Right ventricle-to-pulmonary artery shunt related complications after Norwood procedure

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Abstract

Objective: The right ventricle-to-pulmonary artery (RV-PA) shunt in the Norwood procedure (NP) for children with hypoplastic left-heart syndrome (HLHS) provides stable early hemodynamics and improves survival in many centers. However, lower pulmonary-to-systemic flow ratio causes early cyanosis and may require earlier second-stage procedure. The aim of the study was to present shunt-related results after NP with RV-PA shunt and our technique of RV-PA shunt construction. Methods: Between June 2001 and August 2010, 236 children with HLHS and variants underwent NP with RV-PA shunt, and were operated on by the same surgeon. The medical records were retrospectively reviewed. Results: To date, 180 children at a mean age of 7.0 ± 1.6 months with a mean weight of 6.4 ± 0.9 kg underwent second-stage procedure. The mean systemic oxygen saturation before stage 2 operation was 74.8 ± 6.6% and mean arterial partial oxygen pressure was 32.8 ± 6.7 mmHg. These two parameters were significantly lower than after NP (p = 0.029, p < 0.001, respectively). Between stage 1 and 2 operation, three children (1.3%) died due to the shunt obstruction. Four children (1.7%) underwent re-operations due to shunt problems (one of them died), and the other four (1.7%) underwent re-operations due to shunt problems (one of them died). The other four (1.7%) underwent re-operations due to shunt problems (one of them died). Conclusions: The RV-PA shunt can be a safe and efficient technique in providing optimal pulmonary blood flow in the children with HLHS after Norwood procedure, performed with minimal rate of complications. In our experience, the use of RV-PA shunt in NP does not require earlier second-stage procedure.

1. Introduction

The right ventricle-to-pulmonary artery (RV-PA) shunt is an alternative to the modified Blalock–Taussig (BT) shunt source of pulmonary blood flow in the Norwood procedure (NP) for children with hypoplastic left-heart syndrome (HLHS). First proposed in the pioneering works of William Norwood for almost 30 years [1], and recently popularized by Japanese surgeons [2,3], the RV-PA shunt led to an ongoing debate regarding early and late hemodynamics after NP, survival, and optimal preparation of the single right ventricle and pulmonary vasculature for Fontan operation. The evidence of the favorable early hemodynamics after NP associated with the RV-PA shunt has been widely reported by many centers, including ours [4–6]. The hemodynamic advantages of the RV-PA shunt include: higher diastolic blood pressure, higher coronary perfusion pressure, more balanced and predictable pulmonary-to-systemic flow ratio (Qp:Qs), and decreased ventricular volume loading due to lower pulmonary blood flow. There are numerous reports citing hemodynamic stability and improved survival following NP with RV-PA shunt [5–9]. Concerns remain about the consequences of the ventriculotomy and diastolic flow regurgitation. Lower Qp:Qs causes early cyanosis, and the children may require earlier second-stage procedure [5,10–12]. Some centers report also about an increased number of surgical interventions associated with the RV-PA shunt between the first and second stage of palliation [10,13].

The aim of the study was to present shunt-related results after NP with the RV-PA shunt and our technique of RV-PA shunt construction.
2. Materials and methods

Between June 2001 and August 2010, 236 children (159 (67.4%) males, 77 (32.6%) females) with HLHS and variants underwent NP with RV-PA shunt. We retrospectively reviewed clinical records, echocardiographic studies, cardiac catheterization reports, electrocardiograms, surgical notes, reports provided by referring cardiologists and pertinent information obtained from the parents. All operations were performed by the same surgeon in two centers: Department of Pediatric Cardiac Surgery (Collegium Medicum, Jagiellonian University, Cracow, Poland) and Department of Cardiac Surgery (Klinikum Grosshadern, Ludwig Maximilians University, Munich, Germany). Similar pre-, intra-, and postoperative protocols were applied in both institutions. The study was approved by the Institutional Review Boards of both institutions. Informed consent for treatment was obtained from the parents of each child. No patients were refused surgical intervention during the study period.

The diagnosis of heart defect was based on two-dimensional and color flow Doppler transthoracic echocardiography. HLHS was diagnosed if mitral and aortic hypoplasia/stenosis or atresia with small left ventricle and normal segmental anatomy of the heart (S,D,S) were present. Variant of HLHS was defined as a functional single ventricle with systemic outflow tract obstruction and ductal dependency of the systemic circulation. HLHS was diagnosed in 214 (90.7%) children; the remaining 22 (9.3%) patients had an HLHS variant.

