Long-term Speech Outcomes of Cleft Palate Repair in Robin Sequence versus Isolated Cleft Palate

Robrecht J. H. Logjes, MD*§
Susanna Upton, CCC-SLP†
Bryce A. Mendelsohn, MD, PhD‡
Ryan K. Badiee, BA, BS*
Corstiaan C. Breugem, MD, PhD§
William Y. Hoffman, MD*†
Jason H. Pomerantz, MD*†

Background: Whether treatment of cleft palate (CP) associated with Robin sequence (RS) should attain outcomes similar to those of isolated cleft palate (ICP) remains unknown. This study compares treatment and outcomes in both conditions and delineates predictors of long-term outcome.

Methods: This retrospective case series of consecutive syndromic and isolated RS- and ICP-patients (1990–2016) includes indications and outcomes of straight-line repair with intravelar veloplasty (SLIV) or Furlow repair depending on cleft and airway characteristics.

Results: Seventy-five RS and 83 ICP patients underwent CP repair. Velopharyngeal insufficiency (VPI) occurred in 41% of RS versus 17% of ICP patients ($P = 0.012$), and in 60% of patients with syndromic RS versus 16% with isolated RS ($P = 0.005$). In multivariable logistic regression analysis, wider and more severe CP anatomy was the only factor independently associated with VPI ($P = 0.028$), in contrast to age at repair, syndromic RS compared with isolated RS, and isolated RS compared with ICP and initial tongue-lip adhesion. Secondary Furlow after primary SLIV was used to treat VPI in all groups, and more frequently in syndromic versus isolated RS patients ($P = 0.025$).

Conclusions: Variability of RS anatomy and airway compromise necessitates individualized treatment protocols. Despite differing CP etiology and other variables, our findings demonstrate cleft anatomy as the only independent variable predictive of VPI comparing RS and ICP patients. Patients with isolated RS should ultimately attain similar VPI outcomes compared with ICP patients. Obstructive speech operations in RS patients can be avoided without compromising speech outcome by reserving the prsocedure for secondary cases. (*Plast Reconstr Surg Glob Open 2021;9:e3351; doi: 10.1097/GOX.0000000000003351; Published online 21 January 2021.*)

INTRODUCTION

Robin sequence (RS) refers to micrognathia, glossoptosis, and upper airway obstruction, with cleft palate (CP) present in 90% of cases.[1–4] In RS, there are unique challenges and considerations in the treatment of CP, and questions remain about speech outcomes when compared with isolated cleft palate (ICP).[5–8] In particular, it is

*From the *Department of Surgery, Division of Plastic and Reconstructive Surgery, University of California San Francisco, San Francisco, Calif.; †Craniofacial Center, University of California San Francisco, San Francisco, Calif.; ‡Department of Pediatrics, Division of Medical Genetics & Genomics, University of California San Francisco, San Francisco, Calif.; and §Department of Surgery, Division of Plastic and Reconstructive Surgery, University Medical Center Amsterdam, Emma Children's Hospital, Amsterdam, the Netherlands.*

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unknown whether the presence of RS negatively impacts attainable speech outcomes.

Distinct pathogenetic mechanisms lead to different cleft anatomy, raising the possibility that intrinsic cleft characteristics could differentially affect speech. In RS, the tongue is forced into a posterior and superior position because of the reduced size of the mandible, resulting in the wide U-shaped CP characteristic of RS.[9–11] The etiology of ICP is multifactorial, including genetic and environmental causes distinct from RS that could influence the intrinsic growth and closure of the palatal shelves.[11,12] Airway obstruction and congenital anomalies associated with RS make CP treatment more challenging compared with ICP and often prompt modified approaches, such as delaying surgery. For some surgeons (including the authors), the choice of primary repair technique depends on cleft anatomy and presence of airway obstruction, whereas for others, the technique is independent of these factors.[5–7,13–17]

