Early Outcomes of Cardiac Surgery in Patients with Noonan Syndrome

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There is a paucity of cardiac surgery outcomes data for patients with Noonan syndrome (NS). Our objective was to evaluate early results in these patients. Between January 1999 and December 2015, 29 patients (18 males, 62%) with NS underwent cardiac surgery at our institution. Mean age was 23 ± 17.9 years; 12 (41%) were under 18 years of age. Fourteen patients (48%) had prior sternotomies. The primary operations for the main diagnosis were pulmonary valve/conduit replacement/repair ($n = 14$, 48%), septal myectomy for obstructive hypertrophic cardiomyopathy ($n = 7$, 24%), aortic valve replacement/repair ($n = 4$, 14%), atrial septal defect (ASD) repair ($n = 2$, 7%), and cardiac transplantation ($n = 2$, 7%). Concomitant procedures were performed in 24 patients (83%), most commonly right ventricular outflow tract reconstruction ($n = 13$, 45%), mitral valve repair/replacement ($n = 7$, 24%), and ASD repair ($n = 6$, 21%). Mean bypass and cross-clamp times were 88.8 ± 51 minutes and 54.7 ± 67 minutes, respectively. There was 1 early death (3%). Postoperative morbidity occurred in 18 patients (62%), most commonly arrhythmias ($n = 14$, 48%) or respiratory insufficiency/pneumonia ($n = 6$, 21%). There were 2 early reoperations and 4 early readmissions. Univariate factors associated with morbidity included male gender ($P = 0.03$) and longer cross-clamp time ($P = 0.02$). Median length of hospital stay was 6 days (interquartile range 5–10.5 days). Patients with NS frequently have multiple cardiac lesions requiring a broad spectrum of operations. Early mortality is low despite procedure complexity. Although early postoperative morbidity is common, patients overall do well with reasonable hospital lengths of stay. Additional studies are needed to evaluate long-term outcomes and quality of life.

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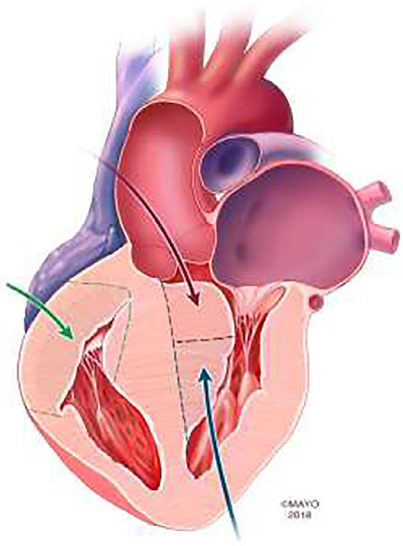
Keywords: Noonan Syndrome, Congenital heart disease, Pulmonary stenosis, Hypertrophic cardiomyopathy, Septal myectomy



Septal myectomy approaches for biventricular obstruction in hypertrophic cardiomyopathy.

Central Message

Patients with Noonan syndrome frequently have multiple cardiac lesions and can undergo complex cardiac surgery safely.

Perspective Statement

Noonan syndrome is the second most common genetic syndrome associated with congenital heart disease. Our study shows that complex cardiac surgery to address multiple cardiac defects can be performed safely with low early mortality. A multidisciplinary approach to pre-, intra-, and postoperative care is essential to optimize outcomes.

Abbreviations: ASD, atrial septal defect; AV, aortic valve; CI, confidence interval; CHD, congenital heart disease; HCM, hypertrophic cardiomyopathy; ICU, intensive care unit; LV, left ventricle; LVOT, left ventricular outflow tract; NS, Noonan syndrome; OR, odds ratio; PV, pulmonary valve; RV, right ventricle; RVOT, right ventricular outflow tract; SD, standard deviation

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BACKGROUND

Noonan syndrome (NS) is the second most common genetic syndrome associated with congenital heart disease.[1] This autosomal dominant disorder has an incidence of 1:1000–2500 live births.[2] Over 80% of patients with NS have cardiac involvement and the most common lesions are pulmonary stenosis, atrial septal defects (ASD), and hypertrophic cardiomyopathy (HCM).[1,3] Most patients have multiple congenital cardiac defects that may require complex cardiac operations.[1,4]

