Perioperative management and considerations in pediatric patients with connective tissue disorders undergoing cardiac surgery

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Abstract

Background: Marfan syndrome and Loeys-Dietz syndrome are connective tissue disorders associated with cardiac and vascular disease. Patients often require surgical repair, but limited data exist to describe their perioperative management.

Aims: Our goals were to review the perioperative features of patients with Marfan and Loeys-Dietz syndrome that may affect anesthesia care and to describe the differences in preoperative clinical characteristics and intra-operative anesthetic management.

Methods: We conducted a retrospective cohort study of patients with Marfan and Loeys-Dietz syndrome who underwent cardiac surgery at a single institution. We collected demographic and perioperative data from the electronic medical record and performed descriptive statistics to characterize the patient populations and describe their anesthetic management.

Results: In 71 patients (40 Marfan, 31 Loeys-Dietz), we found significant differences between the Marfan and Loeys-Dietz patients in airway difficulty, preoperative weight, blood utilization, valvular disease, and age at first cardiac surgery. Patients with Loeys-Dietz syndrome had higher preoperative rates of severe noncardiac co-morbidities, including gastroesophageal reflux and asthma that required chronic medical therapy.

Conclusions: Despite undergoing similar surgical procedures, patients with Marfan and Loeys-Dietz syndrome have different intrinsic patient characteristics and comorbidities that may affect their perioperative care. This retrospective cohort study identified some factors, but additional collection and reporting of patient data based on multicenter experience are essential for the ongoing optimization of perioperative care in these patient populations.

Keywords: connective tissue disorders, loeys-dietz, marfan
1 | INTRODUCTION

Connective tissue diseases are a relatively rare, heterogeneous group of disorders that include Marfan syndrome and Loeys-Dietz syndrome (LDS). Both syndromes convey a predisposition toward cardiac valvar and aortic aneurysmal disease, which may require initial surgical intervention during childhood or adolescence.1,2 Some studies suggest that patients with LDS tend to have more aggressive aortic phenotypes than patients with Marfan syndrome that may necessitate surgery at an earlier age.3 In particular, patients with LDS type I, as compared to type II, have a median age of first surgery in adolescence versus adulthood.3 Other studies show that patients in both populations may have equally aggressive disease that requires surgery at a young age to prevent fatal complications, though death from disease complications tends to occur earlier and with greater frequency in the LDS population.4–6 A review of the Pediatric Health Information System registry, which includes pediatric patients at 40 participating institutions, showed that 294 patients with Marfan syndrome under the age of 25 were hospitalized over an 11-year period.6 Of these 294 patients, 213 (72%) required at least one aortic root and/or valve surgery, 51 (17%) required at least one mitral valve surgery, and 43 (15%) underwent operations on both valves during a single hospitalization.6 Some evidence suggests that patients with LDS have a similar risk of aneurysmal disease but that aortic dissections may occur at smaller diameters than they do in Marfan syndrome patients with comparably sized aortic vasculature and may be affected more distally than the aortic root.3,7,8

In addition to cardiovascular disease, patients often have other prominent comorbidities, including scoliosis and chest wall deformities, high-arched palate, obstructive sleep apnea (OSA), and global low muscle tone.1,3,7–9 Many of these common, noncardiovascular comorbidities have the potential to impact airway management, hemodynamic stability, intra-operative blood loss, and extubation planning while patients are under anesthesia care.

Much of the perioperative literature characterizing Marfan syndrome and LDS is surgical in nature, primarily describing novel surgical techniques and related outcomes.5,9–12 However, the body of literature describing patient care under general anesthesia is notably limited and largely restricted to orthopedic and obstetric procedures in adult patients.13–15 A few small case reports discuss the specifics of the anesthetic management of patients with Marfan syndrome and LDS undergoing cardiothoracic surgery.16,17 Patients with LDS are even less well-studied, given that the genotype and phenotype were much more recently described than those for Marfan syndrome.8,17,18

Our institution is a pediatric quaternary care center with a large referral population of pediatric and young adult patients with Marfan syndrome and LDS undergoing cardiac surgical repair of their valvaral and aortic disease. Using an institutional database of perioperative patient data, we sought to describe this cohort of patients, which is larger than any similar cohort previously described in the pediatric cardiac anesthesia literature. For this study, we narrowed our focus to identify the preoperative characteristics of these patients that are often associated with increased risk under anesthesia, such as known difficult airway, younger age, or prior cardiac surgery. We also described the salient features of intra-operative management, such as blood product transfusion, cardiopulmonary bypass times, and rates of immediate postsurgical extubation. Additionally, although patients with Marfan syndrome and LDS are commonly grouped together under the umbrella of connective tissue diseases, we aimed to identify the patient characteristics and comorbidities that distinguish these individual disease entities, which might enable pediatric cardiac anesthesia providers to better understand their patients with distinct connective tissue diseases.
2 | METHODS

