Impact of prior diaphragm plication on subsequent stages of single ventricle palliation

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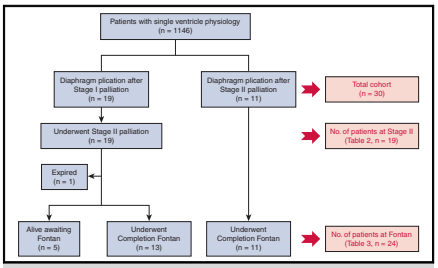
ABSTRACT

Background: Phrenic nerve injury is a known cause of morbidity after single ventricle palliation. Previous studies have shown that hemidiaphragm plication improves short-term outcomes. The effect of plication on the outcomes of subsequent stages of single ventricle palliation is unknown.

Methods: From 1997 to 2015, 1146 patients underwent surgical management of single ventricle physiology at our institution. We reviewed the records of 30 patients who had undergone diaphragm plication for phrenic nerve injury before Fontan completion. Each patient was compared with 2 propensity-matched controls identified from patients who underwent the Glenn or Fontan procedure during the same period without diaphragm plication. Propensity matching was achieved for each test subject using the nearest neighbor algorithm. Data are presented as the median and quartiles or numbers and percentages.

Results: The cohort included 18 boys (60%). Of the 30 patients, 19 (63%) had undergone plication after first-stage palliation. Of these, 13 have undergone completion Fontan, 5 were awaiting Fontan at the last follow-up, and 1 had died. An additional 11 patients had undergone plication after Glenn and proceeded to Fontan completion. Thus, 24 patients with diaphragm plication have undergone Fontan completion. No difference was found in pulmonary pressure or resistance between the plicated patients and their propensity-matched controls. Both groups had comparable chest tube output and hospital lengths of stay. Equal proportions of patients in both groups required pulmonary vasodilator therapy and/or supplemental oxygen at hospital discharge.

Conclusions: Prior diaphragm plication does not adversely affect Fontan completion in children with single ventricle physiology. The hospital course during subsequent stages of palliation for plicated patients was no different than that of matched controls. (J Thorac Cardiovasc Surg 2020;160:1291-6)



Schematic of single ventricle patients who had undergone diaphragm plication before Fontan completion.

CENTRAL MESSAGE

Prior diaphragm plication does not adversely affect surgical outcomes at subsequent stages of palliation or progression to Fontan completion.

PERSPECTIVE

Phrenic nerve injury and consequent diaphragm paresis is a well-recognized complication of particular relevance in single ventricle physiology, which is highly reliant on favorable pulmonary dynamics. Although recovery of diaphragmatic function can be expected for most patients, it is not possible to predict which patients will recover function nor to what extent. We show that diaphragm plication does not adversely affect surgical outcomes at subsequent stages of single ventricle palliation but does eliminate the variability associated with recovery of diaphragmatic function such that all patients will have favorable pulmonary hemodynamics and progress to Fontan completion.

See Commentaries on pages 1297 and 1299.

Diaphragm paresis due to phrenic nerve injury is a known complication of congenital cardiac surgery.[1,2] Especially in infants and young children, phrenic nerve injury prolongs the duration of mechanical ventilation and is a source of

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The present study was supported in part by an American Association for Thoracic Surgery Summer Internship to J. Bainiwal.

Read at the 42nd Annual Meeting of the Western Thoracic Surgical Association, Waikoloa, Hawaii, June 22-25, 2016.

Received for publication July 1, 2016; revisions received June 11, 2020; accepted for publication June 13, 2020; available ahead of print June 20, 2020.