All the NPs were performed as previously described [4]. A polytetrafluoroethylene (PTFE) RV-PE shunt (IMPRA® ePTFE Vascular Graft, BARD, Tempe, USA; Gore-Tex Vascular Graft, W.L. Gore & Associates, Dundee, Scotland, UK) was used to provide pulmonary blood flow, 4 mm in neonates weighing less than 2500 g, 5 mm — in infants between 2500 and 3500 g, and 6 mm in children over 3500 g. If cardiopulmonary bypass was established by arterial cannulation of the ascending aorta or brachiocephalic artery, during the cooling phase, ductus arteriosus was ligated and the distal shunt anastomosis was constructed. A PTFE tube had been already anastomosed with a circular pulmonary homograft patch by another surgeon during the midline sternotomy (Fig. 1). The main PA was divided at the level of the branch PAs, and the confluence was closed using the previously performed anastomosis between the PTFE tube and the homograft patch (Figs. 2 and 3). If the main PA was used for arterial cannulation, the distal end of the RV-PA was performed during the circulatory arrest in the same way. During the rewarming phase on beating heart, the proximal end of the RV-PA shunt was constructed. About 1 cm beneath the pulmonary annulus, a small ventriculotomy was made in the outflow tract of the right ventricle using a coronary punch biopomt (Fig. 4). After the appropriate length of the tube graft had been trimmed by perpendicular cutting, the proximal end of the shunt was directly anastomosed to the ventriculotomy. All anastomoses were performed with continuous 6/0 polypropylene sutures. The RV-PA shunt was placed to the left or to the right side of the neo-aorta (Fig. 5). The retrosternal protective pericardial ePTFE membrane (Gore-Tex membrane, 0.1-mm thick; W.L. Gore & Associates Inc., Flagstaff, AZ, USA) has been routinely used during the sternal closure in the last 4 years. Patient weight/shunt ratio (g/mm) was calculated by dividing the patient’s weight (g) by the shunt size (mm). In nine patients, the shunt lumen was reduced by means of standard vascular clips, depending on individual systemic-to-pulmonary blood flow balance.

Anticoagulation therapy after the NP included: heparin (5—10 U kg$^{-1}$ h$^{-1}$) started if there was no bleeding on the day of surgery, discontinued when the central venous line was removed, and acetylsalicylic acid (2—5 mg kg$^{-1}$ day$^{-1}$) started on the postoperative day 2—5 and continued till the second stage.

Cardiovascular function was assessed before the second stage by echocardiography (ECHO) (in all children). The diameter of the PA branches was measured in ECHO from the high parasternal short-axis view and the suprasternal short-axis view.
axis view. The measurements were made just proximal to the takeoff of the first upper-lobe branch. More than 50% reduction in PA diameter was defined as a stenosis of the artery. ECHO was also used for qualitative assessment of ventricular function (good, depressed, or poor). A post-operative electrocardiogram was performed before discharge in all cases. Data from routine blood tests performed at discharge after NP and on admission for the second stage (hematocrit value, hemoglobin concentration, red blood cell count, and capillary blood gas analysis) were also collected. The systemic arterial saturation was measured at discharge after NP and on admission for the second stage using the standard pulsoxymetry technique.

The trans-catheter approach to relieve proximal shunt stenosis between the stages included the implantation of one or two stents (5.0/18 mm, PRO-Kinetic Energy stent, Medtronic, Germany) into the RV-PA shunt.

As the second-stage procedure, hemi-Fontan operation and/or bidirectional Glenn anastomosis was performed. The surgical techniques of hemi-Fontan and Glenn operation used in our center have been previously described [14]. During the second-stage procedure, the RV-PA shunt was routinely completely removed. Immediately after institution of cardiopulmonary bypass, the shunt was divided, the proximal end was removed and ventriculotomy oversewed. The distal end of the shunt was also removed, and the PA confluence was enlarged using a homograft patch (in case of the hemi-Fontan operation) or was incorporated into the Glenn anastomosis with or without patch augmentation.