The most common genetic anomaly in NS, found in 50% of patients, is a germline mutation of the protein tyrosine phosphatase *PTPN11*.[5] This is associated with classic NS with features of widely spaced eyes (hypertelorism), low-set ears, short stature, and chest deformities. The *PTPN11* mutation results in the highest incidence of pulmonary stenosis and ASD.[6] The other known NS genetic mutations are typically in Ras/mitogen-activated protein kinase pathway proteins, such as *RAF1* and *MRAS*, which are both associated with HCM.[7]

Despite the strong association of NS with congenital cardiac disease, there is a paucity of outcomes data for cardiac surgery in these patients. Our objective was to evaluate the early results of cardiovascular surgery in patients with NS, focusing on indications for surgery, the spectrum of cardiac operations and concomitant procedures, and risk factors for early morbidity and mortality. This is the largest cohort of patients with NS and early cardiac surgical outcomes data reported in the literature.

METHODS

Following approval by the Mayo Clinic Institutional Review Board (July 20, 2017), the Mayo Clinic congenital and adult cardiac surgery research databases were searched for patients with a diagnosis of NS who had provided research authorization. Between January 1, 1999, and December 31, 2015, there were 585 cardiac operations performed on patients with genetic syndromes at the Mayo Clinic in Rochester, Minnesota. Patients with a documented clinical (phenotypic) and/or genetic (genotypic) diagnosis of NS prior to cardiac surgery were included. We excluded patients with ambiguous ("possible diagnoses" noted in the chart) or those with other concomitant genetic syndromes.

We identified 29 patients with NS who underwent cardiac surgery. Data were extracted on demographics, cardiac diagnoses, related symptoms, comorbidities, types of primary operations (for the primary cardiac diagnosis) and concomitant procedures (for additional cardiac lesions or diagnoses), early morbidity and mortality (less than 30 days postoperatively and/or in-hospital), and early readmissions. The techniques of some of the individual surgical procedures were straightforward (ASD closure, aortic valve replacement, etc.) but the technique for myectomy, particularly biventricular myectomy, has not been previously described and deserves further comment.

Technique of Left Ventricular Septal Myectomy

Transaortic extended septal myectomy is most effective for left-sided basal septal hypertrophy with systolic anterior motion-mediated left ventricular outflow tract (LVOT) obstruction and mitral regurgitation. The apical extent of the muscular resection is crucial and should mirror the anterior mitral leaflet, chordal apparatus, and papillary muscles. The size of the aortic annulus dictates the feasibility of how far down into the ventricle (ie, apical extent) the resection can be performed.

In situations when muscular resection in the mid-ventricle cannot be safely reached from a transaortic approach, a concomitant left ventricular (LV) apical ventriculotomy can be performed. This is accomplished with a small LV apical incision lateral and parallel to the left anterior descending coronary artery. A generous septal and free wall resection can be performed depending on the degree of hypertrophy. The most important technical maneuver is to avoid injury to the papillary muscles, which are commonly displaced closer to the apex of the LV cavity. The papillary muscles always arise from the free wall of the LV. Muscle resection is initiated along the septum that is free of chordal structures, and once intracavitary visualization is optimized, additional resection is done on the anterolateral and posterolateral free walls. Further resection can also be performed on hypertrophied papillary muscles. It is important not to perform muscle resection along the ventriculotomy in order to minimize the development of late apical aneurysm formation.

