

Predictors of Pericardial Effusion in Patients Undergoing Pulmonary Artery Banding

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Abstract:	<p>Background. Although pulmonary artery banding (PAB) is a common palliative procedure for pediatric heart malformation, there are concerns of pressure overload and concomitant immune reactions in the right ventricle causing post-surgical complications such as pericardial effusion. At this time, no clear guidelines as to potential risk factors or procedural contraindications have been widely disseminated. Therefore, a study was undertaken to examine wide-ranging factors to find potential biomarkers for post-surgical PE formation risk.</p> <p>Methods. A retrospective study was conducted on all cardiac surgeries conducted over an 8-year period and the main inclusion criterion was PE development after PAB that required surgical drainage. 9 patients were then analyzed against a control group of 45 patients with respect to body measurements, concomitant surgeries, genetic screens, lab tests and cardiac function parameters.</p> <p>Results. Trisomy 21 was strongly associated with development of severe PE (requiring surgical drainage) after PAB and postoperative serum albumin levels in trisomy 21 patients were associated with PE development. Other parameters showed no significant correlation with PE development.</p> <p>Conclusions. Our data indicates a strong association between trisomy 21 and PE</p>

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	requiring drainage after PAB which is in line with translational research findings. Pressure overload from PAB may play a role in the formation of severe PE that is exacerbated by cardiac structural defects commonly associated with trisomy 21. Surgical teams should therefore use caution and plan to implement drainage in PAB cases, and postoperative serum albumin may serve as a useful biomarker for PE formation.

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Title.

Predictors of pericardial effusion in patients undergoing pulmonary artery banding

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Abstract

Background.

Although pulmonary artery banding (PAB) is a common palliative procedure for pediatric heart malformation, there are concerns of pressure overload and concomitant immune reactions in the right ventricle causing post-surgical complications such as pericardial effusion. At this time, no clear guidelines as to potential risk factors or procedural contraindications have been widely disseminated. Therefore, a study was undertaken to examine wide-ranging factors to find potential biomarkers for post-surgical pericardial effusion formation risk.

Methods.

A retrospective study was conducted on all cardiac surgeries conducted over an 8-year period and the main inclusion criterion was pericardial effusion development after PAB that required surgical drainage. 9 cases were then analyzed against a control group of 45 cases with respect to body measurements, concomitant surgeries, genetic screens, lab tests and cardiac function parameters.

Results.

Trisomy 21 was strongly associated with development of severe pericardial effusion after PAB and postoperative serum albumin levels in trisomy 21 patients were associated with pericardial effusion development. Other parameters showed no significant correlation with pericardial effusion development.

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4 *Conclusions.*

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6 Our data indicates a strong association between trisomy 21 and pericardial effusion requiring
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8 drainage after PAB which is in line with translational research findings. Pressure overload
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10 from PAB may play a role in the formation of severe pericardial effusion that is exacerbated
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12 by cardiac structural defects commonly associated with trisomy 21. Surgical teams should
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14 therefore use caution and plan to implement drainage in PAB cases, and postoperative serum
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16 albumin may serve as a useful biomarker for pericardial effusion formation.
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23 (249words)
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Introduction:

Pulmonary artery banding (PAB) is a common palliative procedure for cardiac malformations with shunt-related pulmonary overflow, especially in low birth weight infants. However, animal modeling has shown that pressure overload as a consequence of PAB accelerates inflammation in the right ventricular myocardium which may lead to pericardial effusion production [1-2]. Such a result may lead to undesirable surgical outcomes if drainage is delayed [3-5]. As its etiology is poorly understood, postoperative pericardial effusion is often reported as post pericardiotomy syndrome (PPS) and the reported incidence varies widely [6]. As PPS describes any immune-mediated reaction to post-surgical trauma to the pericardium, precise PPS diagnoses are therefore difficult because of overlapping definitions [7-8]. A preliminary analysis of our institutional experience showed that the most prevalent procedure related to pericardial effusion was PAB. Therefore in this study, we looked exclusively into PAB cases to elucidate the predictors of postoperative pericardial effusion requiring drainage and tested multiple factors associated with the surgeries, including genomic screening, operation time and blood testing data.

Materials and Methods:

As a preliminary analysis, we reviewed all cardiac surgeries (532 cases) performed at the University of Tsukuba Hospital for structural congenital heart disease between April 2008