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0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2020.06.007

CONG

Abbreviations and Acronyms
PA = pulmonary artery
PVR = pulmonary vascular resistance

major morbidity.[3,4] This might be, in part, because young children have weaker intercostal muscles and the diaphragm generates a large portion of their inspiratory forces. In addition, paradoxical movement of the paretic diaphragm can also compromise the function of the contralateral normal hemithorax. Previous reports have shown that hemidiaphragm plication can effectively improve the short-term hospital outcomes in children with unilateral phrenic nerve injury.[2,3]

Respiratory dynamics are of particular importance in children with single ventricle physiology, given that pulmonary blood flow is significantly influenced by changes in the intrathoracic pressure. Previous studies have demonstrated additional short-term morbidity resulting from phrenic nerve injury after single ventricle palliation.[5,6] However, to the best of our knowledge, no study to date has considered the effect of diaphragm plication on subsequent surgical interventions. We, therefore, studied the effects of prior diaphragm plication on pulmonary hemodynamics and the hospital course during subsequent stages of single ventricle palliation.

METHODS

From 1997 to 2015, 1146 patients had received surgical management of single ventricle physiology at our institution. Under institutional review board–approved protocols, we reviewed the records of 30 patients who had required hemidiaphragm plication for phrenic nerve injury before completion of Fontan circulation.

After neonatal palliation, our patients with single ventricle physiology usually undergo a bidirectional Glenn procedure between 4 and 8 months of age. Completion extracardiac Fontan is performed at ~3 years of age, with selective fenestration according to the pulmonary vascular status. Before the Glenn and Fontan procedures, all patients undergo preoperative cardiac catheterization. After surgery, if a patient is unable to be weaned from mechanical ventilatory support as expected or if a hemidiaphragm is found elevated on chest radiography, fluoroscopic evaluation during spontaneous breathing is performed to assess diaphragm movement. If a hemidiaphragm is found to move paradoxically or is immobile in an elevated position, hemidiaphragm plication will be performed. This is accomplished via a seventh interspace lateral thoracotomy and, in most patients, central plication using mattress sutures to create pleats.[7]

The function of the plicated diaphragm was subsequently assessed with cine fluoroscopy during spontaneous respiration at preoperative Glenn and/or Fontan catheterization. Fluoroscopy was viewed in the anteroposterior or lateral projections using the dome of the diaphragm as a standardized point of reference. The extent of movement was calculated as previously reported.[2] In brief, excursion of the plicated hemidiaphragm at the point of maximal inspiration was compared with the excursion of the contralateral normal, nonplicated diaphragm, and the difference expressed as a percentage.

All data were collected by retrospective medical record review. Propensity score matching was used to select a comparable cohort of patients with single ventricle physiology who had undergone stage II (bidirectional Glenn) and Fontan procedures during the same period at our institution who had not required diaphragm plication.[8] The results of the baseline unadjusted comparison between the study (plication) cohort of 30 patients and the entire cohort of 1146 patients is shown in Table 1. To balance the baseline differences between cohorts, a multivariable logistic model was built to predict assignment to the 2 cohorts. In the model, the need for diaphragm plication was the dependent variable. We chose independent variables according to the known factors that can affect long-term single ventricle outcomes. These independent variables included sex, dominant single ventricle, birth weight, prematurity, chromosomal abnormality or syndrome, noncardiac congenital anatomic abnormality, and race/ethnicity. In addition, for each specific stage of surgery, the patient's age and weight at surgery were used as independent variables. Propensity matching was achieved for each test subject using the nearest neighbor algorithm with a caliper size of 5% of the estimated propensity score, 1:2 matching, and the option of replacement without oversampling. The characteristics of the matched-paired sample are summarized for stage II in Table 2 and for Fontan completion in Table 3. The standardized differences for the 9 matching variables before and after matching are shown in Figure E1, demonstrating excellent matching quality. The data were tabulated and analyzed using SAS, version 9.4 (IBM Corp, Armonk, NY). Continuous non-normally distributed data are presented as the median and quartiles. Groups were compared using the Wilcoxon rank-sum test for non-normally distributed continuous variables and the χ^2 test for discrete variables.