Early mortality was defined as death within 30 days of the operation, regardless of whether in or out of the hospital. Death after this period until the next stage was defined as late mortality. Data were presented as means ± standard deviation and range for continuous variables and as a count and percentage for categorical variables. The comparative
univariable analyses were carried out by means of unpaired t-test for continuous and chi-square test for categorical variables. Pearson’s correlation coefficient (r) was calculated as a measurement of association for continuous variables. Statistical significance was defined as a p value less than 0.05. All analyses were performed using STATISTICA 8.0 statistical software (StatSoft, PL).

3. Results

The mean age at the stage 1 operation was 15.1 ± 10.7 days (range, 2—82 days), and the mean weight was 3421 ± 531 g (range, 2070—4840 g). The sizes of the used PTFE tube grafts were: 4 mm in three (1.3%), 5 mm in 225 (95.3%) and 6 mm in eight (3.4%) children. The mean weight-to-shunt ratio for the whole series was 675.4 ± 92.9 g mm⁻¹ (414—968 g mm⁻¹). The shunt was placed to the left of the neo-aorta in 205 (86.9%) and to the right in 31 (13.1%) children. Delayed chest closure after NP was used in 40 (16.9%) children. The patients with right-sided to the neo-aorta shunt had significantly more frequent delayed sternal closure than children with left-sided shunt (35.5% vs 14.1%; p = 0.008).

The early and late mortality after NP were 11.8% (N = 28) and 5.9% (N = 14), respectively. Between stage 1 and 2 procedures, three children (1.3%) died due to the shunt obstruction (one of them underwent operation and died shortly afterward; two others died outside the hospital and the autopsy identified shunt thrombosis). Four children (1.7%) underwent re-operations due to the shunt obstruction (one of them died): three children had revisions of the proximal end of the RV-PA shunt (two neonates on the day of the NP and one infant 43 days after NP), and one child underwent construction of the BT shunt with closure of the RV-PA shunt 2.5 months after NP. Four (1.7%) children underwent trans-catheter stent implantation in the RV-PA shunt to address proximal shunt stenosis (placement of one or two stents) in a median time interval from NP of 2.02 months (range, 1.6—5.9 months). One child required early (before fifth month of age) second-stage procedure due to the proximal and distal shunt obstruction. Four other children were admitted to the hospital due to cyanosis, but cardiac catheterization did not reveal shunt obstruction — these children also underwent second-stage procedure before 5 months of age.

Follow-up was complete in 92.4% patients (18 children from the whole group were lost to follow-up). To date, 180 children underwent second-stage procedure: hemi-Fontan operation, 140/180 (77.8%) children; right bidirectional Glenn operation, 31/180 (17.2%); hemi-Fontan + left bidirectional Glenn operation, 4/180 (2.2%); bilateral bidirectional Glenn operation, 3/180 (1.7%); and biventricular correction, 2/180 (1.1%) infants. There was no incidence of shunt injury during the chest reopening.

The mean age of the children at the time of second-stage palliation was 7.0 ± 1.6 months (range, 4.1—14.0 months) and the mean weight was 6.4 ± 0.9 kg (range, 4.6—8.9 kg). The mean hematocrit value was 50.6 ± 5.9% (range, 35.8—67.7%), the mean hemoglobin concentration was 16.9 ± 2.1 g dl⁻¹ (range, 11.6—24.2 g dl⁻¹) and the mean red blood cell count was 6.4 ± 0.9 × 10⁶ ml⁻¹ (range, 3.9—8.6 × 10⁶ ml⁻¹). The mean systemic oxygen saturation before stage 2 operation measured by pulsoxymetry was 74.8 ± 6.6%, the mean arterial oxygen saturation in capillary blood gas analysis was 59.3 ± 9.9%, and the mean arterial partial oxygen pressure was 32.8 ± 6.7 mmHg. The same parameters measured at the time of discharge after NP were: 77.4 ± 5.6%, 72.2 ± 7.0%, and 37.6 ± 4.4 mmHg, respectively, and all were significantly higher than before second-stage palliation (p = 0.029, p < 0.001, and p < 0.001, respectively). There was no statistical correlation between these three parameters and weight (r = 0.15, r = 0.28, r = 0.18, respectively) as well as height (r = 0.14, r = 0.16, r = 0.11, respectively) before second-stage procedure.