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3 and July 2016. As a need for drainage can be taken as a measure of pericardial effusion
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6 severity, the main inclusion criterion was pericardial effusion after PAB which required
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9 drainage. From a safety and reliable outcome perspective, our first choice for pericardial
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12 effusion after cardiac surgery is surgical drainage. In these cases, especially when the effusion
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15 envelops the heart in the pericardial cavity, we prefer to create a small reopening of the
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18 surgical site incision rather than use other interventional drainage techniques (such as
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20 pericardiocentesis). Nineteen cases were selected from the larger patient pool with 45
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23 non-drainage cases serving as control. Clinical data were reviewed retrospectively. Data
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25
26 collected for comparison included gender, age, height, weight at PAB, and trisomy 21 for
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29 patient characteristics. Detailed data for concomitant procedures (arch repair for coarctation
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31 or interruption of the aortic arch), approach (lateral thoracotomy or median sternotomy), site
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34 of PAB (main or bilateral pulmonary arteries), and, if main, length of the banding tape were
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37 collected for analysis. Operation time, amount of bleeding, and in/out water balance per body
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40 weight during PAB were collected as surgical data. Daily water balance (per body weight),
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43 urine amount, and amount of chest tube drainage were also investigated for the first through
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46 third postoperative days. Maximum postoperative doses of dopamine and/or epinephrine, and
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49 peak serum lactate levels (LAC) were collected to assess cardiac function. Minimum values
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52 of serum albumin (ALB) as well as maximum values of blood urea nitrogen (BUN),
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55 creatinine (CRE), white blood cell count (WBC), and C-reactive protein (CRP) were also
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6 Standard descriptive statistics were used to summarize the data and are expressed as
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8 median with range. Group comparisons were performed using Mann-Whitney U testing since
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10 the data were not normally distributed. Categorical variables are expressed as frequency with
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12 percentage. A p value < 0.05 was taken to indicate statistical significance. Statistical analysis
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14 was performed using SPSS statistical software (version 22, IBM SPSS Inc., Armonk, NY).
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16 Informed consent was waived because of our retrospective study design and the study was
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18 approved by the Institutional Review Board for Ethics in Human Subject Research of the
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26 University of Tsukuba Hospital (Approval No. H29-84).
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32 **Results:**

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34 Postoperative pericardial effusion which required drainage occurred in 19 out of 532
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36 cases (3.6%) and among these, 10 pericardial effusion incidences were after PAB (10/60 cases,
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38 16.7%) held during the same period. Five incidents were after closures of isolated ventricular
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40 septal defects (5/90cases, 5.6%) with the other 4 incidents concomitant with 4 different
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42 procedures (repair of atrial septal defect, atrioventricular septal defect, systemic-pulmonary
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44 shunt for tetralogy of Fallot, and mitral valve replacement). One case with trisomy 18, one
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46 case with massive pleural effusion and ascites since the fetal period, and one case that had
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48 mediastinitis after PAB were excluded from the study. Three cases that underwent
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4 cardiopulmonary bypass for concomitant procedures were also excluded. In total, we
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6 experienced 54 cases of PAB and all procedures were performed as the first palliative surgery
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8 without using cardiopulmonary bypass. Among 54 cases, 9 developed eventual moderate to
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10 severe amount of pericardial effusion after removing the chest tube and required surgical
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12 drainage. We compared the perioperative factors between these 9 cases (pericardial effusion
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14 group) with 45 other cases that did not develop pericardial effusion (No pericardial effusion
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21 group).

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23 The perioperative factors between 9 cases that required surgical drainage for pericardial
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25 effusion and 45 cases that did not develop pericardial effusion were compared. All absolute
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27 data for each factor are shown in Table 1-2. The most notable finding was the higher
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29 incidence of trisomy 21 within the pericardial effusion group, with 6 out of 9 cases in the
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31 pericardial effusion group and 10 out of 45 in the No pericardial effusion group ($p = 0.008$)
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38 (Table 1). Minimum values of ALB after PAB were lower in the pericardial effusion group
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40 compared to the No pericardial effusion group ($p = 0.009$) while pre-PAB baseline values did
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42 not differ between the groups. This difference in minimum ALB after PAB disappeared when
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44 we isolated values from the 38 cases without trisomy21 (Table 2). Other perioperative
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46 parameters did not differ between groups. Taken together, this data indicates that genetic
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48 screening for trisomy 21 may be an important pre-surgical biomarker for potential
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50 development of pericardial effusion after PAB and that postoperative serum albumin may be a
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4 useful indicator of pericardial effusion for trisomy 21 patients who must undergo PAB. Two
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7 out of the 16 cases with trisomy 21 had hypothyroidism before PAB and 6 cases developed
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10 hypothyroidism soon after PAB. Three of the cases with hypothyroidism were in the
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12 pericardial effusion group (3/6 cases), and the other 5 were in the No pericardial effusion
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15 group (5/10 cases).
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21 **Comment:**
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23 PAB has been largely abandoned in leading cardiac centers since the advantages of
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26 early primary repair for congenital heart disease became clear. Nevertheless, for immature
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29 patients with low birth weight and serious conditions due to complex cardiac malformations,
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32 the relatively low invasiveness of PAB makes it a singular choice for palliative control of
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35 pulmonary blood flow that also prevents pulmonary vascular obstructive disease. According
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38 to the 2014 annual report by the Japanese Association for Thoracic and cardiovascular
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41 Surgery (JATS), there were 661 PAB performed mostly on newborns and infants, and within
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44 the “main procedure” classification, it was the most frequently selected in Japan for
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47 congenital heart disease even surpassing the second-place (549 cases) systemic-pulmonary
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50 (SP) shunt procedure [9].