Technique of Right Ventricular Septal Myectomy

In contrast to left-sided myectomy, the strategy to relieve right-sided obstruction is different. The approach to right-sided myectomy includes a high right ventriculotomy beginning just inferior to the pulmonary valve. The distal extent down the anterior free wall of the right ventricle (RV) is determined by the extent of hypertrophy. Muscle resection through the ventriculotomy along the RV free wall is straightforward; care is taken to avoid injury to the tricuspid valve apparatus. Only a limited resection on the right side of the ventricular septum can be performed since the chordal support of the tricuspid valve is present along the ventricular septum. The combination of severe, diffuse hypertrophy of the RV free wall and ventricular septum, in combination with a variable tricuspid subvalvar apparatus with attachments to both the free wall and septum, make transatrial muscular resection rarely adequate. Importantly, the ventriculotomy is closed with a patch in order to completely alleviate and prevent recurrent right ventricular outflow tract (RVOT) obstruction (see framed illustrations in Fig. 1). Figure 1 also summarizes the approaches and areas of resection for right- and left-sided myectomies.

Statistical Analysis

Categorical variables are reported as frequencies with percentages and continuous variables are reported as mean ± standard deviations or median (interquartile range). To test the association of pre- and perioperative factors with presence of postoperative morbidity, univariate logistic regression models were used to determine odds ratios with 95% confidence intervals and *P* values. The Kaplan-Meier method was used to estimate survival at 1, 5, and 10 years. The reverse Kaplan-Meier method (where death is considered censored) was used to summarize the median follow-up time. All statistical tests were two-sided with the alpha level set at 0.05 for statistical significance. Analyses were carried out in SAS version 9.4M5 (SAS Institute, Cary, NC).

Patient Population

Mean age of the patients was 23 ± 17.9 years (range: 2 months to 63 years) and 12 patients (41%) were under 18 years of age. The most prevalent preoperative symptoms

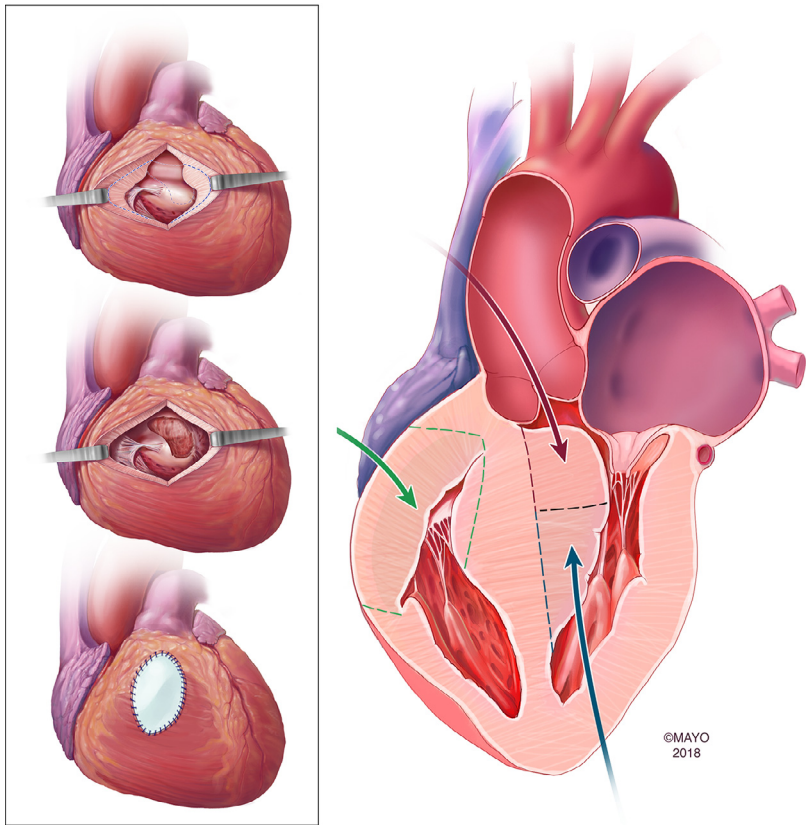


Figure 1. Myectomy approaches (arrows) include transaortic (purple) and transapical (blue) for the LV, and transventricular (green) for the RV. The associated areas of resection are shown with dotted lines. The framed illustrations show the transventricular right-sided approach with patch reconstruction of the RVOT. (Color version of figure is available online at http://www.semthorcardiovascsurg.com.)

were fatigue (55%) and dyspnea (48%). None of the patients had a documented diagnosis of hypertension, coronary artery disease, or diabetes mellitus. Nearly half of patients had a prior sternotomy prior to the study period ($n = 14$, 48%). Other relevant comorbidities and preoperative information are outlined in Table 1 and the primary cardiac diagnoses are shown in Table 2.

