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## THE PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH VENTRICULAR SEPTAL DEFECTS: A SINGLE-CENTRE EXPERIENCE IN THE REPUBLIC OF KAZAKHSTAN

The aim of this study was to evaluate the impact of pulmonary arterial hypertension on outcomes following surgical or transcatheter repair of isolated ventricular septal defect in the Republic of Kazakhstan.

Echocardiography and catheterisation reports of children with isolated ventricular septal defect complicated pulmonary arterial hypertension surgical or transcatheter repair between 2012 and 2016.

Amongst 38 children ventricular septal defect mean size was  $10.92 \pm 6.38$ mm. The mean systolic pressure in the right ventricle on Echocardiography was  $55.42 \pm 18.47$  mmHg. Mean pulmonary arterial pressure by right heart catheterisation was  $52.12 \pm 29.44$  mmHg. The mean end diastolic index for all children was registered as  $76.78 \pm 19.58$ ml. Cardiac output was preserved in all children. In the pre-operative period, 9 of these children were treated with sildenafil.

One week after the operation, mean right ventricle systolic pressure decreased as for children who did not receive preoperative sildenafil (from  $55.5 \pm 14.8$ mmHg to  $32.2 \pm 14.4$ mmHg) ( $p < 0.01$ ), as for children who did (from  $81.4 \pm 10.3$ mmHg. to  $48.1 \pm 12.4$ mmHg ( $p$  value  $< 0.01$ )). End diastolic index normalized in 92.5% of cases. Right ventricle systolic pressure decreased  $>40\%$  in all children a month after the surgery.

In our study prescription of specific drug therapy of pulmonary arterial hypertension with the purpose of preparing for surgery has no effect on the effectiveness of surgical treatment of ventricular septal defect. We had had no early postoperative mortality.

**Key words:** ventricular septal defect, pulmonary arterial hypertension, children, cardiac surgery, outcomes.

### Introduction

Pulmonary arterial hypertension in children with congenital heart defects is a common consequence of left-to-right shunts, known as associated pulmonary arterial hypertension. As reported by Denise van Der Linde et al. in 2011 [1] over the last decades, number of newborns born with congenital heart defects every year is over 1.35 million worldwide. However significant geographical differences were found. Asia reported the highest congenital heart defects birth incidence, with 9.3 per 1,000 live births (95% CI: 8.9 - 9.7). Republic of Kazakhstan is a Central Asian country with the total population over 17 million [2]. There is a significant increase in the detection of congenital heart defects in the Republic of Kazakhstan from 4.4 per 1,000 live births in 2003 to 8.9 per 1,000 live births in 2012 [3].

Amongst congenital heart defects lesions which cause pulmonary arterial hypertension, ventricular

septal defects is leading in frequency, with pulmonary arterial hypertension in between 18% [4] and 41.4% [5] in western countries. Previous experience of surgical repair of ventricular septal defect in children shows importance of preoperative hemodynamic assessment of pulmonary circulation. Data, including mean pulmonary arterial pressure and pulmonary vascular resistance have a strong impact on outcomes following surgery [6-8]. However, the risk of repair may be significantly ameliorated by the use of preoperative specific drug treatment to modify pulmonary vascular resistance [9,10].

The Scientific Centre of Paediatrics and Paediatric Surgery of the Ministry of Health of the Republic of Kazakhstan is a multidisciplinary national centre of excellence in child health. Since 2011, Scientific Centre of Paediatrics and Paediatric Surgery provides cardiac surgery and intervention cardiology care for children with pulmonary arterial

hypertension-congenital heart defects. This study was to analyse, in a single centre, the influence of pulmonary arterial hypertension on outcome following cardiac surgery or transcatheter repair of ventricular septal defect in children, between 6 months and 16 years of age, with isolated ventricular septal defect.

### **Materials and Methods**

We conducted a retrospective analysis of 38 hospital records of children with pulmonary arterial hypertension associated with ventricular septal defect from 2012 to 2016.