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52 However, frequent use may not be indicative of superior outcome. Our experience
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55 showed a high incidence of postoperative pericardial effusion with PAB. While no literature
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4 has clearly described PAB as a risk factor of postoperative pericardial effusion, hemodynamic
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6 and mechanical stress changes accompanying PAB might play a key role in formation of
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9 postoperative pericardial effusion. Recently, the literature reports an activated inflammatory
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12 process in the RV myocardium after pressure overload from animal experiments [1-2]. Luite
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14 and colleagues suggested from their murine PAB model that pressure overload leads to right
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17 ventricular accumulation and increased activity of cardiac mast cells which are known as a
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20 component of the inflammatory response in adverse ventricular remodeling [1]. Earlier animal
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23 experiments also suggest that multiple molecular mechanisms (such as proteasomal changes
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26 and proteins like CYLD) play a synergistic role in this adverse remodeling [10]. Dewachter
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29 and colleagues concluded from their canine PAB model that acute afterload-induced RV
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32 failure from PAB is associated with increased myocardial expression of inflammatory
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35 cytokines and infiltration of neutrophils and macrophages [2]. Although the exact
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38 pathogenesis of postoperative pericardial effusion still remains unclear, underlying
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41 inflammation, autoimmune processes and molecular mechanisms may play a pivotal role in
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44 this clinical presentation [7-8].

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46 Interestingly, the proportion of patients with trisomy 21 was high in the pericardial
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49 effusion group. Since there was no difference between groups when we investigated the
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52 values exclusively on patients without trisomy 21, postoperative minimum ALB values
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55 became a trisomy-associated risk factor instead of an independent one. Therefore, we could
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4 conclude that the presence of trisomy 21 is associated with increased likelihood of
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6 PAB-induced pericardial effusion that requires surgical drainage. Among various risk factors
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9 which have been reported [11-13], a recent high volume cohort study first pointed out trisomy
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11 21 as an independent risk factor predicting postoperative pericardial effusion [14]. In trisomy
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13 21 cases, more popularly known as Down syndrome (DS), pericardial effusion had often been
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15 reported with co-morbidities such as hypothyroidism, celiac disease, infectious disease, and
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17 transient abnormal myelopoiesis [15-16]. In a critical study, however, Concolino and
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19 colleagues showed a significant increase in the prevalence of isolated pericardial effusion in
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21 DS individuals apart from any associated disease or cardiac malformations [17]. From this
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23 finding, Elias and colleagues speculated that cardiac surgery and the resulting inflammatory
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25 process may provide the trigger to develop a significant postoperative pericardial effusion in
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27 children with DS who suffer from a greater propensity to develop pericardial effusion, in
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29 general [14].
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40 It is well known that DS, in addition to cardiac malformations with shunt-related
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42 pulmonary overflow, contains a higher potential for developing pulmonary vascular
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44 obstructive disease [18]. One of the most common shunt-related cardiac malformations
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46 associated with DS is the atrioventricular septal defect (AVSD) so our therapeutic strategy in
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48 this case is to achieve precision repair via PAB as an initial palliative in the neonate period to
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50 improve immediate condition and prevent the development of pulmonary vascular obstructive
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4 disease. We then perform full cardiac repair within the infancy period. Therefore, our
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6 experience with high pericardial effusion incidence after PAB might be due to the fact that we
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8 are performing PAB on DS-associated AVSD which biases outcomes to pericardial effusion
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12 (Figure 1).

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15 There are several limitations to this study, including the small number of patients
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17 with pericardial effusion and retrospective nature of the study. There is a potential for
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19 selection bias in exclusively analyzing severe cases (which may exclude true prevalence)
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21 since we limited the study cohort to pericardial effusion cases that required drainage. In less
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23 severe cases, pericardial effusion can be self-limiting or spontaneous resolution can occur
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25 while first-line treatments such as aspirin, non-steroidal anti-inflammatory agents, and
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27 corticosteroids are commonly used in less severe cases when hemodynamics are not
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29 threatened [12].
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38 In conclusion, based on our observations and those of other investigators, patients
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40 with DS are prone to develop pericardial effusion after PAB that requires surgical drainage.
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42 Postoperative serum albumin may play a role as a biomarker of pericardial effusion formation
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44 in DS patients and should be considered in the recovery plan as an essential lab test.
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51 **Conflicts of interest**

