Meier survival curves for the different clinical subgroups. The estimated postconception age was used to determine the survival curves for the foetuses. When an elective termination of pregnancy occurred, the foetus was censored as it lost follow-up. A log-rank test was performed to compare the survival of the 2 groups. The Cox regression model was used to investigate the effect of the RA area index and the management approach on survival rates in the cohort of neonates with Ebstein anomaly.

RESULTS
Outcomes of rapid 2-stage Starnes procedure
Outcomes in the perinatal period. Before 2008, there was only one early survivor among 8 live-born patients. This baby later died of congestive heart failure at 50 days of life. As shown in Fig. 3, however, after 2009, there were 6 survivors in the high-risk group with an RA area index of >1.5. These neonates in the study group were managed surgically with our newly developed management approach. Table 1 summarizes the preoperative characteristics of the 6 neonates who met the criteria for and underwent the rapid 2-stage Starnes procedure. Foetal echocardiography showed an RA area index of >1.5 and a low velocity of tricuspid regurgitation of <3.0 m/s across the tricuspid valve and pulmonary regurgitation, leading to a circular shunt in all 6 high-risk neonates. All but 1 neonate were delivered by Caesarean section. All were intubated immediately after birth due to respiratory distress (Table 1). We noted low cardiac output syndrome, with a maximum serum lactate level of 7.3 ± 3.1 mmol/l and a minimum base excess of -7.0 ± 5.3 before the first stage (Table 2).

| Case | GA at birth | RA area index | PR | TR (m/s) | Delivery | BW (g) | Intubated (min) |
|------|-------------|---------------|----|----------|----------|--------|----------------|
| 1    | 38w 5d      | 1.9           | +  | 2.0      | Vaginal  | 2700   | 4              |
| 2    | 36w 0d      | 2.5           | +  | 2.5      | CS       | 2664   | 10             |
| 3    | 39w 0d      | 1.8           | +  | 2.6      | CS       | 3006   | 3              |
| 4    | 37w 3d      | 1.6           | +  | 2.7      | CS       | 2168   | 5              |
| 5    | 36w 6d      | 1.7           | +  | 3.0      | CS       | 2314   | 3              |
| 6    | 38w 2d      | 2.1           | +  | 2.5      | CS       | 2786   | 4              |
| Mean (SD) | 19 (0.3)    | 2.6 (0.3)     |    | 2506 (377)|         |        |                |
| Median | 38w 0d      | 1.9           |    | 2.6      |          | 2507   | 4              |

BW: body weight; CS: caesarean section; d: day; GA: gestational age; PR: pulmonary regurgitation; RA: right atrium; SD: standard deviation; TR: tricuspid regurgitation; w: week.
Within several hours or days of the completion of the first stage, the serum lactate level gradually increased, and the septal motion started to become paradoxical on the echocardiogram. The appropriate time to begin the second stage was thus determined by observing the signs of low cardiac output and the appearance of the paradoxical septal motion. Concerned with the duration of times between 2 stages, there appeared to be 2 patterns: 1 for a shorter, 15–25 h (case 3-6 in Table 2), and the other for a longer, several days or more.

**Second stage.** All 6 of the high-risk neonates underwent the rapid 2-stage Starnes approach. There were 6 neonatal survivors out of 7 high-risk live-borns with 1 palliative care in the study group and only one survivor out of 8 live-born babies in the control group, showing an early survival rate of 6/7 (85.7%) and 1/8 (12.5%), respectively (P = 0.004). A bidirectional cavopulmonary shunt (BCPS) was performed at a median age of 3.7 months in all 6 patients, and all but 1 patient completed the staged Fontan at a median age of 16 months. The remaining patient is awaiting a Fontan operation (Table 2). The overall hazard ratio in the study group was 0.12 (95% confidence interval 0.03–0.43) compared with the control group (P = 0.0007) (Fig. 4). After the follow-up period of 7.5 ± 3.3 years (range 1.2–10.4 years, median 8.5 years), all patients are currently in the New York Heart Association class I.