Inclusion criteria: 1. age between 6 months and 16 years old, both sexes; 2. isolated ventricular septal defect; 3. pulmonary arterial hypertension defined by tricuspid regurgitation velocity on Echocardiography  $>36$  mmHg., and confirmed by Catheterization or intraoperative measurements of mean pulmonary arterial pressure  $>25$  mmHg.

Exclusion criteria: 1. Age under 6-month-old and over 16 years old; 2. additional left-to-right shunts as patent ductus arteriosus or arterial septal defect; 3. Pulmonary stenosis or right ventricle outflow tract obstruction; 4. presence of the other causes of pulmonary arterial hypertension, such a lung disease, connective tissues disease; 5. No follow up data; 6. Improper or lack of measurements.

Accordingly the retrospective data, in the preoperative period 23 patients were assessed by the echocardiographic examination alone, while 15 had had continuous echocardiographic assessment (high right ventricle systolic pressure with bidirectional or right-to-left shunt) and underwent additional right heart catheterization measurement to determine the pulmonary arterial hypertension status.

### **Echocardiographic assessment.**

Patients were assessed at baseline clinically and echocardiographically and followed up for a minimum of one month after discharge from the hospital. The echocardiographic measurements of the size and function of the heart structures and ventricular septal defect features were made in the subcostal view, apical four-chamber view, the apical five-chamber view, the parasternal long axis view, the parasternal short axis view of the left ventricle at the aortic root level, mitral valve, papillary muscles and apical level. To optimize the calculations, we used left ventricle end diastolic index greater than 75, for defining left ventricle dilatation, right ventricle/left ventricle ratio greater than 0.7 to define right ventricle dilatation. For pulmonary artery and aorta dilatation we used calculations of z

score  $>2.0$  [11,12]. And for ventricular septal defect, the largest defect diameter was indexed to the size of the aortic root recorded from the parasternal long axis view in systole. Thus, the ratio of the maximum size of the ventricular septal defect (mm) to the diameter of the aortic valve in systole (mm) as a representation of the shunt's size (ventricular septal defect/aorta), or the ventricular septal defect index. When analysing the data, the ventricular septal defect index from 0 to 0.3 was interpreted as a minor or small defect, 0.3 to 0.7 moderate, and greater than 0.7 as a large defect. For primary evaluation tricuspid regurgitation velocity was assessed and right ventricle systolic pressure was calculated as a sum of tricuspid regurgitation gradient and right atrium pressure (defined by inferior vena cava collapsing during the breathing). Right ventricle systolic pressure  $>36$ mmHg. accepted as a sign of pulmonary arterial hypertension associated with congenital heart defects. For secondary pulmonary arterial hypertension assessment the mean systemic arterial pressure to mean pulmonary arterial pressure ratio was calculated. The mean pulmonary arterial pressure / mean systemic arterial pressure  $>0.3$  defined as pulmonary arterial hypertension,  $>0.75$  children were registered as a high mortality risk [13].

### **Right heart catheterization.**

The mean pulmonary artery pressure was measured by right heart catheterization or during the surgical operation. In case of preoperative right heart catheterization the full protocol for the procedure with measurement of cardiac output, mean pulmonary arterial pressure, mean pressure in right ventricle, right atrium with the blood samples for  $sO_2$  taken from inferior vena cava, superior vena cava, right atrium was performed. Pulmonary vascular resistance index was calculated using the Fick formula. After acute vasoreactivity test (nebulised iloprost inhalation; 2 mcg/kg during 3-5 min) the same measurements were repeated. A positive test was defined as a PVRI decline  $>20\%$  with the stable cardiac output.

### **Postoperative data.**

For assessment of surgery or transcatheter closure outcome the following criteria were analysed: clinical status; (1) oxygen saturation, haemoglobin's levels, (2) Echocardiographic indices (end diastolic index, cardiac index, ventricular septal defect index), right ventricle systolic pressure in pre- and postoperative period, right ventricle to left ventricle ratio. Furthermore, duration of staying in intensive care unit and bed days were analysed.