Prediction of surgical and speech outcomes of palate repair in RS-patients remains deficient because of limited patient cohorts in which diagnostic and treatment information is adequately robust. RS is pathogenically heterogeneous, which further complicates analysis.[9] Thus, meaningful evaluation of RS-associated cleft palate (RCP) repair outcomes requires categorization of whether RS occurs in the presence of a syndrome or other congenital anomalies ("syndromic RS"), or not ("isolated RS").[9]

Several studies have examined the treatment of CP in patients with RS, with some investigating total RS cohorts and others comparing isolated RS versus ICP, or syndromic RS versus isolated RS.[5–8,13–20] These previous studies describe the challenges associated with treatment of CP in RS and variables possibly affecting outcomes, such as craniofacial anatomy, comorbidities, and associated airway treatments. Because prior studies have had discrepant results and long-term assessment is lacking, open questions remain, precluding consensus on expected outcomes and optimal surgical protocols. To improve outcome prediction and patient counseling, and to inform treatment protocol selection, we compared surgical and long-term speech outcomes in RS and ICP at a single institution and tried to identify outcome predictors.

METHODS

After approval by the institutional review board at the University of California, San Francisco (UCSF) Medical Center, we conducted a retrospective chart review of all consecutive patients who underwent CP repair at UCSF (1990–2016). Patients diagnosed with RCP or ICP (excluding submucous CP) were included. RS was defined in patients with micrognathia, glossoptosis, and upper airway obstruction, and in ICP-patients there was documented absence of syndromes or other congenital anomalies after genetic evaluation.

All patients were treated by the interdisciplinary craniofacial team at UCSF.[21] Genetic evaluation by a pediatric medical geneticist was introduced at the first team evaluation. Syndromic RS was defined in patients with an associated syndrome, chromosomal abnormality, or other congenital anomaly. Isolated RS was determined after genetic evaluation in patients with only the RS triad, without any concomitant clinical anomaly, negative results from genetic tests, and normal development during follow-up.

ICP repair was performed between 10 and 12 months of age and occurred 1–2 months later in patients with RS. For RS-patients, the decision to proceed with repair was based on clinical judgment and interdisciplinary consensus incorporating criteria that always included speech development supporting repair, adequate weight gain, and the demonstrated absence of respiratory compromise, desaturations, or apneas on room air. Clinical readiness in candidate patients also included observation of mandible growth over time and the absence of cardiac anomalies precluding surgery. Clinical suspicion of unresolved airway obstruction was always assessed via polysomnography.

The protocol used for all patients in this study involved straight-line repair with intravelar veloplasty (SLIV) for severe and wide clefts and/or airway obstruction, and primary Furlow repair for mild and narrow clefts with resolved or minimal airway obstruction at the time of surgery. The choice of surgical technique relates to our protocol of minimizing postoperative respiratory compromise by using SLIV in at-risk RS-patients, and of reserving the Furlow as a secondary procedure in patients with severe CP anatomy if velopharyngeal insufficiency (VPI) develops after SLIV. Two cleft surgeons (WYH, JHP) performed all repairs. Additional speech operations to resolve VPI in patients who had a secondary Furlow included sphincter pharyngoplasty or pharyngeal flap with pushback.

Data collected included date of birth, sex, pre-operative maximum cleft width (narrow <5 mm; medium ≥5 mm and <10 mm; wide ≥10 mm and ≤14 mm; extremely wide ≥15 mm), CP severity according to the Jensen classification (1: soft palate only; 2: soft palate and less than one-third of the hard palate; 3: greater than one-third but less than two-thirds of the hard palate; 4: complete soft and hard palate to the incisive foramen),[22] age at repair, type of repair, oronasal fistula, diagnosis of VPI, secondary and/or tertiary speech operation to resolve VPI, postoperative perceptual speech evaluation, and postoperative obstructive sleep apnea (OSA) in follow-up confirmed by polysomnography.