On admission for second-stage operation, there was no difference in branch PA size (p = 0.16): the mean diameter of the right pulmonary artery (RPA) was 6.2 ± 1.6 mm (range, 3.3—12 mm) and the mean diameter of the left pulmonary artery (LPA) was 6.0 ± 1.8 (2.5—12 mm). There were also no significant differences between the size of the RPA and LPA in subgroups with the right-sided (p = 0.30) and left-sided (p = 0.23) to the neo-aorta RV-PA shunts. There was no statistical correlation between the weight-to-shunt ratio and the size of RPA (r = 0.16) and LPA (r = −0.06). PA stenosis was identified in 35/180 (19.4%) children on the right side and in 39/180 (21.7%) on the left side — almost all were localized near the PA confluence. Patch augmentation of the central pulmonary artery was performed during all hemi-Fontan operations, and in 3/34 (8.8%) children who underwent Glenn anastomosis.

Two infants (0.8%) developed aneurysm of the right ventricle infundibulum, which was resected during stage 2 without complications. The aneurysms were asymptomatic and were diagnosed during routine ECHO examination. The remaining children did not show any evidence of anterior-wall regional dyskinesia. The right ventricular function at the time of the second stage was good in 166/180 (92.2%) children and depressed in 14/180 (7.7%) infants (none had poor cardiac function). Ventricular arrhythmias were not present at any stage of treatment in analyzed electrocardiograms.

4. Discussion

The hemodynamic result of the flow though the RV-PA shunt only during the systole (and even the reversal flow into the right ventricle during the diastole) is the significantly lower Qp:Qs ratio in comparison with the BT shunt [5,7,14]. Lower volume load on the single RV is the positive consequence of that fact. In spite of no differences in oxygen delivery shortly after Norwood operation [4,5], the children, after RV-PA shunt, have significantly lower oxygen saturation and higher concentration of hemoglobin before second-stage procedure than the children after NP with BT shunt [13,14]. The decrease in oxygen saturation between the time of discharge after NP and the time of admission for the second stage was significant among our children (from 77.4% to 74.8%). However, we did not observe any complications, which can be related to the more intensive hypoxemia or a high hematocrit value. Because of early hypoxemia, some centers now perform earlier second-stage procedure [5,10—12]. The mean age of the children at the
time of second-stage palliation in the present study was 7.0 months, and only five children were admitted earlier than scheduled due to cyanosis and underwent second-stage procedure before the fifth month of age. The oxygen saturation did not correlate in our study with the physical development, which was, in our opinion, sufficient for the age. The impact of the more intensive cyanosis on neuropsychological development requires longer follow-up.

The late cyanosis after NP with RV-PA shunt may be related to the development of shunt stenoses—most frequent at the proximal or distal end of the shunt [15]. Distal-end stenosis can be associated with the central pulmonary artery stenosis, a high incidence of which (50–85%) after the RV-PA shunt was described in previous studies [11,13]. Pulmonary homograft patch augmentation of the pulmonary confluence at the shunt insertion, which was performed in all our children at the time of NP or pericardial patch enlargement perform by other surgeons [12,16], might result in less frequent central pulmonary artery stenosis during late follow-up. This problem can be also addressed by using commercially available PTFE cuff grafts, which significantly reduces the need of PA patch angioplasty at the second stage [17].

Proximal-end shunt stenosis is mostly caused by endocardial proliferation and/or hypertrophy of the ventricle [16,18,19]. Dynamic myocardial narrowing can even cause cyanotic spells similar to those occurring in children with tetralogy of Fallot. Problems with the proximal-end stenosis can, however, occur early after operation due to inadequate ventricular resection. We routinely use the coronary punch biopom to prepare the opening for the proximal shunt construction. In our opinion, this is the most effective method because it allows removing the whole wall myocardium. From the other side, the traumatization of single ventricle wall using this method is minimal, and future development of the scar tissue in this place can be avoided.