RESULTS

Patient Cohort

During the study period, 1146 patients with single ventricle physiology had undergone surgical palliation at our institution. Of the 1146 patients, 30 (2.6%) had required diaphragm plication before the Fontan procedure. Of the 30 patients, 19 had required plication after the first stage of palliation and 11 after the second stage (Figure 1). The characteristics of this patient cohort are shown in Table 1. This cohort was compared with the total cohort of patients with single ventricle physiology who had undergone surgical palliation during the study period. Nearly three quarters of the patients in the plication cohort had hypoplastic left heart syndrome compared with one half of the patients in the total cohort. Chromosomal anomalies and syndromes were also more prevalent in the plication cohort. Nearly one half the patients were of Hispanic ethnicity.

Fate of Plicated Diaphragm

Of the 30 patients, 13 (43%) had undergone plication of the right diaphragm (Figure 2) and 17 the left. The presence and extent of movement of the plicated hemidiaphragm were assessed during cardiac catheterization before the subsequent stage of surgical palliation. Nineteen patients (63%) had regained some diaphragmatic excursion on the affected site. Of those who had regained any diaphragm mobility, the median extent of diaphragmatic excursion was 70% (range, 45%-95%) compared with the contralateral nonaffected side. Of the 19 patients who had required hemidiaphragm plication after first-stage palliation, 12 (63%) had regained some diaphragm movement by the time of the Glenn procedure. However, 7 patients had not regained any appreciable movement, which persisted

TABLE 1. Patient demographics

Characteristic	Total cohort	Plication cohort	*P* value
Patients, n	1146	30	
Male sex, n (%)	619 (54)	18 (60)	.52
Dominant ventricle, n (%)			.01
Right	596 (52)	22 (73)	
Left	412 (36)	5 (17)	
Bilateral or undetermined	138 (12)	3 (10)	
Chromosomal abnormality/syndrome, n (%)	126 (11)	6 (20)	.04
Prematurity, n (%)	195 (17)	6 (20)	.67
Noncardiac anatomic abnormality, n (%)	80 (7)	4 (13)	.18
Birth weight, kg*	2.8 (2.6-3.2)	2.7 (2.6-3.3)	.21
Ethnicity, n			.34
Hispanic	56	48	
White	22	26	
African-American	8	9	
Other	14	17	

*Data presented as median (quartiles).

TABLE 2. Demographics, pulmonary hemodynamics, and hospital course during Glenn procedure

Characteristic	Plication	No plication	*P* value
Patients, n	19	38	
Male sex, n (%)	12 (63)	24 (63)	1.00
Dominant ventricle, n (%)			1.00
Right	14 (74)	28 (74)	
Left	3 (16)	6 (16)	
Bilateral or undetermined	2 (11)	4 (11)	
Chromosomal abnormality/syndrome, n (%)	4 (21)	7 (18)	.81
Prematurity, n (%)	4 (21)	8 (21)	1.00
Noncardiac anatomic abnormality, n (%)	3 (16)	6 (16)	1.00
Age, d			.63
Median	207	217	
Quartile	179-252	164-297	
Weight, kg			.74
Median	5.6	5.8	
Quartile	5.4-7	4.9-7.1	
Mean PA pressure, mm Hg			.83
Median	11.5	12.4	
Quartile	10.1-13	9.4-13.3	
PVR, Wood units/m^2			.88
Median	1.8	1.7	
Quartile	1.6-2.1	1.4-2	
Hospital stay, d			.45
Median	9	8	
Quartile	6.5-18	6-17	
Chest tube output for last 24 h, mL			.32
Median	71	64	
Quartile	36-144	34-137	
Supplemental oxygen at discharge, n (%)	3 (16)	5 (13)	.79
Sildenafil at discharge, n (%)	4 (21)	8 (21)	1.00

PA, Pulmonary artery; *PVR*, pulmonary vascular resistance.

through to pre-Fontan catheterization. Of the 11 patients who had required hemidiaphragm plication after second-stage palliation, 7 (64%) had regained some diaphragm movement by the time of the Fontan procedure.