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54 The authors declare that they have no conflict of interest.
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Table 1. Comparison of clinical characteristics and perioperative parameters in patients with or without pericardial effusion who underwent PAB

	pericardial effusion (n=9)	No pericardial effusion (n=45)	p value
patient characteristics			
Male sex, n (%)	4(44.4%)	19(42.2%)	0.90
Age at PAB (days)	24(6-53)	13(3-147)	0.60
height at PAB (cm)	48(43.8-54.0)	48.0(36.0-61.3)	0.81
weight at PAB (g)	2935(2250-3420)	2909(1162-5495)	0.08
trisomy21, n (%)	6(66.7%)	10(22.2%)	0.008
cardiac diagnosis			
	AVSD 4	CoA with VSD 12	
	CoA with VSD 3	VSD 9	
	VSD 1	IAA 7	
	Tricuspid atresia 1	HLHS 7	
		AVSD 6	
		Single ventricle 3	
		Truncus arteriosus 1	
operation details			
concomitant procedure of arch repair, n (%)	3(33.3%)	15(33.3%)	1.00
lateral thoracotomy approach, n (%) (not median sternotomy)	4(44.4%)	21(46.7%)	0.90
main PAB, n (%) (not bilateral PAB)	9 (100%)	33(73.3%)	0.08
length of banding tape for main PAB (mm)	21.0(18.0-26.0) (n=9)	21.5(19.0-23.0) (n=33)	0.88
operative parameters			
operation length (mins)	139(118-226)	145(101-347)	0.88
bleeding (ml/kg)	3.4(0.0-30.4)	3.0(0.0-25.2)	0.50
In/out water balance (ml/kg)	+28.9(-15.5- +35.9)	+27.6(-28.4- +145.2)	0.52
postoperative parameters			
1st POD (ml/kg)			
In/out water balance	+40.7(-28.8- +91.5)	+37.8(-76.7- +133.6)	0.60
urine	90.4(46.1-168.0)	83.2(12.6-201.8)	0.44
drainage of chest tube	3.4(0.0-16.4)	4(0.0-26.6)	0.54
2nd POD (ml/kg)			
In/out water balance	+0.7(-123.3- +34.8)	-0.8(-87.9- +111.3)	0.70
urine	111.3(54.7-222.8)	96.1(5.3-203.5)	0.16
drainage of chest tube	1.5(0.0-23.9)	1.5(0.0-24.1)	0.73
3rd POD (ml/kg)			
In/out water balance	-16.3(-85.8- +88.4)	+0.8(-60.6- +66.9)	0.77
urine	109.4(30.3-194.2)	103.9(9.2-165.2)	0.95
drainage of chest tube	0.8(0.0-20.4)	0.0(0.0-12.4)	0.41
total drainage of chest tube (ml/kg)	15.9(0.0-114.8)	15.0(0.0-302.0)	0.63
max dopamine (γ)	7(4.0-9.0)	5(0.0-8.5)	0.25
usage of epinephrine, n (%)	3(33.3%)	10(22.2%)	0.48
max LAC (mmol/dl)	2.0(1.4-5.5)	2.3(0.9-8.0)	0.82
min ALB (g/dl)	2.2(1.5-2.5)	2.5(1.7-3.6)	0.009
max BUN (mg/dl)	15.3(8.6-39.1)	15.6(5.5-37.3)	0.55
max CRE (mg/dl)	0.50(0.32-0.90)	0.60(0.29-1.35)	0.61
max WBC (/μl)	14700(5500-21400)	15400(5000-23500)	0.31
max CRP (mg/dl)	10.17(4.83-12.98)	9.99(1.08-18.80)	0.74

Results reported as median (range) or frequency (%). PAB = pulmonary artery banding; POD = post operative day; ALB = albumin; LAC = lactate; BUN = blood urea nitrogen; CRE = creatinine; WBC = white blood cell count; CRP = C-reactive protein. AVSD = atrioventricular septal defect; CoA = coarctation of the aorta; VSD = ventricular septal defect; IAA = interruption of the aortic arch; HLHS = hypoplastic left heart syndrome

Table 2. Comparison of serous ALB in patients with or without pericardial effusion who underwent PAB

			pericardial effusion	No pericardial effusion	<i>p</i> value
pre-PAB	ALB (g/dl)	in total patients	3.0 (2.5-3.5) (n=9)	3.1 (2.0-4.6) (n=45)	0.78
post-PAB	min ALB (g/dl)	in total patients	2.2 (1.5-2.5) (n=9)	2.5 (1.7-3.6) (n=45)	0.009
		patients without trisomy21	2.4 (2.2-2.5) (n=3)	2.6 (1.7-3.6) (n=35)	0.32
		patients with trisomy21	2.1 (1.5-2.3) (n=6)	2.4 (2.0-2.9) (n=10)	0.04

Results reported as median (range) or frequency (%). Minimum values of ALB after PAB were lower in the pericardial effusion group compared to the No pericardial effusion group while pre-PAB baseline values did not differ between the groups. This difference in minimum ALB after PAB disappeared when we isolated values from the patients without trisomy 21. PAB = pulmonary artery banding; ALB = albumin.

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Figure Legends

Figure 1.

Schematic diagram showing the relation between the contents.

For Peer Review

Title.

Predictors of pericardial effusion in patients undergoing pulmonary artery banding

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Abstract

Background.

Although pulmonary artery banding (PAB) is a common palliative procedure for pediatric heart malformation, there are concerns of pressure overload and concomitant immune reactions in the right ventricle causing post-surgical complications such as pericardial effusion.