Table 1. Patient Demographics and Preoperative Comorbidities

Variable	Frequency (%) or Mean ± SD
Age (y)	23.0 ± 17.9
Male gender	18 (62%)
Premature*	4 (15%)
Arrhythmia	8 (28%)
History of stroke	2 (7%)
Previous sternotomy	14 (48%)
Ejection fraction (%)	65 ± 10
Creatinine (mg/dL)	0.7 ± 0.3
Hemoglobin (g/dL)	12.8 ± 2.6

SD, standard deviation.
*Premature defined as born before 39 weeks' gestation.

RESULTS

All patients had a median sternotomy and underwent hypothermic or normothermic cardiopulmonary bypass with aortic occlusion and cardioplegic arrest. Mean cardiopulmonary bypass and aortic cross-clamp times were 88.8 ± 51 minutes and 54.7 ± 67 minutes, respectively. The primary operations, outlined in Table 3A, were defined as the main procedures performed for patients' primary diagnoses during the study period at Mayo Clinic. Of the 29 patients, 24 (83%) required concomitant procedures, which are outlined in Table 3B. Concomitant procedures included any operative intervention for secondary diagnoses or additional cardiac lesions at the time of the primary operation.

There was 1 in-hospital death, secondary to multiple organ failure. The patient was a 13-month-old child who was born at 29 weeks gestation with NS (*RAF1* missense mutation). The patient was diagnosed with biventricular HCM and restrictive cardiomyopathy, severe pulmonary stenosis, single coronary artery arising from the right sinus, and transitional atrioventricular septal defect (primum ASD and inlet ventricular septal defect). Given the extent of the cardiac pathologies with restrictive cardiomyopathy, failure to thrive, failed balloon pulmonary valvuloplasty, and single right coronary artery, the patient underwent cardiac allotransplantation. The operation was

Table 2. Preoperative Primary Cardiac Diagnoses

Diagnosis	Frequency	%
PV stenosis/regurgitation	15	52
Obstructive HCM	8	28
AV stenosis/regurgitation ± aortopathy	4	14
Atrial septal defect	2	7

AV, aortic valve; HCM, hypertrophic cardiomyopathy; PV, pulmonary valve/conduit.

uneventful but the child required significant inotropic support for systemic vasoplegia. Despite adjusting inotropic support, persistent and progressive vasoplegia with hypotension occurred in the ICU and cardiac arrest ensued. The patient required open cardiac massage several hours after transplantation and was placed on extracorporeal membrane oxygenation. Renal and respiratory failure eventually developed and the care team and the family decided to have extracorporeal circulatory support withdrawn on postoperative day 49.

Two patients underwent delayed sternal closure. There were 2 early reoperations; 1 for sternal dehiscence and the other for epicardial permanent pacemaker placement. Postoperative morbidity was documented in 18 patients (62%) and subtypes are shown in Table 4. Univariate analysis of pre- and perioperative factors determined that male gender and longer cross-clamp times were associated with higher frequency of postoperative morbidity (Table 5).

Table 3. (A) Primary Operations, (B) Concomitant Procedures

Primary Operation	Frequency	% Patients ($n = 29$)
PV replacement/repair	14	48
Septal myectomy[†]	7	24
AV replacement/repair	4	14
Atrial septal defect repair	2	7
Cardiac transplant	2	7
Concomitant Procedure ($n = 41$)	**Frequency**	**% Patients ($n = 29$)***
RVOT reconstruction	13	45
MV replacement/repair	7	24
Atrial septal defect repair	6	21
Ascending aortic replacement	3	10
TV replacement/repair	3	10
Ventricular septal defect repair	2	7
Other operation	7	24

AV, aortic valve; MV, mitral valve; PV, pulmonary valve/conduit; RVOT, right ventricular outflow tract; TV, tricuspid valve.
Primary operations are defined as the main operation performed during the study period at Mayo Clinic for the primary cardiac diagnosis. A total of 41 concomitant procedures were performed for additional diagnoses/lesions at the time of the primary operation in 24 of 29 patients (83%).
*The total of the percentages exceeds 100% because some patients had multiple concomitant procedures.
[†]Two patients underwent biventricular myectomies.