All our patients, who required re-operation due to proximal shunt obstruction early after NP, underwent revision of the RV-PA shunt with repeated proximal-end construction. We prefer revision of the RV-PA over the BT shunt construction because we believe that the child can make more profit from the RV-PA shunt than from the BT shunt. One child underwent conversion to the BT shunt with closure of the RV-PA shunt later after NP. We have remedied later stenosis with the BT shunt because the time to the possible second-stage procedure was short, and, in our opinion, there was not enough time to profit from the shunt type (BT shunt construction is a shorter operation and does not require cardiopulmonary bypass). Computational modeling has proved that if the BT shunt has been added as a remedy for RV-PA shunt stenosis, the RV-PA shunt should be taken down, because diastolic runoff through the stenotic RV-PA shunt dramatically increases retrograde flow into the single ventricle [20]. Some authors suggest balloon angioplasty to address proximal shunt obstruction [16], but the majority of centers perform stent placement in these cases [19]. In our opinion, stent enlargement of the proximal shunt stenosis is the most effective and safe procedure in the late period after NP. We did not observe any difficulties of the RV-PA shunt takedown at the second-stage operation after prior stent implantation.

The obstruction of the RV-PA shunt in its course was not observed in our material. On the other hand, the children with right-sided to the neo-aorta RV-PA shunt had more frequent delayed sternal closure, which can cause some problems with the shunt location directly beneath the sternum. More surgical or trans-catheter shunt interventions reported by some centers may reflect the learning curve associated with optimal shunt placement [10].

Underdevelopment of the PAs has been found to be an independent risk factor for morbidity and mortality after bidirectional Glenn and Fontan operation. Despite lower Qp:Qs ratio, better development of the branch PAs after NP with RV-PA shunt than after NP with BT shunt was widely reported [11–14,21]. In our opinion, this phenomenon is caused by two reasons: more centrally located distal end of the shunt, which promotes more symmetrical growth of the right and left PA, and more pulsatile blood flow (the higher pulse pressure in the shunt).

The RV-PA shunt can be positioned on the left side (as originally described), or on the right side of the neo-aorta. The left-sided course of the shunt was described to be the possible cause of the asymmetric branch PAs growth (the left PA tended to be smaller) and an increased incidence of the central pulmonary artery stenosis [11,22]. We could not observe such a relationship in our study group. Comparable diameters of the LPA and RPA were also described by other investigators [12,21]. However, we have changed our strategy and, now, we perform right-sided shunts because they facilitate preparations for Glenn anastomosis. Right-sided RV-PA shunt makes access to the shunt from the right side easier, and shortens the time of cardiopulmonary bypass at the time of second-stage procedure [11]. The place of the shunt insertion to the PA can be incorporated to the Glenn or hemi-Fontan anastomosis and allows avoiding, in the future, pulmonary stenosis due to insufficient growth of the scar tissue. Any necessary PA reconstruction is also more accessible and easier from the right side. Barron and co-workers [11] have recently described even the survival benefit after stage 2 operation of the right-sided over the left-sided shunt, which can be associated with longer length of the tube used for right-sided shunt construction (greater resistance to the pulmonary blood flow and lower regurgitant fraction imposed on the single ventricle). In the last few cases with right-sided shunts, we have used larger tubes (i.e., in children below 3.5 kg, we have used 6.0-mm tubes). In our opinion, the diameter rules have to be changed in patients with right-sided RV-PA shunt.

Interstage mortality after NP with RV-PA shunt tends to be lower than after NP with BT shunt [23]. Whether events of the sudden and unexpected deaths among our children were related to the shunt is difficult to state on the basis of the available data. The home surveillance program proposed by Ghanayem and co-workers [24] could help clear the causes of unexpected deaths and improve interstage survival.

Despite the incision of the single-ventricle anterior wall for the proximal RV-PA shunt insertion, most investigators describe good ventricular function, even better than in children after NP and BT shunt [6,7,11]. Preservation of the ventricular function is crucial for long-term results and merits further investigation. For now, however, right ventriculotomy does not result in ventricular dysfunction.
or ventricular arrhythmias in the majority of centers where this modification of NP is performed [25].

According to our experience, the RV-PA shunt can be a safe and efficient technique in providing optimal pulmonary blood flow in children with HLHS after NP, performed with a minimal rate of complications. In our opinion, the use of RV-PA shunt in NP does not require earlier second-stage procedure.

References


Appendix A. Conference discussion

Dr C. Pizarro (Wilmingtom, USA): The study presented by Dr Januszewska and colleagues probably represents one of the largest experiences ever reported with a Norwood procedure in Europe. This study, to some extent, reaffirmed some of the notions regarding the postoperative course of patients who received a conduit from the right ventricle to the pulmonary artery, their postoperative course, and the need for reinterventions, as well as some technical issues.