Clinical Characteristics at Glenn Procedure

A total of 19 patients had undergone diaphragm plication after first-stage palliation of single ventricle physiology. We compared these patients with 38 propensity-matched infants who had undergone the Glenn procedure during the study period but had not undergone diaphragm plication (Table 2). No difference was found in the patients' age or weight at the Glenn procedure. Both pulmonary artery (PA) pressure and vascular resistance measured at pre-Glenn catheterization were comparable between the 2 groups. We then studied the clinical parameters likely to be adversely affected by phrenic nerve injury, such as chest tube output and duration of hospitalization. These were also comparable between the 2 groups. No mortality occurred in either group. The proportion of patients discharged home with supplemental oxygen and/or pulmonary vasodilator therapy was also similar between the 2 groups. At the latest follow-up examination, of these 19 patients, 13 have undergone completion Fontan, 5 were awaiting completion Fontan, and 1 had died (Figure 1).

The 7 patients who had not regained any diaphragmatic function by the time of the Glenn procedure had a mean PA pressure of 12.3 mm Hg (interquartile range, 11.2-13.8 mm Hg) and pulmonary vascular resistance (PVR) of 1.8 Wood units/m^2 (interquartile range, 1.6-2.0 Wood units/m^2). Their median hospital stay was 8 days (interquartilerange, 7-9 days). One patient (14%) was discharged with supplemental oxygen and sildenafil. None of these values was significantly different from those for the patients who had regained diaphragmatic function, with the caveat of the small patient numbers. In these 7 patients, plication had pulled the diaphragms down by 3 interspaces (interquartile range, 2-3 interspaces), thereby reclaiming lost space for lung expansion. We propose that this improvement in lung expansion, even in the absence of diaphragmatic excursion, was potentially responsible for the improved pulmonary hemodynamics.

Clinical Characteristics at Fontan Procedure

A total of 13 patients who had undergone diaphragm plication after first-stage palliation and an additional 11

TABLE 3. Demographics, pulmonary hemodynamics, and hospital course during Fontan procedure

Characteristic	Plication	No plication	*P* value
Patients, n	24	48	
Male sex, n (%)	17 (71)	34 (71)	1.00
Dominant ventricle, n (%)			1.00
Right	17 (71)	34 (71)	
Left	5 (21)	10 (21)	
Bilateral or undetermined	2 (8)	4 (8)	
Chromosomal abnormality/syndrome, n (%)	5 (21)	9 (19)	.83
Prematurity, n (%)	4 (17)	9 (19)	.83
Noncardiac anatomic abnormality, n (%)	3 (13)	6 (13)	1.00
Age, d			.64
Median	1064	1132	
Quartile	976-1321	864-1497	
Weight, kg			.31
Median	14	15	
Quartile	12.1-14.5	11.9-16.1	
Mean PA pressure, mm Hg			.47
Median	11	12	
Quartile	10-13	9-14.1	
PVR, Wood units/m^2			.56
Median	2.1	2	
Quartile	1.8-2.1	1.6-2.2	
Fenestration, n (%)	4 (17)	7 (15)	.82
Hospital stay, d			.54
Median	8	8.5	
Quartile	7-9	8-14	
Chest tube output for last 24 h, mL			.37
Median	122	136	
Quartile	62-171	60-179	
Supplemental oxygen at discharge, n (%)	1 (4)	2 (4)	1.00
Sildenafil at discharge, n (%)	4 (17)	8 (17)	1.00

PA, Pulmonary artery; *PVR*, pulmonary vascular resistance.

patients who had undergone plication after the Glenn procedure had undergone Fontan completion at the last follow-up point (Figure 1). We analyzed these 24 patients as a single cohort and compared them with 48 propensity-matched Fontan patients who had not required diaphragm plication (Table 3). Again, patient age and weight were comparable between the 2 groups. No differences were found in pulmonary hemodynamics as measured by the mean PA pressure or PVR. An equally small percentage of patients in each group required Fontan fenestration, which was selectively performed based on the preoperative hemodynamics. Neither hospital stay nor chest tube output were significantly different between the 2 groups. No mortality occurred. The requirement for supplemental oxygen (4%) and/or pulmonary vasodilator therapy (17%) was similar between the 2 groups.