2.1 | Study design

We conducted a retrospective observational cohort study of all patients between 0 and 21 years of age with a diagnosis of Marfan syndrome or LDS who underwent cardiovascular surgery at our institution between 2010 and 2017. If a patient underwent more than one operation during this period, each surgery was counted as a separate patient encounter. This study was approved by the Johns Hopkins Institutional Review Board with a waiver of consent. The Figure 1 was self-made by a member of our team.

2.2 | Data collection

We collected electronic medical record data from preoperative outpatient appointments, preoperative ward, or intensive care unit (ICU) for those patients admitted before surgery, the operating room, and the immediate postoperative ICU admission.

Preoperative patient demographic data included age, sex, weight, and body mass index (BMI). Preoperative clinical data included echocardiographic descriptions (absolute size and z-scores) of the aortic valve, aortic root, and ascending and descending aorta. Additional echocardiographic abnormalities were recorded, including evidence of valvular or ventricular dysfunction or coronary disease. Home medications were recorded, specifically antihypertensive or afterload-reducing agents, pulmonary medications, and gastrointestinal medications. Medical comorbidities such as presence or absence of chest wall anomalies, OSA, pulmonary disease or positive pressure ventilation requirements, and spinal disease were documented. Data describing previous cardiac surgeries and anesthetic complications, including history of difficult ventilation or intubation, were recorded.

The intra- and postoperative records were reviewed for duration of cardiopulmonary bypass and aortic cross-clamping, type and quantity of blood products and factors administered, use and maximum dosage of vasoactive medications, whether the patient was extubated in the operating room, peak intra-operative lactate levels, and first postoperative hemoglobin in the ICU.

2.3 | Statistical analyses

We used descriptive statistics to analyze the demographic and perioperative characteristics of the study population. We report continuous variables as medians with interquartile ranges (IQR) and categorical variables as counts with percentages. Bivariate group comparisons were made with t tests and Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables.

3 | RESULTS

Forty patients with Marfan syndrome and 31 patients with LDS met criteria for inclusion. Two patients with Marfan syndrome had two surgeries each (n = 42 encounters). Two patients with LDS had two separate surgeries, and one had three surgeries (n = 35 encounters).

Perioperative characteristics are summarized in Table 1. Patients with Marfan syndrome had a median age of 16 years (IQR, 11–18),
**TABLE 1** Distribution of characteristics among patients with Loeys-Dietz syndrome and Marfan syndrome