At this time, no clear guidelines as to potential risk factors or procedural contraindications have been widely disseminated. Therefore, a study was undertaken to examine wide-ranging factors to find potential biomarkers for post-surgical pericardial effusion formation risk.

Methods.

A retrospective study was conducted on all cardiac surgeries conducted over an 8-year period and the main inclusion criterion was pericardial effusion development after PAB that required surgical drainage. 9 cases were then analyzed against a control group of 45 cases with respect to body measurements, concomitant surgeries, genetic screens, lab tests and cardiac function parameters.

Results.

Trisomy 21 was strongly associated with development of severe pericardial effusion after PAB and postoperative serum albumin levels in trisomy 21 patients were associated with pericardial effusion development. Other parameters showed no significant correlation with pericardial effusion development.

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3
4 *Conclusions.*

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6 Our data indicates a strong association between trisomy 21 and pericardial effusion requiring
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8 drainage after PAB which is in line with translational research findings. Pressure overload
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10 from PAB may play a role in the formation of severe pericardial effusion that is exacerbated
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12 by cardiac structural defects commonly associated with trisomy 21. Surgical teams should
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14 therefore use caution and plan to implement drainage in PAB cases, and postoperative serum
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16 albumin may serve as a useful biomarker for pericardial effusion formation.
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Introduction:

Pulmonary artery banding (PAB) is a common palliative procedure for cardiac malformations with shunt-related pulmonary overflow, especially in low birth weight infants. However, animal modeling has shown that pressure overload as a consequence of PAB accelerates inflammation in the right ventricular myocardium which may lead to pericardial effusion production [1-2]. Such a result may lead to undesirable surgical outcomes if drainage is delayed [3-5]. As its etiology is poorly understood, postoperative pericardial effusion is often reported as post pericardiotomy syndrome (PPS) and the reported incidence varies widely [6]. As PPS describes any immune-mediated reaction to post-surgical trauma to the pericardium, precise PPS diagnoses are therefore difficult because of overlapping definitions [7-8]. A preliminary analysis of our institutional experience showed that the most prevalent procedure related to pericardial effusion was PAB. Therefore in this study, we looked exclusively into PAB cases to elucidate the predictors of postoperative pericardial effusion requiring drainage and tested multiple factors associated with the surgeries, including genomic screening, operation time and blood testing data.

Materials and Methods:

As a preliminary analysis, we reviewed all cardiac surgeries (532 cases) performed at the University of Tsukuba Hospital for structural congenital heart disease between April 2008

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3 and July 2016. As a need for drainage can be taken as a measure of pericardial effusion
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6 severity, the main inclusion criterion was pericardial effusion after PAB which required
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9 drainage. From a safety and reliable outcome perspective, our first choice for pericardial
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12 effusion after cardiac surgery is surgical drainage. In these cases, especially when the effusion
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15 envelops the heart in the pericardial cavity, we prefer to create a small reopening of the
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18 surgical site incision rather than use other interventional drainage techniques (such as
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21 pericardiocentesis). Nineteen cases were selected from the larger patient pool with 45
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24 non-drainage cases serving as control. Clinical data were reviewed retrospectively. Data
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27 collected for comparison included gender, age, height, weight at PAB, and trisomy 21 for
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30 patient characteristics. Detailed data for concomitant procedures (arch repair for coarctation
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33 or interruption of the aortic arch), approach (lateral thoracotomy or median sternotomy), site
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36 of PAB (main or bilateral pulmonary arteries), and, if main, length of the banding tape were
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39 collected for analysis. Operation time, amount of bleeding, and in/out water balance per body
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42 weight during PAB were collected as surgical data. Daily water balance (per body weight),
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45 urine amount, and amount of chest tube drainage were also investigated for the first through
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48 third postoperative days. Maximum postoperative doses of dopamine and/or epinephrine, and
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51 peak serum lactate levels (LAC) were collected to assess cardiac function. Minimum values
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54 of serum albumin (ALB) as well as maximum values of blood urea nitrogen (BUN),
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57 creatinine (CRE), white blood cell count (WBC), and C-reactive protein (CRP) were also
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6 Standard descriptive statistics were used to summarize the data and are expressed as
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9 median with range. Group comparisons were performed using Mann-Whitney U testing since
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12 the data were not normally distributed. Categorical variables are expressed as frequency with
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15 percentage. A p value < 0.05 was taken to indicate statistical significance. Statistical analysis
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18 was performed using SPSS statistical software (version 22, IBM SPSS Inc., Armonk, NY).
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20 Informed consent was waived because of our retrospective study design and the study was
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23 approved by the Institutional Review Board for Ethics in Human Subject Research of the
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26 University of Tsukuba Hospital (Approval No. H29-84).
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32 **Results:**