### Statistical analysis.

The variables are quantitative and continuous. Shapiro-Wilk criterion was calculated for verification of the normal distribution of a small number of variables. To exclude false results for a small number of variables, we used the Wilcoxon test to determine the statistical significance of the differences in the repeated measurements (right ventricular systolic pressure before and after the operation). This nonparametric test does not require a normal distribution as a mandatory condition. For all calculations we used the R studio statistical software. Continuous variables were expressed as mean  $\pm$  standard deviation and analysed by R studio. P value more than 0.05 was considered non-significant.

### Results

#### *Demographic data.*

We identified 38 children, 22 boys and 16 girls; age 6 - 12 months 10 children, 1-3 years 9 children, 3-7 years 10 patients, 7-11years 5 children and 11-16 years 4, with a diagnosis of isolated ventricular septal defect complicated by pulmonary arterial hypertension. Body mass index among the boys were between 50<sup>th</sup> and 5<sup>th</sup> percentiles and girls were between 25<sup>th</sup> and 5<sup>th</sup>.

#### *Preoperative data.*

The mean sO<sub>2</sub> for all children was 92.17 $\pm$ 4.7%; sO<sub>2</sub> less than 90% was in 6 children, 90-95% in 21 children and >95% in 8. Red blood cells mean amount was normal in all children 4.6 $\pm$ 0.57\*10<sup>12</sup>/l, and mean haemoglobin's level was 119.4 $\pm$ 15.45g/l.

The mean size of the ventricular septal defect was 10.92  $\pm$  6.38 mm. Mean ventricular septal defect index was 0.72  $\pm$  0.49. It was interpreted as small ventricular septal defect in 8 children (0.188 $\pm$ 0.119), as moderate in 13 (0.49 $\pm$ 0.1) and as large ventricular septal defect in 17 children (1.2 $\pm$ 0.44). The mean systolic pressure in the right ventricle on Echocardiography was 55.42  $\pm$  18.47 mmHg. In children who underwent cardiac catheterisation (N = 15) mean pulmonary arterial pressure by right heart catheterization was 52.12  $\pm$  29.44 mmHg. Systolic and diastolic systemic blood pressure were registered respectively 92.6 $\pm$ 11.04 and 57.19 $\pm$ 8.99mmHg. For the mean pulmonary arterial pressure to mean systemic arterial pressure ratio mean level was 0.63 $\pm$ 0.22. 27 children had have mean systemic arterial pressure to mean pulmonary

arterial pressure ratio <0.75. and 11 children were >0.75.

The mean end diastolic index for all children was registered as 76.78 $\pm$ 19.58ml. Cardiac output was preserved in all children. Dilatation of the left ventricle was recorded in 23 patients, for them basic drug treatment including diuretics (spironolactone 2mg/kg/dose 2 t/day per os); and afterload reduction with low-doses of angiotensin converting enzyme inhibitors (captopril 0.1mg/kg/dose 3 t/day per os) was prescribed.

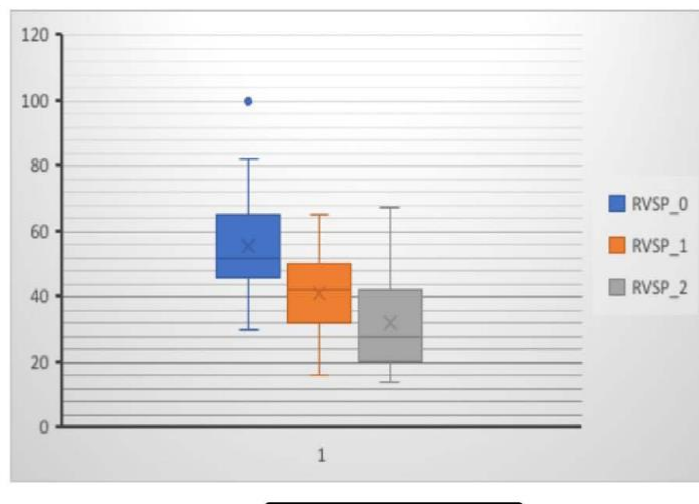
Mean z score for pulmonary artery size was 1.4 $\pm$ 1.3. In 11 children pulmonary artery dilation was registered. In 9 children a acute vasoreactivity test with inhaled iloprost was performed. A positive response, with a reduction in pulmonary vascular resistance index >20% was noted in 8 children. In the pre-operative period, all 9 of these children were, subsequently, treated with sildenafil in a dosage of 1.5 mg/kg 3 times a day (weight of up to 20 kg) and 20 mg 3 t/day (weight over 20 kg)