| Characteristic | Loeys-dietz syndrome | Marfan syndrome | p value |
|---------------|----------------------|-----------------|---------|
| Total, n      | 35                   | 42              | .1090   |
| Male, n (%)   | 17 (49)              | 28 (67)         |         |
| Age at time of surgery, median (IQR) | 13 (9–17) | 16 (11–18) | .2120   |
| Weight, median (IQR) | 43.0 (24.5–56.3) | 60.5 (41.5–75.7) | .0083   |
| BMI, median (IQR) | 16.8 (14.3–21.4) | 18.7 (15.5–22.0) | .3845   |
| Ventricular dysfunction, n (%) |         |                 |         |
| Systolic      | 3 (9)                | 5 (12)          | .6080   |
| Diastolic     | 2 (6)                | 1 (2)           | .4650   |
| Aortic root Z-score, median (IQR) | 4.27 (2.23–8.82) | 6.58 (4.93–8.95) | .0271   |
| Aortic valve Z-score, median (IQR) | 4.03 (2.25–6.00) | 3.00 (1.30–4.66) | .3555   |
| Ascending aorta Z-score, median (IQR) | 1.26 (–0.17–2.71) | 0.65 (–0.10–1.76) | .2613   |
| Bicommissural aortic valve, n (%) | 5 (14) | 3 (7) | .3240   |
| Total valve disease score, median (IQR) | 1 (1–3) | 3 (1–4) | .0287   |
| STAT score, median (IQR) | 2 (2–2) | 2 (2–2) | .6182   |
| No. previous cardiac surgeries, n (%) |         |                 |         |
| 0             | 19 (54)              | 35 (83)         |         |
| 1             | 9 (26)               | 6 (14)          |         |
| ≥2            | 7 (20)               | 1 (2)           |         |
| Age at first cardiac surgery, median (IQR) | 7 (4–13) | 14 (10–17) | .0034   |
| Pectus present, n (%) | 16 (47) | 16 (38) | .4310   |
| Pulmonary disease, n (%) | 4 (12) | 7 (17) | .5460   |
| Spine disease, n (%) | 22 (65) | 19 (45) | .0900   |
| Medications, n (%) |         |                 |         |
| Pre-op angiotensin receptor blocker or ACE inhibitor | 35 (100) | 36 (86) | .0200   |
| Pre-op beta blocker | 12 (34) | 28 (67) | .0200   |
| GI (reflux, constipation) | 10 (33) | 4 (10) | .0120   |
| Pulmonary (asthma, allergy) | 20 (65) | 5 (12) | <.0001  |
| Pain | 5 (17) | 4 (10) | .3660   |
| Type of surgery, n (%) |         |                 |         |
| VSSR | 22 (63) | 33 (79) | .1290   |
| MV repair/replacement | 3 (9) | 13 (31) | .0160   |
| AV repair/replacement | 5 (14) | 3 (7) | .3060   |
| Other or additional surgery | 16 (46) | 12 (29) | .1190   |
| Airway difficulty, n (%) | 7 (21) | 0 (0) | .006   |
| CPB time, median (IQR) | 141 (119–170) | 143 (128–173) | .6269   |
| Cross-clamp time, median (IQR) | 91 (68–119) | 101 (81–114) | .3900   |
| Intra-operative vasopressor use, n (%) |         |                 |         |
| Epinephrine | 17 (49) | 26 (62) | .1080   |
| Vasopressin | 11 (31) | 13 (31) | .9630   |
| Milrinone | 6 (17) | 4 (10) | .3450   |
| Blood products given, median no. units (IQR) |         |                 |         |
| pRBC | 1 (0–4) | 0 (0–1) | .0282   |
| FFP | 0 (0–2) | 0 (0–1) | .2837   |
| Peak lactate in OR, median (IQR) | 2.9 (2.4–5.1) | 2.7 (2.1–3.7) | .2826   |
| Extubated in OR, n (%) | 9 (26) | 9 (21) | .7370   |
| Immediate post-op Hb, median (IQR) | 10.7 (10.0–11.9) | 11.3 (9.5–12.5) | .5193   |
| Length of stay at hospital, median (IQR) | 7 (5–10) | 7 (6–9) | .7157   |

Note: Significant differences are highlighted in bold.

Abbreviations: ACE, angiotensin-converting enzyme; AV, aortic valve; BMI, body mass index; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; GI, gastrointestinal; Hb, hemoglobin; IQR interquartile range; MV, mitral valve; OR, operating room; pRBC, packed red blood cells; pre-op, preoperative; STAT, Society of Thoracic Surgery and European Association for Cardiothoracic risk stratification system; VSSR, valve-sparing aortic root replacement.
and 28 (67%) were male. Patients with LDS had a median age of 13 years (IQR, 9–17), and 17 (49%) were male. There was no significant difference in the BMI between groups.

Surgical complexity as defined by the STAT score was similar between the groups. Ventricular dysfunction was rare overall, with 6 (14%) Marfan cases and 5 (14%) LDS cases involving either systolic or diastolic dysfunction. For more than half of patients, the surgery captured in this study was the patient’s first cardiac surgery. For the remainder, there was no significant difference between groups in the number of previous cardiac surgeries that took place outside the study period. However, those with Marfan syndrome were older than patients with LDS at the time of first surgery (median age = 14 years vs 7 years, p = .003). Aortic root size, defined by z-score on echocardiogram, was significantly larger for patients with Marfan syndrome. Patients in the two groups shared similar rates of preoperative co-morbidities, including pectus excavatum and carinatum, scoliosis, pulmonary disease such as restrictive lung disease, asthma or allergy, and gastrointestinal diseases including constipation and gastroesophageal reflux. However, patients with LDS appeared to be more severely affected, more frequently requiring bronchodilators, anti-allergy medications, pro-motility agents, and acid reducers (p = .012 and p < .001, respectively) to treat these conditions. Both groups were managed preoperatively with afterload-reducing agents at comparable rates, with angiotensin receptor blockers used most frequently.