In the absence of a group for comparison, it seems appropriate to use the recently published SVR trial experience as a frame of reference, given the fact that this represents the largest and best study group of patients undergoing the Norwood operation, and the fact that this study had objective assessment of imaging data using core laboratories for angiographic and echocardiographic studies.

One of the findings of this particular cohort was a significant crossover rate at the time of surgery which was of the order of about 10% for a number of different reasons.

One was the fact that surgeons thought at the time of surgery that the RV-PA conduit could not be safely performed and/or, secondly, that after surgery some of these patients would experience significant hypoxemia to the extent that a shunt conversion was undertaken.

I was surprised to see that there was only one patient in your cohort who underwent a change, and I would like to ask you, What do you think or what do you believe are the reasons why your crossover rate was exceedingly low compared to a significant, let’s say, ten-fold increase in the other cohort?

Dr Januszewska: So the question is why so few children underwent re-operation?

Dr Pizarro: No. The question is why do you believe that in your series, the crossover rate is almost zero, meaning that there was only one patient who was changed from an RV-PA conduit to a BT shunt, whereas in the SVR trial, which includes 555 patients, that rate was 10%?

Dr Januszewska: Our current strategy is to revise RV-PA shunt if there are problems, i.e., obstruction, in the early period after the operation; this means days, weeks after the Norwood procedure. We believe that the child has enough time to the second-stage procedure to benefit from this type of shunt.

Only one child underwent a construction of the Blalock—Taussig shunt, and this operation was performed at the age of 3 months. There was not enough time to the second-stage procedure to benefit from this type of shunt.
shorter operation, which is why it was performed. Of course, we closed the RV-PA shunt during the BT shunt construction.

Dr Pizarro: In addition, I noticed in the manuscript that the mean age at the time of surgery was about 15 days, which is distinctly different from the experience of many other centers. As a matter of fact, some data from the Congenital Heart Surgeons’ Society suggests that a cutoff of about 14 days represents a significant increase in the risk of mortality immediately after surgery, probably to some extent because you leave pulmonary vasculature unprotected from high volume, high pressure in those patients who behave as having increased pulmonary vascular resistance after surgery.

So could you tell us a little bit about how you managed patients in the postoperative period? How long were they in the ICU? Were they ventilated? Did you use nitric oxide?

Dr Januszewska: That is right, it was a relatively old group of patients because the majority of the children had been operated in Poland, and a lot of patients had no prenatal diagnosis. Because of this, the diagnosis was very often made after birth and the mean age at the operation was high.

Regarding the postoperative management, we did not really observe that these children had increased pulmonary resistance due to the late operation. So in the majority of children, we did not use nitric oxide or other methods of management to decrease the pulmonary resistance.

Dr Pizarro: Lastly, in reference to your conclusions, while your statement about the merits of the RV-PA conduit is supported by a number of other reports, including the SVR trial, I would tend to slightly disagree with your second statement regarding the absence of hypoxemia during follow-up, given the fact that the aortic saturation and arterial blood gas sample had a mean under 60%. This was also associated with hematocrit of the order of about 50%, which led me to believe that in fact some of these patients were quite hypoxemic. And perhaps a number of different centers might have taken a different attitude in terms of moving ahead a little bit earlier regarding that intervention.

Therefore, I think that your last statement might not necessarily be substantiated by data, but rather, the attitude or conduct of your particular preference regarding that issue.

Dr Januszewska: The mean saturation before the second-stage procedure measured by pulse oximetry was 74%, and we think it is completely acceptable.

This measurement that you are talking about, this was arterial saturation from the capillary blood gas. In our opinion this is not an adequate and accurate method of measurement because the percentage of failure in this method of measurement is very high. Because of this, as shown in the presentation, measurement was by pulse oximetry.

Dr Pizarro: Do you have any cath data in preparation for second stage, that could provide the saturation of blood gases?

Dr Januszewska: Yes.

Dr Pizarro: I think that would be important.

Dr Januszewska: The slide shows that the mean aortic saturation in cardiac catheterization before the second stage was 71%.

Dr Pizarro: I think this is very important information. Perhaps you should include this in the manuscript.

Dr Januszewska: Yes we will do it.

Dr Pizarro: Given the size of your cohort, I would encourage you to establish a prospective follow-up protocol in order that we can learn from the lessons this large cohort has to offer in general.