**Changes in paradoxical septal motion.** One of the most important echocardiographic findings in this study may be a change in septal motion, from paradoxical to normal during each procedure and vice versa after the procedure (Video 1). Consequently, echocardiographic changes were compatible with clinical sequelae. After the first stage of our management approach, the septal motion and haemodynamic stabilization were normalized, which shows that the serum lactate level was also normalized for a while. Several hours or days after the first stage, however, the septal motion gradually became paradoxical and the serum lactate level increased. In contrast, the second-stage procedure resulted in a completely normalized septal motion, with an improvement of the haemodynamics in all but 1 patient (case 4).

**Case 4.** The patient’s mother was referred to us at the gestational age of 31 weeks, with an RA area index of 1.6 on her foetal echocardiogram. When she came to us for further observation, however, the foetal status appeared to be dangerous, which meant that an emergency Caesarean section had to be performed.

---

**Table 2:** Preoperative conditions of high-risk patients and timing of surgical intervention

| Case | Maximum lactate (mmol/l) | Minimum BE | First stage (h) | Second stage (days) | Age at BCPS (months) | Age at TCPC (months) |
|------|--------------------------|------------|----------------|---------------------|----------------------|----------------------|
| 1    | 4.3                      | -5.0       | 16             | 12                  | 4.3                  | 12                   |
| 2    | 12.7                     | -17.0      | 20             | 7                   | 4.6                  | 14                   |
| 3    | 5.9                      | -3.0       | 5              | 1                   | 3.3                  | 16                   |
| 4    | 6.7                      | -8.1       | 3              | 0                   | 2.2                  | 40                   |
| 5    | 5.1                      | -6.0       | 4              | 0                   | 3.5                  | 18                   |
| 6    | 9.0                      | -2.6       | 22             | 1                   | 4.0                  | Waiting              |
| Median| 6.3                      | -5.5       | 10             | 1                   | 3.7                  | 16                   |

BCPS: bidirectional cavopulmonary shunt; BE: base excess; TCPC: total cavopulmonary connection.

---

![Figure 4: Overall outcomes of Kaplan–Meier survival. The survival of the study group (n = 27) was remarkably improved compared with that of the control group (n = 25) as a whole. The HR for foetuses in the study group, compared with the control group, was 0.12 (95% CI 0.03–0.43; P = 0.0007). These excellent results could be attributed to the newly developed, rapid 2-stage Starnes procedure. CI: confidence interval; HR: hazard ratio.](image)

**Video 1:** Remarkable improvement in the echocardiographic septal motion in the video of case 6. In the first half of the video, the paradoxical septal motion is prominent immediately after birth. The video in the latter half shows the remarkable improvement of the septal motion after the second stage.
performed to save the baby’s life. After this, the RA area index increased to 2.7, which signalled foetal hydrops with pericardial effusion and myocardial oedema. The LV ejection fraction (EF) was ~10% with severely affected paradoxical septal motion. After the emergency Caesarean section, the baby was carried to the operating room for the first stage of the procedure; the paradoxical septal motion improved, but only temporarily. The haemodynamics became unstable shortly after the first stage of the procedure. Eighteen hours later, we carried the baby to the operating room to perform the second stage of the procedure, which led to a normalized septal motion. However, the LV EF was unchanged at ~10%. To restore the LV systolic function, 7 days of ventricular assist device (VAD) assistance was required. The modified Blalock-Taussig shunt was used as a PA blood source. As the respiratory function of the native lungs was kept stable, the VAD could work well without an oxygenator. The LV EF improved to 50% on the seventh day, and then, the baby was successfully weaned from VAD. However, the patient was respiratory dependent because of congestive heart failure, which was in turn caused by a high PA blood flow due to their small body weight (<2.2 kg). Extubation became possible only after 2 months. BCPS was performed at the age of 77 days; this process helped result in volume unloading, and the patient was successfully extubated 2 days after BCPS. In addition, BCPS was performed via a right thoracotomy due to a superficial sternal wound infection. The patient was discharged from hospital on the 15th postoperative day.