Table 4. Early Postoperative Morbidity

Morbidity	Frequency	% Patients*
Arrhythmia	14	48
Respiratory	6	21
Chylothorax	3	10
Dialysis	3	10
Stroke	2	7
Pericardial effusion	2	7

Overall, 18 patients (62%) experienced some type of postoperative morbidity. All 14 patients with arrhythmia had atrial arrhythmias and 3 also had ventricular arrhythmias. Respiratory complications included respiratory insufficiency (prolonged ventilation) and/or pneumonia (1 patient experienced both).
*The percentage refers to percentage of total patients and exceeds 100% as some patients had more than 1 type of morbidity.

Table 5. Risk Factors Associated With Early Morbidity

Predictor	OR	95% CI	*P* Value
Male gender	6.13	1.17–32.10	0.03
Cross-clamp time (per 10 min)	1.53	1.07–2.21	0.02
Age <18	5.63	0.94–33.76	0.06
Age (y)	0.97	0.93–1.02	0.25
Bypass time (per 10 min)	1.19	0.96–1.48	0.12
Previous sternotomy	0.36	0.08–1.72	0.20

CI, confidence interval; OR, odds ratio.
Univariate logistic regression; *P* values <0.05 were deemed to be statistically significant.

Median length of hospital stay was 6 days (interquartile range of 5–10.5 days). There were 4 early readmissions that occurred for the following indications: atrial fibrillation, ventricular tachycardia, gastrointestinal bleeding, and unspecified abdominal pain. In addition to early results, we determined late survival for these patients. Median follow-up time was 5.3 years (interquartile range of 1.8–13.0 years). Survival at 1, 5, and 10 years was 97%, 97%, and 80%, respectively (Fig. 2).

Of note, 1 patient required late cardiac transplantation. He was a 51-year-old male with restrictive cardiomyopathy, end-stage biventricular failure, and severe pulmonary stenosis with associated severe RV hypertrophy. The patient initially underwent pulmonary valvotomy with subtotal ASD closure at 8 years of age. Given the patient's progressing restrictive cardiomyopathy, dyspnea with oxygen dependency, and severe diastolic dysfunction with biatrial enlargement, the patient subsequently underwent cardiac transplantation. The postoperative course was notable for early reoperation for sternal dehiscence, pericardiocentesis for symptomatic pericardial effusion, and temporary dialysis catheter placement for acute renal failure. After resolution of these issues, the patient was dismissed home on postoperative day 23 with improving renal function and is alive 15 years after transplantation.