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34 Postoperative pericardial effusion which required drainage occurred in 19 out of 532
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37 cases (3.6%) and among these, 10 pericardial effusion incidences were after PAB (10/60 cases,
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40 16.7%) held during the same period. Five incidents were after closures of isolated ventricular
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43 septal defects (5/90cases, 5.6%) with the other 4 incidents concomitant with 4 different
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46 procedures (repair of atrial septal defect, atrioventricular septal defect, systemic-pulmonary
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49 shunt for tetralogy of Fallot, and mitral valve replacement). One case with trisomy 18, one
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52 case with massive pleural effusion and ascites since the fetal period, and one case that had
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55 mediastinitis after PAB were excluded from the study. Three cases that underwent
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4 cardiopulmonary bypass for concomitant procedures were also excluded. In total, we
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6 experienced 54 cases of PAB and all procedures were performed as the first palliative surgery
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8 without using cardiopulmonary bypass. Among 54 cases, 9 developed eventual moderate to
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10 severe amount of pericardial effusion after removing the chest tube and required surgical
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12 drainage. We compared the perioperative factors between these 9 cases (pericardial effusion
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14 group) with 45 other cases that did not develop pericardial effusion (No pericardial effusion
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16 group).

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23 The perioperative factors between 9 cases that required surgical drainage for pericardial
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25 effusion and 45 cases that did not develop pericardial effusion were compared. All absolute
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27 data for each factor are shown in Table 1-2. The most notable finding was the higher
28
29 incidence of trisomy 21 within the pericardial effusion group, with 6 out of 9 cases in the
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31 pericardial effusion group and 10 out of 45 in the No pericardial effusion group ($p = 0.008$)
32
33 (Table 1). Minimum values of ALB after PAB were lower in the pericardial effusion group
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35 compared to the No pericardial effusion group ($p = 0.009$) while pre-PAB baseline values did
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37 not differ between the groups. This difference in minimum ALB after PAB disappeared when
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39 we isolated values from the 38 cases without trisomy21 (Table 2). Other perioperative
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41 parameters did not differ between groups. Taken together, this data indicates that genetic
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43 screening for trisomy 21 may be an important pre-surgical biomarker for potential
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45 development of pericardial effusion after PAB and that postoperative serum albumin may be a
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4 useful indicator of pericardial effusion for trisomy 21 patients who must undergo PAB. Two
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7 out of the 16 cases with trisomy 21 had hypothyroidism before PAB and 6 cases developed
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10 hypothyroidism soon after PAB. Three of the cases with hypothyroidism were in the
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12 pericardial effusion group (3/6 cases), and the other 5 were in the No pericardial effusion
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15 group (5/10 cases).
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21 **Comment:**
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23 PAB has been largely abandoned in leading cardiac centers since the advantages of
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26 early primary repair for congenital heart disease became clear. Nevertheless, for immature
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29 patients with low birth weight and serious conditions due to complex cardiac malformations,
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32 the relatively low invasiveness of PAB makes it a singular choice for palliative control of
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35 pulmonary blood flow that also prevents pulmonary vascular obstructive disease. According
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38 to the 2014 annual report by the Japanese Association for Thoracic and cardiovascular
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41 Surgery (JATS), there were 661 PAB performed mostly on newborns and infants, and within
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44 the “main procedure” classification, it was the most frequently selected in Japan for
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47 congenital heart disease even surpassing the second-place (549 cases) systemic-pulmonary
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50 (SP) shunt procedure [9].

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52 However, frequent use may not be indicative of superior outcome. Our experience
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55 showed a high incidence of postoperative pericardial effusion with PAB. While no literature
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4 has clearly described PAB as a risk factor of postoperative pericardial effusion, hemodynamic
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6 and mechanical stress changes accompanying PAB might play a key role in formation of
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8 postoperative pericardial effusion. Recently, the literature reports an activated inflammatory
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10 process in the RV myocardium after pressure overload from animal experiments [1-2]. Luite
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12 and colleagues suggested from their murine PAB model that pressure overload leads to right
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14 ventricular accumulation and increased activity of cardiac mast cells which are known as a
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16 component of the inflammatory response in adverse ventricular remodeling [1]. Earlier animal
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18 experiments also suggest that multiple molecular mechanisms (such as proteasomal changes
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20 and proteins like CYLD) play a synergistic role in this adverse remodeling [10]. Dewachter
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22 and colleagues concluded from their canine PAB model that acute afterload-induced RV
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24 failure from PAB is associated with increased myocardial expression of inflammatory
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26 cytokines and infiltration of neutrophils and macrophages [2]. Although the exact
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28 pathogenesis of postoperative pericardial effusion still remains unclear, underlying
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30 inflammation, autoimmune processes and molecular mechanisms may play a pivotal role in
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32 this clinical presentation [7-8].
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46 Interestingly, the proportion of patients with trisomy 21 was high in the pericardial
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48 effusion group. Since there was no difference between groups when we investigated the
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50 values exclusively on patients without trisomy 21, postoperative minimum ALB values
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52 became a trisomy-associated risk factor instead of an independent one. Therefore, we could
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4 conclude that the presence of trisomy 21 is associated with increased likelihood of
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6 PAB-induced pericardial effusion that requires surgical drainage. Among various risk factors
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9 which have been reported [11-13], a recent high volume cohort study first pointed out trisomy
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12 21 as an independent risk factor predicting postoperative pericardial effusion [14]. In trisomy
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15 21 cases, more popularly known as Down syndrome (DS), pericardial effusion had often been
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18 reported with co-morbidities such as hypothyroidism, celiac disease, infectious disease, and
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21 transient abnormal myelopoiesis [15-16]. In a critical study, however, Concolino and
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24 colleagues showed a significant increase in the prevalence of isolated pericardial effusion in
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27 DS individuals apart from any associated disease or cardiac malformations [17]. From this
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30 finding, Elias and colleagues speculated that cardiac surgery and the resulting inflammatory
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33 process may provide the trigger to develop a significant postoperative pericardial effusion in
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36 children with DS who suffer from a greater propensity to develop pericardial effusion, in
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39 general [14].