Outcomes of perceptual speech evaluation were collected at a minimum age of 4 years. Perceptual speech evaluation was performed by 2 senior craniofacial speech pathologists, using the guidelines described by Henningsson et al and modified by Peterson-Falzone et al.[23,24] VPI was assessed as a binary outcome (present or absent), without grading by a quantitative scale. Perceptual speech evaluation to diagnose cleft speech characteristics included binary assessment of hypernasality and 2 groups of cleft-related articulation disorders: (1) audible nasal air emission/turbulence (NAE/T), which are passive errors directly related to nasal air loss, and (2) maladaptive compensatory articulation (MCA) errors, which are active errors that are learned to compensate nasal air loss

in speech. Besides hypernasality, both articulation error groups are indicators for VPI. In patients with a fistula at the time of speech evaluation, nasal air loss due to VPI was confirmed by a nasopharyngeal endoscopy and obturation of the fistula. When VPI was confirmed, patients underwent another speech operation except in the absence of patient's and parental experience of personal or social consequences of the VPI.

Statistical Analysis

IBM SPSS Statistics 24.0 and SAS 9.4 were used to analyze data. Descriptive statistics were calculated for all patient characteristics. Data are reported as mean ± SD, median and range, or percentages. Categorical variables were compared using the Chi-square test or Fisher's exact test, and quantitative variables by the independent t-test or Mann Whitney U test. Multivariable logistic regression analysis was performed with Firth correction to avoid small sample bias. The goodness of fit of our multivariable logistic regression model was assessed by the Area under the Receiver Operating Characteristic Curve (AUROC). A 2-tailed value of $P < 0.05$ was considered significant.

RESULTS

Patient Characteristics

A total of 158 patients (75 RCP, 83 ICP) were included, of whom 128 were operated on by WYH and 30 by JHP. Patient characteristics are summarized in Tables 1 and 2. Mean age at repair was 13.7 ± 5.3 months in RS, and 11.3 ± 5.1 months in ICP ($P = 0.004$). Repair occurred beyond 12 months of age in 32 RS-patients (43%, Table 3).

Associated syndromes are listed in Table 4. Syndromic RS was diagnosed in 55%: 22% had associated syndromes, and 33% had chromosomal defects or other congenital anomalies. At repair, syndromic RS-patients were older

than isolated RS-patients (14.9 ± 6.4 months versus 12.2 ± 3.1 months; $P = 0.027$).

Of the 75 RS-patients, 26 were cleared for repair by pulmonology based on polysomnography, 1 by home oximetry findings, and 2 were cleared after echocardiogram showed resolution of septal defects. Readiness for surgery was clinically assessed (see Methods) in the remaining 49 RS-patients.

Median postoperative follow-up was 4.4 years (range: 0.1–19.5 years). The RCP was significantly wider ($P = 0.001$) and more severe ($P = 0.001$), according to the Jensen classification, than ICP. The majority of RS-patients (83%) underwent SLIV, whereas the majority of ICP-patients (67%) underwent Furlow repair ($P = 0.001$). Surgical airway intervention in the neonatal period was needed in 40% of the RS-group (Table 1). Data on OSA in follow-up were available for 93 patients (48 RS, 45 ICP).

The authors' protocol using SLIV compared to Furlow evaluated by multivariable logistic regression analysis is presented in Supplemental Digital Content 1 (**See table, Supplemental Digital Content 1,** multivariate logistic regression analysis for SLIV technique compared to Furlow according to the authors' CP protocol. http://links.lww.com/PRSGO/B544). A wider and more severe CP anatomy, and the diagnosis of RS (compared with ICP), respectively, demonstrated increased odds ratios for SLIV of 48.5 (95%CI: 13.1–180.3, $P < .0001$) and 8.0 (95%CI: 2.8–23.1, $P = 0.0001$).