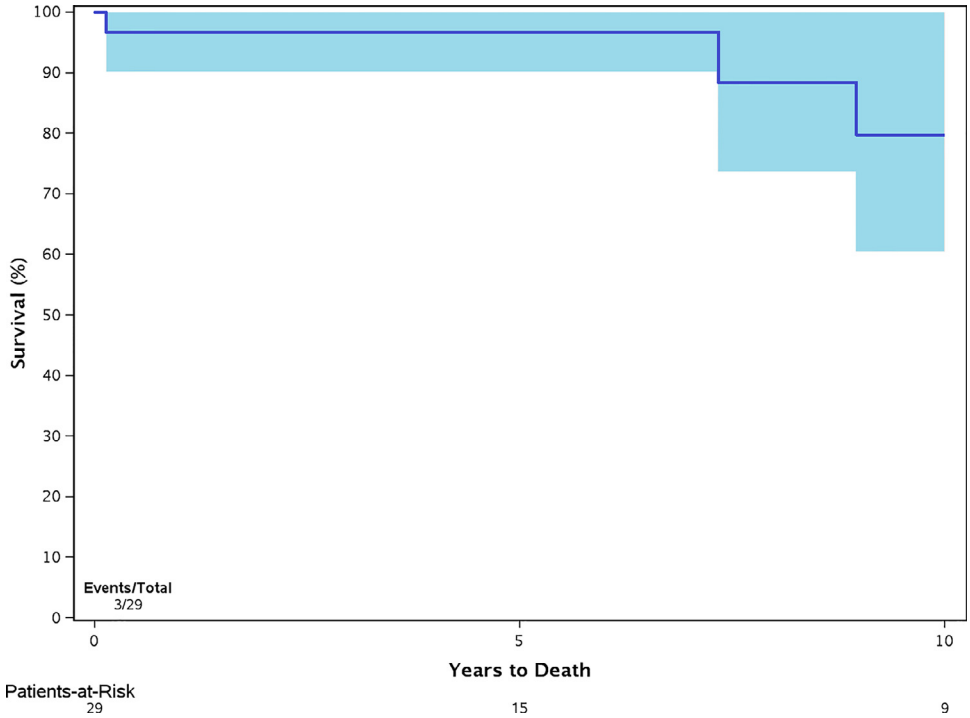


Figure 2. Long-term survival is shown using the Kaplan-Meier method with 1-, 5-, and 10-year rates at 97%, 97%, and 80%, respectively.

DISCUSSION

This study cohort is one of the largest groups of cardiac surgery patients with NS and the largest with early outcomes data analysis. The congenital heart defects in these patients may require multiple cardiac procedures at the time of operation. This study demonstrates that isolated and multiple cardiac surgical procedures can be performed safely in this patient population.

Limited data on results of interventions performed in patients with NS are available elsewhere in the literature. In a large retrospective review, patients with NS with pulmonic stenosis had higher reintervention rates than patients without NS who had undergone prior percutaneous balloon valvuloplasty.[1] The authors attribute this to the dysplastic nature of the valve. In addition, patients typically require RVOT reconstruction (due to subpulmonic stenosis) in addition to pulmonary valve intervention, which was concordant with our study results.

Patients with NS, left ventricular hypertrophy, and LVOT obstruction present with symptoms at an earlier age compared to nonsyndromic patients with HCM.[8] A study from the Mayo Clinic in 2015 evaluated 12 patients with NS and symptomatic isolated LVOT obstruction.[9] In this earlier study, we concluded that septal myectomy was safe and effective with improved New York Heart Association functional class and successful reduction in LV intracavitary gradients. In addition, we noted that these patients with NS had more mitral valve interventions due to structural mitral abnormalities. As a result, longer bypass and cross-clamp times secondary to increased need for papillary muscle bundle resection and concomitant mitral valve repair were noted. In this current group of patients, the indication for mitral valve intervention was most commonly severe mitral regurgitation.

Another important observation in the 2015 study of patients with NS was higher frequency of endocardial fibrosis (moderate or greater) compared to nonsyndromic patients. This pathologic finding was correlated with higher mean grade of mitral regurgitation. We suggested that subendocardial fibrosis was a result of both shear stress forces from systolic anterior motion at the point of mitral-septal contact and a more advanced restrictive cardiomyopathy.

HCM in this patient population with NS presents other challenges, such as biventricular outflow tract obstruction, increased likelihood of congestive heart failure at time of diagnosis, and increased incidence of other structural cardiac malformations. In 1 series of 30 children with NS and HCM, 57% had a second, coexisting congenital heart defect (compared to 2.5% in nonsyndromic HCM) and had an overall worse risk-adjusted survival rate.[1,10] When the diagnosis was made in infancy (57% of NS-HCM patients present before the first year of life), 1-year mortality rates exceeded 30% and more than doubled when class IV heart failure was present.[8] In summary, the authors reported that risk factors for mortality in NS and HCM were the diagnosis of HCM in the first 6 months of life and congestive heart failure at the time of diagnosis. In addition, they also emphasized that the higher prevalence of

multiple congenital cardiac diagnoses in patients with NS (83% in our study, which was even higher as we included patients with HCM and other diagnoses as well).