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41 It is well known that DS, in addition to cardiac malformations with shunt-related
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44 pulmonary overflow, contains a higher potential for developing pulmonary vascular
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47 obstructive disease [18]. One of the most common shunt-related cardiac malformations
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50 associated with DS is the atrioventricular septal defect (AVSD) so our therapeutic strategy in
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53 this case is to achieve precision repair via PAB as an initial palliative in the neonate period to
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56 improve immediate condition and prevent the development of pulmonary vascular obstructive

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3 disease. We then perform full cardiac repair within the infancy period. Therefore, our
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6 experience with high pericardial effusion incidence after PAB might be due to the fact that we
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9 are performing PAB on DS-associated AVSD which biases outcomes to pericardial effusion
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12 (Figure 1).
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15 There are several limitations to this study, including the small number of patients
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17 with pericardial effusion and retrospective nature of the study. There is a potential for
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19 selection bias in exclusively analyzing severe cases (which may exclude true prevalence)
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21 since we limited the study cohort to pericardial effusion cases that required drainage. In less
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23 severe cases, pericardial effusion can be self-limiting or spontaneous resolution can occur
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25 while first-line treatments such as aspirin, non-steroidal anti-inflammatory agents, and
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27 corticosteroids are commonly used in less severe cases when hemodynamics are not
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29 threatened [12].
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38 In conclusion, based on our observations and those of other investigators, patients
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40 with DS are prone to develop pericardial effusion after PAB that requires surgical drainage.
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42 Postoperative serum albumin may play a role as a biomarker of pericardial effusion formation
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44 in DS patients and should be considered in the recovery plan as an essential lab test.
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51 **Conflicts of interest**

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54 The authors declare that they have no conflict of interest.
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Table 1. Comparison of clinical characteristics and perioperative parameters in patients with or without pericardial effusion who underwent PAB

	pericardial effusion (n=9)	No pericardial effusion (n=45)	<i>p</i> value
patient characteristics			
Male sex, n (%)	4(44.4%)	19(42.2%)	0.90
Age at PAB (days)	24(6-53)	13(3-147)	0.60
height at PAB (cm)	48(43.8-54.0)	48.0(36.0-61.3)	0.81
weight at PAB (g)	2935(2250-3420)	2909(1162-5495)	0.08
trisomy21, n (%)	6(66.7%)	10(22.2%)	0.008
cardiac diagnosis			
	AVSD 4	CoA with VSD 12	
	CoA with VSD 3	VSD 9	
	VSD 1	IAA 7	
	Tricuspid atresia 1	HLHS 7	
		AVSD 6	
		Single ventricle 3	
		Truncus arteriosus 1	
operation details			
concomitant procedure of arch repair, n (%)	3(33.3%)	15(33.3%)	1.00
lateral thoracotomy approach, n (%) (not median sternotomy)	4(44.4%)	21(46.7%)	0.90
main PAB, n (%) (not bilateral PAB)	9 (100%)	33(73.3%)	0.08
length of banding tape for main PAB (mm)	21.0(18.0-26.0) (n=9)	21.5(19.0-23.0) (n=33)	0.88
operative parameters			
operation length (mins)	139(118-226)	145(101-347)	0.88
bleeding (ml/kg)	3.4(0.0-30.4)	3.0(0.0-25.2)	0.50
In/out water balance (ml/kg)	+28.9(-15.5- +35.9)	+27.6(-28.4- +145.2)	0.52
postoperative parameters			
1st POD (ml/kg)			
In/out water balance	+40.7(-28.8- +91.5)	+37.8(-76.7- +133.6)	0.60
urine	90.4(46.1-168.0)	83.2(12.6-201.8)	0.44
drainage of chest tube	3.4(0.0-16.4)	4(0.0-26.6)	0.54
2nd POD (ml/kg)			
In/out water balance	+0.7(-123.3- +34.8)	-0.8(-87.9- +111.3)	0.70
urine	111.3(54.7-222.8)	96.1(5.3-203.5)	0.16
drainage of chest tube	1.5(0.0-23.9)	1.5(0.0-24.1)	0.73
3rd POD (ml/kg)			
In/out water balance	-16.3(-85.8- +88.4)	+0.8(-60.6- +66.9)	0.77
urine	109.4(30.3-194.2)	103.9(9.2-165.2)	0.95
drainage of chest tube	0.8(0.0-20.4)	0.0(0.0-12.4)	0.41
total drainage of chest tube (ml/kg)	15.9(0.0-114.8)	15.0(0.0-302.0)	0.63
max dopamine (γ)	7(4.0-9.0)	5(0.0-8.5)	0.25
usage of epinephrine, n (%)	3(33.3%)	10(22.2%)	0.48
max LAC (mmol/dl)	2.0(1.4-5.5)	2.3(0.9-8.0)	0.82
min ALB (g/dl)	2.2(1.5-2.5)	2.5(1.7-3.6)	0.009
max BUN (mg/dl)	15.3(8.6-39.1)	15.6(5.5-37.3)	0.55
max CRE (mg/dl)	0.50(0.32-0.90)	0.60(0.29-1.35)	0.61
max WBC (/ μ l)	14700(5500-21400)	15400(5000-23500)	0.31
max CRP (mg/dl)	10.17(4.83-12.98)	9.99(1.08-18.80)	0.74