The total valve score is a variable that we created to estimate the valvular abnormalities in each population. Mild, moderate, and severe stenosis or regurgitation were given scores of 1, 2, and 3 respectively. The total valve score for patients with Marfan syndrome was 3 and for LDS was 1 (p = .029).

The majority of surgical procedures included valve-sparing aortic root replacements (79% for Marfan and 63% for LDS). Most other surgical procedures included repair or replacement of the mitral and/or aortic valves. Surgical factors, including duration of cardiopulmonary bypass and aortic cross-clamping, were similar between groups. “Difficult airway” management was more common in the LDS group. Patients in the two groups received vasoactive medications, including epinephrine, vasopressin, and milrinone, with similar frequency. Blood product transfusion was rare overall, though patients with LDS received more red blood cells. Approximately one-quarter of patients in each group were extubated in the operating room post-operatively (p = .737) with an increase in extubation rate over the last 2 years of the study. Postoperatively, the median length of hospitalization for both groups was 7 days (Marfan: IQR, 6–9 days; LDS: IQR, 5–10 days; p = .716).

4 | DISCUSSION

In this retrospective observational study, we recorded data on a relatively large cohort of 71 children, adolescents, and young adults with Marfan syndrome or LDS who underwent a total of 77 cardiovascular surgical procedures.

To our knowledge, this study is the first of its kind to describe the intra-operative course of this size cohort of patients with connective tissue diseases under general anesthesia, specifically for cardiothoracic surgery. Given the relatively large and equal numbers of patients with Marfan syndrome and LDS, we were able to compare these groups to identify the phenotypic features of each population that contribute to anesthetic care and distinguish one syndrome from the other. This information is critically important to perioperative care, as these patients often undergo similar surgical procedures but may respond differently to the physiologic stresses of surgery and general anesthesia. Notably, these data may signal to the anesthesiologist that certain portions of the anesthetic may be more challenging than expected, such as airway management for a patient with LDS as compared to an otherwise similar patient with Marfan syndrome.

Marfan syndrome and LDS occur infrequently, and care of patients with these disorders tends to take place within large-volume centers. The importance of collecting and publishing perioperative data on patients with connective tissue disease undergoing cardiac surgery is widely recognized to inform the collective experience. To date, most large studies of patients with connective tissue disorders undergoing cardiothoracic surgery describe outcomes of greatest relevance to surgeons (ie, aortic complications such as rupture or dissection, need for urgent re-operation, injury to surrounding structures, and time to valve replacement for valve-sparing procedures). Only some outcomes overlap with those related to anesthesia care (ie, bleeding, arrhythmias, respiratory failure, and death). Many of the surgical studies do have the benefit of decades of experience with robust long-term follow-up. However, only a few studies conducted at large-volume children’s hospitals or derived from pediatric healthcare databases are specific to children and young adults. Of the surgical studies focused primarily on children, even fewer dedicate equal weight to patients with LDS as compared to Marfan syndrome.

At present, most peer-reviewed publications concerning the anesthetic care of patients with Marfan and LDS in the operating room make recommendations based on how they are expected to behave under general anesthesia. These recommendations are based on the diseases’ physiologic and anatomic phenotypes and are meant to guide perioperative management, in particular with respect to preoperative assessment, safe induction of anesthesia, securing the airway, positioning the patient to avoid injury, and maintaining hemodynamic stability throughout the case. Craniofacial anomalies including high-arched palate and temporomandibular joint laxity suggest that patients may have a predisposition to difficult ventilation and intubation. Scoliosis and pectus carinatum and excavatum pose challenges to positioning, including risk of injury to the cervical spine. The potential cardiopulmonary sequelae of these long-standing, severe orthopedic deformities, including compression of the lung parenchyma, heart, and great vessels, may cause significant respiratory and hemodynamic instability both preoperatively and intra-operatively. Cardiac and aortic disease is of great concern for all patients with connective tissue disorders who must undergo general anesthesia, but it is of particular relevance for cardiovascular surgery.
Recommendations for care of pediatric patients with Marfan and LDS under anesthesia are supported mostly by anecdotal evidence from single-patient encounters or small case series describing anesthetic methods and observed complications. As early as 1967, Woolley et al. described four young children undergoing five surgical procedures. The details of anesthetic management are limited beyond the absence of apparent anesthetic complications. One of the patients died shortly after an attempted aortic procedure, but no details of the patient’s cardiovascular anesthesia care are provided other than that the patient had “diminished cardiac output.”