Given the need to address multiple abnormalities in these syndromic patients, especially when pathology involved both ventricles, we anticipated longer bypass and cross-clamp times. Importantly, most patients (83%) required multiple procedures. Patients with pulmonary valve/conduit stenosis or regurgitation most often required repair or replacement of the pulmonary valve in addition to RVOT reconstruction. When a septal myectomy was performed for HCM, all but 1 patient required a concomitant procedure. This was most commonly a mitral valve repair (for known mitral regurgitation preoperatively) and/or ASD closure. Four patients required operations on the right side of the heart as well (1 tricuspid valve repair for preoperative tricuspid valve regurgitation, 1 RVOT reconstruction, and 2 biventricular myectomies). In general, we make a concerted effort to offer conventional cardiac surgery to address the structural defect(s) present, particularly when obstructive lesions are the primary abnormality (eg, right- or left-sided outflow tract obstruction). However, it is important to be cautious when evaluating significant (isolated or concomitant) regurgitant lesions, as this may represent an underlying restrictive cardiomyopathy that may be better treated with transplantation.

In the current review, it is not surprising that morbidity was more common relative to rates in nonsyndromic patients undergoing congenital cardiac surgery. Reports in patients with 22q11 deletion and DiGeorge syndrome demonstrated longer mechanical ventilation times and hospital and ICU lengths of stay, higher early reoperation rates, and more subspecialty consultations for noncardiac organ system dysfunction.[11–13] Down syndrome has been associated with longer ventilation times and ICU lengths of stay, but no significant increase in early mortality rates.[14–16]

As outlined in Table 4, over 60% of patients had some type of postoperative morbidity, predominantly related to arrhythmias or respiratory/pulmonary issues (prolonged ventilation or pneumonia). The finding of increased atrial arrhythmias was unexpected in this relatively younger patient population, in contrast to older patients (greater than 70 years of age) where atrial fibrillation, depending on the operation, can occur more than 50% of the time.[17] Whether this increased susceptibility to atrial arrhythmias is related to some degree of diastolic dysfunction with atrial dilation is not clear. While the majority of patients in our series were discharged on beta blocker therapy, we are now more aggressive with the short-term use of perioperative amiodarone therapy in an effort to avoid early hospital readmission for control of atrial arrhythmias. Despite a higher incidence of atrial tachyarrhythmias and some episodes of prolonged ventilatory requirement, patients with NS overall did well. The median hospital length of stay of 6 days was comparable to congenital cardiac surgical patients without genetic syndromes.

Limitations of Study

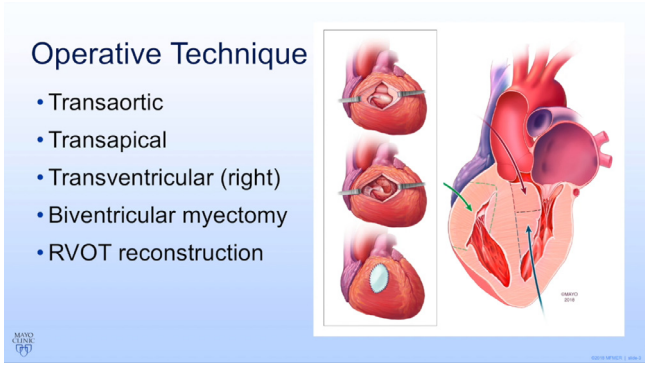
This study is a relatively small retrospective case series given the focus on 1 genetic syndrome. Genotypic evaluation was not performed on every patient and inclusion criteria relied on clinical diagnosis of NS. Moreover, given the 17-year span of the study, many of the patients were operated on prior to the discovery of newer genes associated with NS and gene panels. Also, the results from this case series should not be generalized to every healthcare system. This study was conducted at 1 institution with a long, experienced track record of medical and surgical expertise in adult congenital heart disease, HCM, and the surgical procedures performed, particularly septal myectomy. Finally, the importance of an integrated, multidisciplinary approach to the care of this patient population cannot be overemphasized and was present throughout the duration of the study.