The 9 patients who had not regained any diaphragmatic function by the time of Fontan had a mean PA pressure of 12.8 mm Hg (interquartile range, 11.2-14.3 mm Hg) and PVR of 1.9 Wood units/m^2 (interquartile range, 1.6-2.1 Wood units/m^2). One patient (9%) underwent fenestrated Fontan, and the overall median hospital stay was 8 days (interquartile range, 7-11 days). No patient was discharged requiring supplemental oxygen, although 1 patient (9%) required sildenafil. None of these values was significantly different from those for the patients who had regained diaphragmatic function, with the same caveat of the small patient number. In these 9 patients, plication had pulled the diaphragms down by 3 interspaces (interquartile range, 2-4 interspaces).

DISCUSSION

Phrenic nerve injury resulting in hemidiaphragm paralysis has been well described in patients undergoing multistage surgical palliation for single ventricle physiology.[3,4,9] Several previous studies have shown that diaphragm paresis increases the morbidity in these patients, given the importance of pulmonary dynamics for successful Fontan circulation.[5,6] We have taken an aggressive approach when phrenic nerve injury is suspected in single ventricle patients. We have a high index of suspicion for phrenic nerve injury in patients who cannot be weaned from mechanical ventilation as anticipated or who demonstrate an elevated hemidiaphragm with loss of lung volume on chest radiography. Thus, early fluoroscopy is pursued in these patients to confirm or rule out the suspicion. To the best of our knowledge, no prospective studies have been reported to help guide the management of phrenic nerve paresis in patients with single ventricle physiology. Because single ventricle circulation is a PVR-sensitive physiology, we believe that any adverse effect on PVR, such as an elevated diaphragm causing lung collapse, will adversely affect the physiology in the short and long term. Our preference, therefore, has been to plicate all elevated and paradoxically moving diaphragms in all patients with single ventricle physiology. In patients with biventricular physiology, we will only plicate those diaphragms in patients for whom extubation fails. Because of such an approach, our study could not provide information on the untreated natural history of phrenic nerve injury in patients with single ventricle physiology.

The primary focus of our study was to evaluate the pulmonary hemodynamics and hospital course during subsequent stages of palliation in patients with single ventricle physiology. We, therefore, only included those patients who had undergone hemidiaphragm plication after first- and second-stage palliation. Our study shows that the need for diaphragm plication after the first 2 stages of