DISCUSSION

A newly developed rapid 2-stage Starnes approach was successfully applied to 6 high-risk neonates who were prenatally diagnosed with Ebstein anomaly. This approach resulted in excellent survival rates, with no deaths. All but 1 patient completed the Fontan operation, and the remaining 1 is awaiting Fontan. The overall hazard ratio in the study group was 0.12 (P = 0.0007), as compared with the control group (Fig. 4). Thus, our management approach can be effective in high-risk neonates with Ebstein anomaly.

Six articles in this past decade that focused on high-risk neonates with Ebstein anomaly reported a survival rate of ~10–20% of patients that survived more than 30 days [7–11, 14]. Our approach in the treatment of high-risk and critically ill neonates with Ebstein anomaly is feasible and thus holds promise.

The possible mechanism underlying the successful surgery for high-risk neonates with Ebstein anomaly needs to be addressed. Excessive RV volume loading impedes LV filling and impairs global ventricular function through the mechanism of ventricular interdependence [21, 22]. In this regard, it is important to reduce the size of a dilated right side of the heart to improve LV filling and increase cardiac output. To achieve maximum benefits, the internal RV exclusion technique was added to reinforce the planned approach, including a scheduled delivery to perform the second stage of the procedure, which led to a normalized septal motion. However, the LV EF was unchanged at ~10%. To restore the LV systolic function, 7 days of ventricular assist device (VAD) assistance was required. The modified Blalock-Taussig shunt was used as a PA blood source. As the respiratory function of the native lungs was kept stable, the VAD could work well without an oxygenator. The LV EF improved to 50% on the seventh day, and then, the baby was successfully weaned from VAD. However, the patient was respiratory dependent because of congestive heart failure, which was in turn caused by a high PA blood flow due to their small body weight (<2.2 kg). Extubation became possible only after 2 months. BCPS was performed at the age of 77 days; this process helped result in volume unloading, and the patient was successfully extubated 2 days after BCPS. In addition, BCPS was performed via a right thoracotomy due to a superficial sternal wound infection. The patient was discharged from hospital on the 15th postoperative day.

CONCLUSIONS

We found that the planned management strategy, focusing on the reduction in the size of the right side of the heart, led to improving LV diastolic function and LV pump performance and thus yielded excellent short- and long-term outcomes for high-risk neonates with Ebstein anomaly.

ACKNOWLEDGEMENTS

The authors are significantly indebted to their multidisciplinary team members, discussed in the paper, for their contribution to decision-making concerning foetuses with Ebstein anomaly. The authors also would like to thank Tom R. Karl for his valuable comment on an earlier draft and Albert T. Lopolisa for helping prepare video imaging.

Conflict of interest: none declared.
Author contributions

Toshihide Asou: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Visualization. Motoyoshi Kawataki: Data curation; Methodology; Project administration; Visualization. Yuko Takeda: Data curation; Methodology. Hidetsugu Asai: Data curation; Methodology. Tsuyoshi Tachibana: Methodology. KatsukiToyoshima: Data curation; Methodology; Validation. Ki-Sung Kim: Data curation; Investigation; Methodology; Visualization. Hideaki Ueda: Supervision.