CONCLUSIONS

Patients with NS frequently have multiple cardiac lesions that need to be repaired with a broad spectrum of operations. Early mortality is low despite procedure complexity. Although early postoperative morbidity is common in this relatively younger population, patients overall do well with reasonable hospital lengths of stay. Additional studies are needed to investigate long-term outcomes and quality of life.

SUPPLEMENTARY MATERIAL

The following is the supplementary data to this article:



Video 1. This video highlights the importance of this study and outlines the background, objectives, operative techniques discussed, and conclusions derived from the analysis.

REFERENCES

1. Prendiville T, Gauvreau K, Tworog-Dube E, et al: Cardiovascular disease in Noonan syndrome. Arch Dis Child 99:629–634, 2014
2. Roberts A, Allanson J, Tartaglia M, et al: Noonan syndrome. Lancet 381:333–342, 2013
3. Burch M, Sharland M, Shinebourne E, et al: Cardiologic abnormalities in Noonan syndrome: Phenotypic diagnosis and echocardiographic assessment of 118 patients. J Am Coll Cardiol 22:1189–1192, 1993
4. Calcagni G, Limongelli G, D'Ambrosio A, et al: Cardiac defects, morbidity and mortality in patients affected by RASopathies. CARNET study results. Int J Cardiol 245:92–98, 2017

5. Tartaglia M, Cordeddu V, Chang H, et al: Paternal germline origin and sex-ratio distortion in transmission of PTPN11 mutations in Noonan syndrome. Am J Hum Genet 75:492–497, 2004
6. Aoki Y, Niihori T, Inoue S, et al: Recent advances in RASopathies. J Hum Genet 61:33–39, 2016
7. Razzaque M, Nishizawa T, Komoike Y, et al: Germline gain-of-function mutations in RAF1 cause Noonan syndrome. Nat Genet 39:1013–1017, 2007
8. Wilkinson J, Lowe A, Salbert B, et al: Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: A study from the Pediatric Cardiomyopathy Registry. Am Heart J 164:442–448, 2012
9. Poterucha J, Johnson J, O'Leary P, et al: Surgical ventricular septal myectomy for patients with Noonan syndrome and symptomatic left ventricular outflow tract obstruction. Am J Cardiol 116:1116–1121, 2015
10. Hickey E, Mehta R, Elmi M, et al: Survival implications: Hypertrophic cardiomyopathy in Noonan syndrome. Congenit Heart Dis 6:41–47, 2011
11. O'Byrne M, Yang W, Mercer-Rosa L, et al: 22q11.2 Deletion syndrome is associated with increased perioperative events and more complicated postoperative course in infants undergoing infant operative correction of truncus arteriosus communis or interrupted aortic arch. J Thorac Cardiovasc Surg 148:1597–1605, 2014
12. Yeoh T, Scavonetto F, Hamlin R, et al: Perioperative management of patients with DiGeorge syndrome undergoing cardiac surgery. J Cardiothorac Vasc Anesth 28:983–989, 2014
13. Mercer-Rosa L, Pinto N, Yang W, et al: 22q11.2 Deletion syndrome is associated with perioperative outcome in tetralogy of Fallot. J Thorac Cardiovasc Surg 146:868–873, 2013
14. Lal P, Chavan B, Devendran V, et al: Surgical outcome of congenital heart disease in Down's syndrome. Asian Cardiovasc Thorac Ann 21:166–169, 2013
15. Tóth R, Szántó P, Prodán Z, et al: Down syndrome and postoperative complications after paediatric cardiac surgery: A propensity-matched analysis. Interact Cardiovasc Thorac Surg 17:691–697, 2013
16. Fudge Jr J, Li S, Jaggers J, et al: Congenital heart surgery outcomes in Down syndrome: Analysis of a national clinical database. Pediatrics 126:315–322, 2010
17. Hogue C, Hyder M: Atrial fibrillation after cardiac operation: Risks, mechanisms, and treatment. Ann Thorac Surg 69:300–306, 2000