Of the 38 children 36 had ventricular septal defect surgical repair and 2 underwent transcatheter device closure. There were no deaths. In 8 children with positive acute vasoreactivity test specific pulmonary arterial hypertension medical treatment with sildenafil was prescribed before surgery. 1 patient who did not have a positive response during acute vasoreactivity test also underwent surgery with pre-prescription of sildenafil in preoperative period.

#### *Post-operative findings.*

We had had no early postoperative mortality. In the postoperative period 2 children experienced pulmonary hypertensive crisis. Both cases were soon after the transferring the patient to the ward. As treatment intravenous nitroglycerin and Iloprost inhalations were used with the prolongation of the basic diuretic therapy. However pulmonary hypertensive crisis was a single event for these children, after stabilisation, no recurrence of pulmonary hypertensive crisis was registered. They stayed with the sildenafil prescription for the next 6 months.

One week after the operation a decrease in left ventricle dilatation with preserved function was noted on echo in all operated patients. In children who did not receive specific therapy the mean right ventricle systolic pressure decreased from 55.5 $\pm$ 14.8mmHg to 40.8 $\pm$ 12.6 mmHg (p <0.01). In 1 month mean right ventricle systolic pressure decreased to 32.2 $\pm$ 14.4mmHg (p<0.01) (Figure 1).

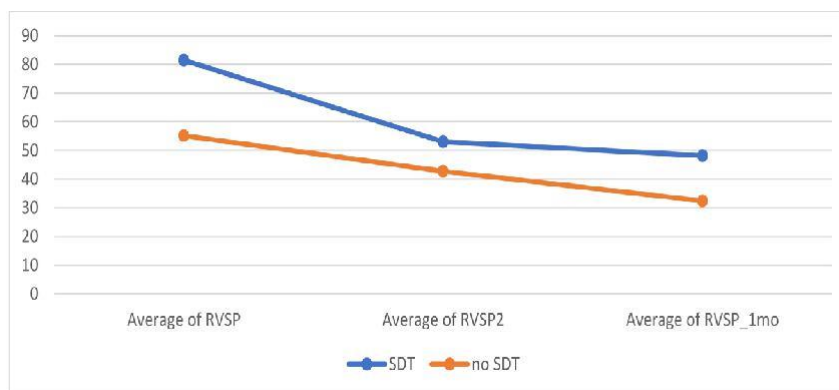


**Figure 1** – Difference between pre- and post-operative right ventricular systolic pressure in children after surgery and after catheterisation

RVSP\_0 – preoperative right ventricle systolic pressure, RVSP\_1 –right ventricle systolic pressure 1 week after operation, RVSP\_2 –right ventricle systolic pressure 1 month after operation

One month after the operation the echocardiographic assessment showed that the right ventricle systolic pressure was improved in all children. Persistent pulmonary arterial hypertension was registered in 4 patients who continued sildenafil therapy.

In children who received specific therapy in the pre-operative period, the right ventricle systolic pressure also decreased >40%, from  $81.4 \pm 10.3$  mmHg. to  $48.1 \pm 12.4$  mmHg in a month after the surgery (p value 0.01), which was not different from that in children without medical preparations for surgery (mean preoperative right ventricle systolic pressure  $55.1 \pm 15.9$  mmHg, 1 month after operation  $32.4 \pm 15.3$  mmHg,  $p > 0.05$ ) (Figure 2).



**Figure 2** – Comparison of mean right ventricle systolic pressure’s dynamic in children who received specific PAH therapy in preoperative period and in children without specific PAH therapy.

SDT – specific drug therapy, RVSP – preoperative right ventricular systolic pressure, RVSP2 - right ventricular systolic pressure 1 week after operation, RVSP\_1mo – right ventricular systolic pressure 1 month after operation.