Reviewer information

The European Journal of Cardio-Thoracic Surgery thanks René Prêtre, Shunji Sano and the other anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] Celermajer DS, Cullen S, Sullivan ID, Spiegelhalter DJ, Wyse RKH, Deanfield JE. Outcome in neonates with Ebstein’s anomaly. J Am Coll Cardiol 1992;19:1041–6.
[2] Celermajer DS, Bull C, Till JA, Cullen S, Vassilikos VP, Sullivan ID et al. Ebstein’s anomaly: presentation and outcome from fetus to adult. J Am Coll Cardiol 1994;23:170–6.
[3] Hornberger LK, Sahn DJ, Kleinman CS, Copel JA, Reed KL. Tricuspid valve disease with significant tricuspid insufficiency in the fetus: diagnosis and outcome. J Am Coll Cardiol 1991;17:167–73.
[4] Sharland GK, Chita SK, Allan LD. Tricuspid valve dysplasia or displacement in intrauterine life. J Am Coll Cardiol 1991;17:944–9.
[5] Yetman AT, Freedman RM, McCrindle BW. Outcome in cyanotic neonates with Ebstein’s anomaly. Am J Cardiol 1991;61:52–54.
[6] Starnes VA, Ptlick PT, Bernstein D, Griffin ML, Choy M, Shumway NE. Ebstein’s anomaly appearing in the neonate: a new surgical approach. J Thorac Cardiovasc Surg 1991;101:1082–7.
[7] McElhinney DB, Salvin JW, Colan SD, Thiagarajan R, Crawford EC, Marcus EN et al. Improving outcomes in fetuses and neonates with congenital displacement (Ebstein’s malformation) or dysplasia of the tricuspid valve. Am J Cardiol 2005;96:582–6.
[8] Andrews RE, Tibby SM, Sharland GK, Simpson JM. Prediction of outcome of tricuspid valve malformations diagnosed during fetal life. Am J Cardiol 2008;101:1046–50.
[9] Barre E, Durand I, Hazefzet T, David N. Ebstein’s anomaly and tricuspid valve dysplasia: prognosis after diagnosis in utero. Pediatr Cardiol 2012;33:1391–6.
[10] Kajihara N, Asou T, Takeda Y, Kosaka Y, Onakato Y, Miyata D et al. Rapid two-stage Starnes procedure for a symptomatic neonate with Ebstein’s anomaly. Ann Thorac Surg 2010;90:2073–5.
[11] Tsukimori K, Morihana E, Fusazaki N, Takahata Y, Oda S, Kado H. Critical Ebstein’s anomaly in a fetus successfully managed by elective preterm delivery and surgical intervention without delay after birth. Pediatr Cardiol 2012;33:343–6.
[12] Davies RR, Pasqualetti SK, Jacobs ML, Jacobs JJ, Wallace AS, Pizarro C. Current spectrum of surgical procedures performed for Ebstein’s malformation: an analysis of The Society of Thoracic Surgeons Congenital Heart Surgery database. Ann Thorac Surg 2013;96:1703–10.
[13] Freud LR, Escobar-Diaz MC, Kalish BT, Komarlu R, Puchalski MD, Jaeggi ET et al. Outcomes and predictors of perinatal mortality in fetuses with Ebstein anomaly of tricuspid valve dysplasia in the current era: a multicentre study. Circulation 2015;132:481–9.
[14] Elzbin C, Subramanian S, Ilbawi M. Surgical management of neonatal Ebstein’s anomaly associated with circular shunt. World J Pediatr Congenit Heart Surg 2019;10:116–20.
[15] Sano S, Ishino K, Kawada M, Kasahara S, Kohimoto T, Takeuchi M et al. Total right ventricular exclusion procedure: an operation for isolated congestive right ventricular failure. J Thorac Cardiovasc Surg 2002;123:640–7.
[16] Takagaki M, Ishino K, Kawada M, Ohtsuki S, Hirota M, Todorita T et al. Total right ventricular exclusion improves left ventricular function in patients with end-stage congestive right ventricular failure. Circulation 2003;108(Suppl 1):II226–9.
[17] Sano S, Fuji Y, Kasahara S, Kuroko Y, Tateishi A, Yoshizumi K et al. Repair of Ebstein’s anomaly in neonates and small infants: impact of right ventricular exclusion and its indications. Eur J Cardiothorac Surg 2013;45:449–55.
[18] Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant 2013;48:452–8.
[19] The Comprehensive R Archive Network. https://cran.r-project.org/ (10 December 2019, date last accessed).
[20] Gravett C, Eckert LO, Gravett MG, Dudley DJ, Stringer EM, Bodjick T et al. Non-reassuring fetal status: case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2016;34:6084–92.
[21] Anastasiadis K, Antonitsis P, Westaby S. Physiology of the failing right heart. In: Anastasiadis K, Westaby S, Antonitsis P (eds). The Failing Right Heart. Heidelberg: Springer International Publishing, Switzerland, 2015, 15–32.
[22] Fukamachi K, Asou T, Nakamura Y, Oe M, Sakamoto M, Kishizaki K et al. Effects of left heart bypass on right ventricular performance. Evaluation of the right ventricular end-systolic and end-diastolic pressure-volume relation in the in situ normal canine heart. J Thorac Cardiovasc Surg 1990;99:275–34.