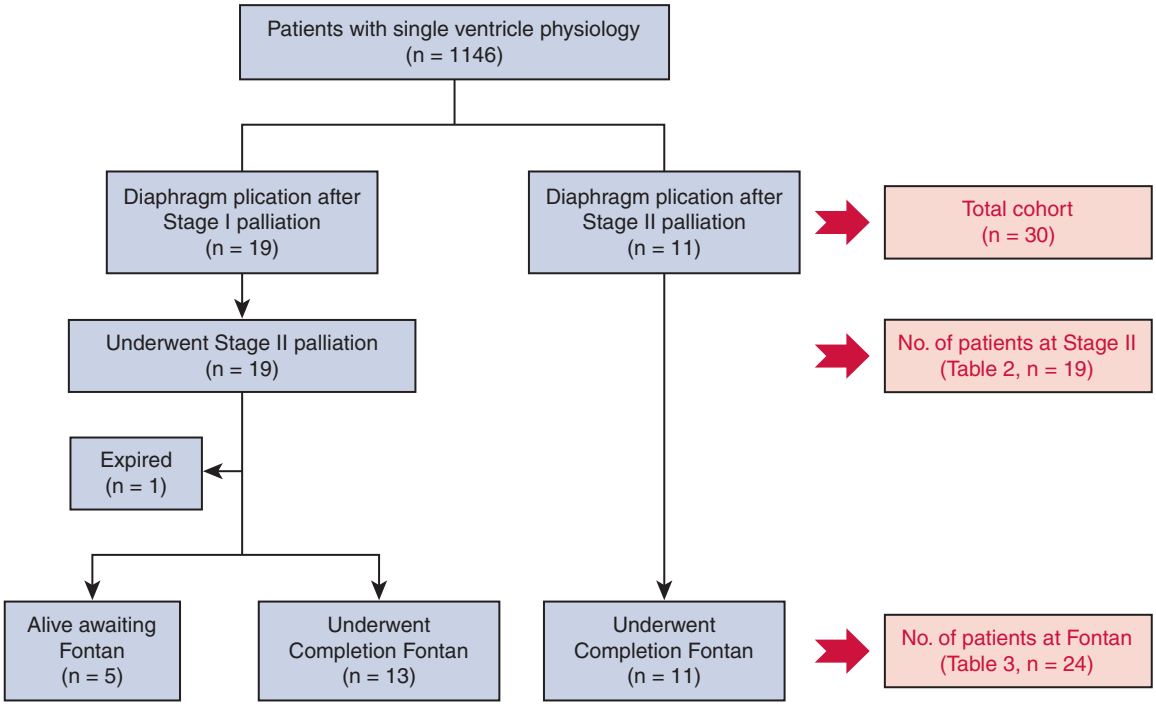

FIGURE 1. Flow chart showing patients with single ventricle physiology who had undergone diaphragm plication before Fontan completion at our institution.

palliation does not adversely affect progression to Fontan circulation. These children also do not require surgical intervention earlier than planned. The pulmonary hemodynamics as measured by the mean PA pressure and PVR were comparable to those of patients without phrenic nerve injury. The need for prior diaphragm plication did not result in prolonged pleural drainage or appreciably increase the duration of the hospital stay. Consistent with the finding that they have comparable pulmonary hemodynamics, patients with previous diaphragm plication do not require more pulmonary vasoactive drugs or supplemental oxygen therapy at discharge compared with nonplicated patients.

Hsia and colleagues[10] have reported alterations in subdiaphragmatic venous hemodynamics in Fontan patients after diaphragm plication. They postulated that these changes in venous pressures might cause prolonged pleural effusions and potentially contribute to late Fontan failure. Given the scope of our study, we did not include patients who had required hemidiaphragm plication after the Fontan procedure. Our follow-up for the present study was also limited to the hospital course during Glenn or Fontan. It would be interesting to evaluate the longer term outcomes of patients who had undergone diaphragm plication at any stage of single ventricle palliation.

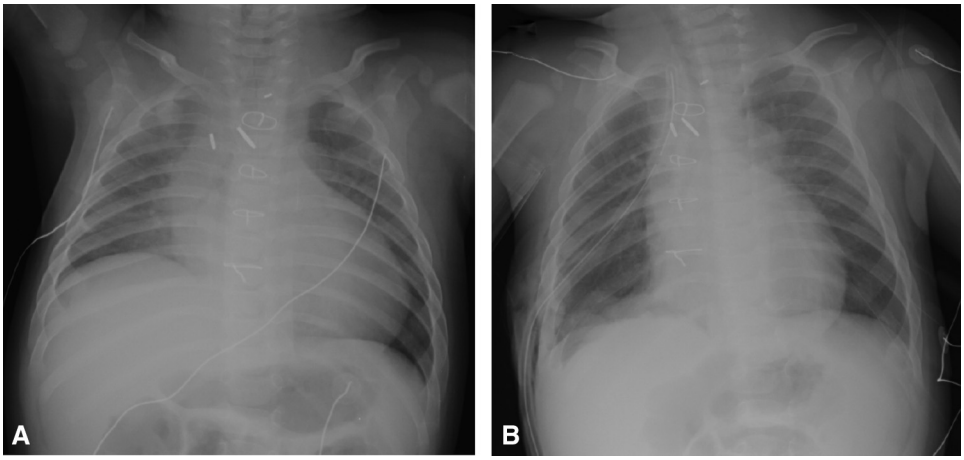

FIGURE 2. Plain radiograph of 1 patient after Glenn procedure with right hemidiaphragm elevation (A) and after right hemidiaphragm plication (B).