In the postoperative period, 7 children who were operated showed rising of right ventricle

systolic pressure above 40 mm.Hg. which resulted in prescription of sildenafil treatment. The volume of the left ventricle cavity normalized in 92.5% of cases (end diastolic index decrease, p value < 0.05).

The mean length of stay in the intensive care unit was  $3.02 \pm 4.6$  days. The mean length of hospitalization was  $17.6 \pm 12.9$  days. In the group

of children without preoperative sildenafil therapy, the length of ICU staying was  $3.7\pm 4.8$  days and the period of hospitalization was  $19.1\pm 13.9$  days. In contrast in children with specific drug treatment the mean length of stay in the intensive care unit for was  $5.6\pm 6.8$  days and the mean length of hospitalization was  $24.1\pm 16.7$  days.

### Discussion

This study is the first to systematically evaluate the outcome from ventricular septal defect repair of children in Kazakhstan. We have demonstrated excellent outcomes with no mortality in 38 patients who underwent surgical or transcatheter repair of a ventricular septal defect complicated by pulmonary arterial hypertension.

From demographic data, we found that 50% of children were 1-7 years old with the slight prevalence of boys vs girls. Surgery outcomes were similar for all children: no heart rhythm complications, zero mortality, de-escalation of pulmonary arterial hypertension progression. Secondary changes such as left ventricle and pulmonary artery dilatation are reversible and controllable after surgery in patients with pulmonary arterial hypertension associated with ventricular septal defect.

Patients who took sildenafil as preoperative specific drug therapy showed the same results with those who didn't. What is controversial to publications, demonstrated the efficacy of sildenafil to prevent and control the pulmonary hypertensive crisis [6,9,10,14]. Surgical treatment was obvious way to decrease mean pulmonary arterial pressure in a short-time, however for the midterm result complex treatment as specific drug therapy after ventricular septal defect repair is more effective for management of pulmonary arterial hypertension in postoperative period. In 1-month period, we registered significant decreasing of right ventricle systolic pressure in patients with residual pulmonary arterial hypertension after ventricular septal defect repair who received sildenafil as specific drug therapy. Our results endorse the previous trials of sildenafil efficacy for pulmonary arterial hypertension associated with congenital heart defects [6,9,10,14-19].

Pulmonary arterial hypertension is an important indicator for operability of ventricular septal defect in children. Nowadays cardiac surgery tends to early operative management of the defect what could prevent pulmonary arterial hypertension development. Most of the patients demonstrated good response for complex approach to treatment. Basic therapy with potassium-sparing diuretics

and ACE-inhibitors in the preoperative period with the prescription of the specific drug therapy after the radical correction showed high efficacy for management of pulmonary arterial hypertension. Residual pulmonary arterial hypertension after the ventricular septal defect repair potentially could cause opposite surgery result with the right ventricle failure, pulmonary hypertensive crisis and increase the risk of mortality. Therefore, moderate and large ventricular septal defect have to be closed in the age under 1 year old. In the presence of ventricular septal defect complicated by pulmonary arterial hypertension the medicaments management of volume overload due to left-to-right shunting is a key for positive outcome of cardiac surgery or intervention.

**Study limitations.** The major limitation of this study that in the Republic of Kazakhstan there were absence of the electronic database for echocardiographic and catheterisation records what is crucial for long-term follow up of the patients in most of the hospital. We have tried to overcome this limitation by studying one centre that keep the record over 5 years, however the sample size is small due to single centre. We are reporting here this experience and we plan to follow up with most report electronic database in the future.

### Conclusion

We have demonstrated excellent outcomes with no mortality in 38 patients who underwent surgical or transcatheter repair of a ventricular septal defect complicated by pulmonary arterial hypertension. Accordingly to this study, the prescription of specific drug therapy of pulmonary arterial hypertension with the purpose of preparing for surgery has no effect on the effectiveness of surgical treatment of ventricular septal defect. Thus, further studies are needed for clarifying the rationality of specific drug therapy prescription in the preoperative period in this category of patients.

**Conflicts of interest:** none

**Ethical Standards:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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