Results reported as median (range) or frequency (%). PAB = pulmonary artery banding; POD = post operative day; ALB = albumin; LAC = lactate; BUN = blood urea nitrogen; CRE = creatinine; WBC = white blood cell count; CRP = C-reactive protein. AVSD = atrioventricular septal defect; CoA = coarctation of the aorta; VSD = ventricular septal defect; IAA = interruption of the aortic arch; HLHS = hypoplastic left heart syndrome

Table 2. Comparison of serous ALB in patients with or without pericardial effusion who underwent PAB

			pericardial effusion	No pericardial effusion	<i>p</i> value
pre-PAB	ALB (g/dl)	in total patients	3.0 (2.5-3.5) (n=9)	3.1 (2.0-4.6) (n=45)	0.78
post-PAB	min ALB (g/dl)	in total patients	2.2 (1.5-2.5) (n=9)	2.5 (1.7-3.6) (n=45)	0.009
		patients without trisomy21	2.4 (2.2-2.5) (n=3)	2.6 (1.7-3.6) (n=35)	0.32
		patients with trisomy21	2.1 (1.5-2.3) (n=6)	2.4 (2.0-2.9) (n=10)	0.04

Results reported as median (range) or frequency (%). Minimum values of ALB after PAB were lower in the pericardial effusion group compared to the No pericardial effusion group while pre-PAB baseline values did not differ between the groups. This difference in minimum ALB after PAB disappeared when we isolated values from the patients without trisomy 21. PAB = pulmonary artery banding; ALB = albumin.

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Figure Legends

Figure 1.

Schematic diagram showing the relation between the contents.

For Peer Review

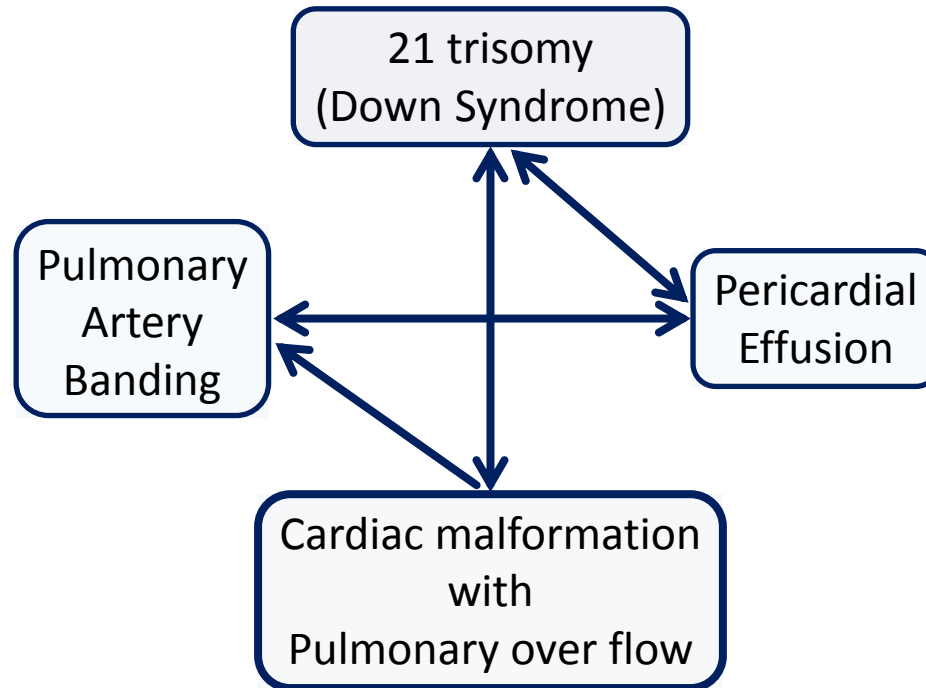


Figure 1. Schematic diagram showing the relation between the contents.