It has been shown that phrenic nerve injury during cardiac surgery and the consequent diaphragm paresis or paralysis is not permanent in all patients.[2,11] Given our practice of routine preoperative catheterization before the second and third stages of single ventricle palliation, we were able to study the return of diaphragmatic function in the plicated patients. The findings from our present study confirm the findings reported in our previous analysis,[2] indicating that roughly two thirds of patients who undergo diaphragm plication demonstrate some recovery in diaphragmatic excursion during the follow-up period. However, more than one quarter of those who recovered function demonstrated <50% excursion compared with the contralateral side. In the absence of routine prespecified follow-up protocols, it is not possible to determine the exact time course of recovery of diaphragmatic function. However, among the patients who underwent diaphragm plication after first-stage palliation, those who had not recovered diaphragmatic function by the time of the Glenn procedure did not demonstrate subsequent recovery by the time of the Fontan procedure. It is not known what factors determine whether diaphragm function will return after phrenic nerve injury.[1] It has been postulated that nerve "stunning" resulting from trauma such as thermal injury is more likely to recover over time but injuries such as transection during dissection are more likely to be permanent. Regardless, it is currently not feasible to reliably predict which patients will recover diaphragm function or to what extent diaphragm function will recover. We, therefore, have favored a policy of early diaphragm plication in patients with single ventricle physiology. In addition to improving the short-term outcomes,[2,3] the results of the present study demonstrate that diaphragm plication itself does not adversely affect the surgical outcomes at subsequent stages of single ventricle palliation. In the small percentage of plicated patients who do not recover any diaphragmatic function, the comparable surgical outcomes would imply that plication is able to overcome the effects of persistent phrenic nerve dysfunction, presumably by reestablishing the lung volume lost secondary to elevation of the paretic diaphragm.

Our study has limitations inherent to any retrospective study. We performed a single-institution study driven by an aggressive approach toward diaphragm plication. As such, our study could not evaluate the natural history of phrenic nerve paresis. For the same reason, there is lack of a natural control group. Despite effective propensity matching, an unintentional bias could not be excluded. It is possible that we had patients with phrenic nerve injury and more subtle signs and symptoms who had not undergone plication and were, therefore, not included in the present analysis. The small number of patients without recovery of diaphragmatic function precluded further detailed analysis. In addition, we did not collect data on the long-term clinical outcomes for this cohort after Fontan circulation. Finally, we used return of diaphragmatic excursion on fluoroscopy as an indicator of functional phrenic never recovery instead of performing more direct nerve conduction analyses.