In the 1980s, Verghese published a case series describing the intra-operative management and postoperative outcomes of 13 patients with Marfan syndrome who underwent surgical repair for scoliosis. This cohort had a high prevalence of pulmonary disease, with vital capacity below 80% of predicted for age in 9 of the 13 patients. Six had normal cardiovascular anatomy and physiology preoperatively. As in our study, none of the patients proved difficult to intubate. Anesthetic outcomes were mostly favorable intra-operatively, with a few exceptions, including one patient who suffered a cardiac arrest after induction of general anesthesia and one who developed a malignant arrhythmia leading to abortion of the surgical procedure. One strength of Verghese’s small case series was the ability to follow patients over time. Additional investigation showed that some patients who survived the initial orthopedic surgery died in the postoperative period after subsequent cardiovascular surgeries. The details of those cases are not documented. Similar to our study, that case series collected detailed preoperative descriptions of each patient’s phenotype. However, Verghese’s series was limited to patients with Marfan syndrome undergoing noncardiac surgery and did not seek to examine association between the patient’s phenotype and anesthetic outcomes.

Few published reports have described anesthetic techniques and outcomes for aortic surgery. Wells and Podolakin described an 18-year-old boy with Marfan syndrome who presented for acute repair of ascending aortic dissection. The anesthetic course was uncomplicated and extubation was within 12 h. The patient was discharged after 12 days, slightly longer than most patients in our study. However, the patient died 2 months later from a suspected abdominal aortic dissection or rupture. Zhang et al. reported on anesthetic management of two young patients with LDS, ages 5 and 7 years, who required deep hypothermic circulatory arrest for repair of the ascending aorta and arch. Both patients did well intra-operatively. Their lengths of stay were 9 and 10 days, respectively, both within the IQR for length of stay among LDS patients in our own study. Both patients experienced postcirculatory arrest coagulopathy, with each requiring 2 units of packed red blood cells and 1 unit of pooled platelets and one patient requiring 1 unit of fresh frozen plasma. The quantity of red cells and plasma transfused in each patient was higher than the median in our study, but within the IQR. This difference may be reflective of the prolonged cardiopulmonary bypass and aortic cross-clamp duration required for this type of operation.

The benefit of reporting these data, including from smaller patient samples, is that it provides a glimpse into a wide range of patient phenotypes and anesthetic practices, which can be beneficial in demonstrating that variation in anesthetic technique can be safe and effective. Additionally, single-patient reports may highlight rare presentations that pose unique challenges, as in a case of Marfan syndrome comorbid with Turner syndrome. Difficult intubation was also largely absent in small case reports, and laryngeal mask airway was successfully used for a minor procedure, but our study showed a high percentage (21%) of difficult airway in LDS patients. Having this data available allows anesthesia providers to judge which expected complications are most likely and to allocate their time and attention most effectively for patient safety. Institutionally, we recommend the continuation of beta blockers during the entire perioperative period. We also suggest a brief (approximately 24 h) perioperative hold on any medication targeting angiotensin-mediated pathways to minimize intra-operative hypotension. The re-initiation should occur as soon as medically possible especially in LDS patients due to their high risk of aortic aneurysm rupture, a severe complication potentially triggered by rebound hypertension secondary to a prolonged hold of preoperative antihypertensive medications.

Our study has limitations, including that it is retrospective and relies on data from an electronic medical record. Therefore, it is subject to omissions and human error. Our sample size is large compared to anything previously published on this patient population, though it is still relatively modest. We also cannot account for the impact of any changes in surgical technique or materials. We recognize that the patient’s immediate postoperative care in the ICU can be considered an extension of their operating room care and may provide more insight into postanesthetic outcomes. Data from this time period were collected for future analysis, but exist outside the scope of this present study.

Cardiovascular surgical techniques to manage the valvular and aortic comorbidities of Marfan syndrome and LDS continue to improve based on decades of follow-up data, permitting the ongoing care of patients with more severe disease. By collecting data and reporting on anesthesiologists’ experience caring for patients with these diseases, anesthesia care will be able to evolve in tandem as patients are diagnosed earlier and require aggressive management of cardiovascular comorbidities at younger ages. Analyzing large databases of pediatric patients who undergo general anesthesia for cardiovascular procedures remains critically important for improving the safety of perioperative care.

DATA AVAILABILITY STATEMENT
Due to medical and ethical concerns, the data that support the findings of this study are available from the corresponding author, DG, upon reasonable request.

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