CONCLUSIONS

To the best of our knowledge, our study is the first to evaluate the effect of prior diaphragm plication on hospital outcomes during subsequent stages of single ventricle palliation. We have shown that most plicated diaphragms regain some mobility before the next stage palliation, similar to the outcomes in patients with 2-ventricle physiology who require diaphragm plication.[2] Also, prior diaphragm plication does not have a negative influence on pulmonary hemodynamics and does not adversely affect the hospital outcomes during subsequent stages of single ventricle palliation.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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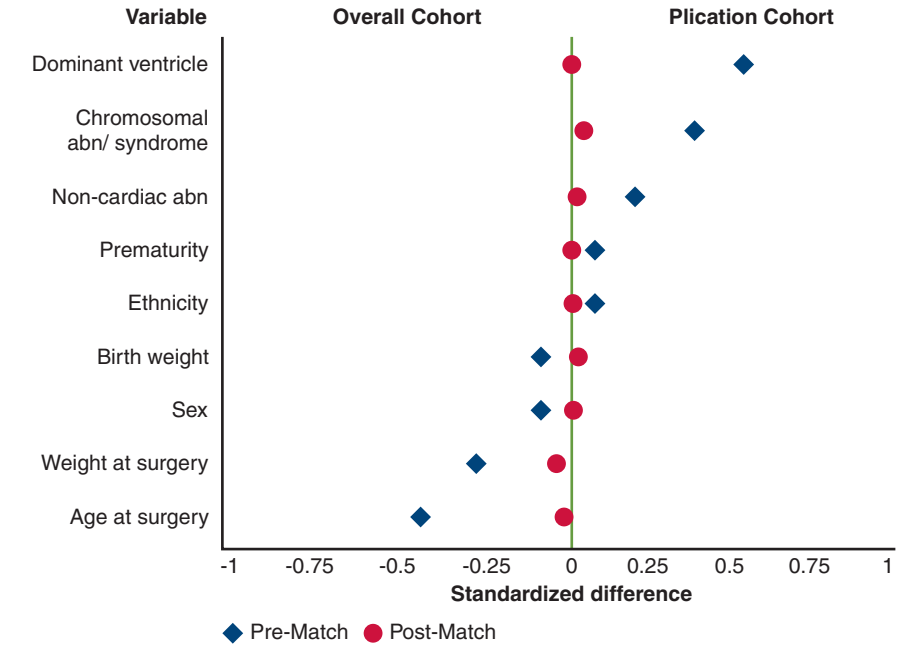
Key Words: single ventricle physiology, diaphragm, PVR



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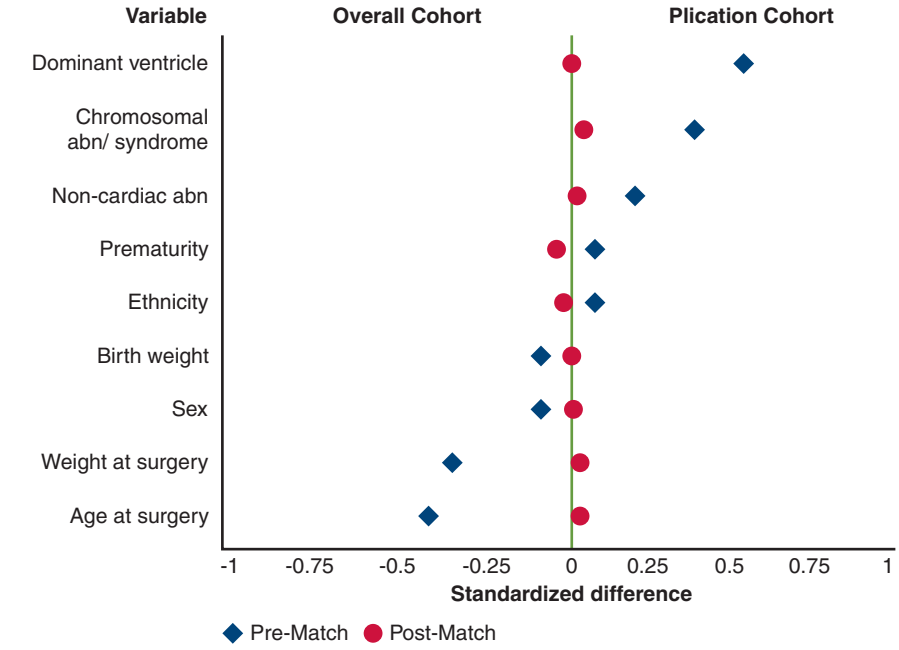

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FIGURE E1. Standardized differences in the 9 independent variables before and after propensity matching in the cohort of patients at Glenn (A) and Fontan (B) palliation.