Surgical Outcomes

Postoperative fistula occurred in 4 RS-patients (5%) and no ICP-patients ($P = 0.049$). No difference was observed between the 2 cleft surgeons (Table 2, $P = 0.573$). All 4 RS-patients with fistula had primary SLIV and required surgical closure. Three RS-patients with fistula had Jensen grade 4 classification, and 2 had wide clefts (≥10 mm). Aside from the diagnosis of RS, there was insufficient

Table 1. Patient Characteristics

	RS Patients (%)	ICP Patients (%)	P
No. patients	75	83	
Mean age at cleft repair (mo)	13.7 (SD 5.3)	11.3 (SD 5.1)	0.004
Female–male ratio	39: 36 (52:48)	56: 27 (67:33)	0.047
Furlow–SLIV repair ratio	13: 62 (17:83)	56: 27 (67:33)	0.001
Surgeon 1–surgeon 2 ratio	67: 8 (89:11)	61: 22 (73:27)	0.014
Jensen cleft classification*			0.001
Grade 1	3 (5)	16 (19)	
Grade 2	7 (11)	27 (33)	
Grade 3	18 (28)	17 (21)	
Grade 4	36 (56)	22 (27)	
Width of the cleft palate†			0.001
Grade 1: narrow (<5 mm)	4 (5)	10 (13)	
Grade 2: medium (≥5 mm and <10 mm)	17 (23)	37 (46)	
Grade 3: wide (≥10 mm and ≤14 mm)	39 (53)	30 (37)	
Grade 4: extremely wide (≥15 mm)	14 (19)	3 (4)	
Syndromic RS	41 (55)	—	
Surgical airway intervention for UAO‡	30 (40)	—	

*Jensen cleft classification was not reported in 12 patients.
†The cleft width was not reported in 4 patients.
‡Surgical intervention for upper airway obstruction included 22 TLAs, 4 MDOs, 2 tracheostomies, 1 TLA + MDO, and 1 TLA + tracheostomy.
Syndromic RS, Robin sequence as part of a syndrome, or RS with a chromosomal abnormality or other congenital anomaly; Furlow repair, Furlow's double opposing Z-plasty; SLIV repair, straight line repair with intravelar veloplasty; Jensen cleft classification (1 = soft palate only, 2 = soft palate and less than one-third of the hard palate, 3 = soft palate and greater than one-third but less than two-thirds of the hard palate, 4 = complete soft and hard palate to the incisive foramen); UAO, upper airway obstruction; TLA: tongue-lip adhesion; MDO: mandibular distraction osteogenesis.

Table 2. Patient Characteristics and Outcomes between the 2 Cleft Surgeons

	Surgeon 1 (%)	Surgeon 2 (%)	P
No. patients	128 (81)	30 (19)	
RS–ICP ratio	67:61 (52:48)	8:22 (27:73)	0.014
Female–male ratio	77:51 (60:40)	18:12 (60:40)	1.000
Furlow–SLIV repair ratio	54:74 (42:58)	15:15 (50:50)	0.540
Jensen cleft classification*			0.001
Grade 1	17 (15)	2 (7)	
Grade 2	18 (16)	16 (53)	
Grade 3	31 (27)	4 (13)	
Grade 4	50 (43)	8 (27)	
Width of the cleft palate†			0.081
Grade 1: narrow (<5 mm)	10 (8)	4 (14)	
Grade 2: medium (≥5 mm and <10 mm)	50 (40)	4 (14)	
Grade 3: wide (≥10 mm and ≤14 mm)	53 (42)	16 (57)	
Grade 4: extremely wide (≥15 mm)	13 (10)	4 (14)	
Results			
Fistula	3 (2)	1 (3)	0.573
VPI	25 (31)	1 (10)	0.271
Secondary Furlow	19 (24)	1 (10)	0.450

*Jensen cleft classification was not reported in 12 patients.
†The cleft width was not reported in 4 patients.
Furlow repair, Furlow's double opposing Z-plasty; SLIV repair, straight line repair with intravelar veloplasty; Jensen cleft classification (1 = soft palate only, 2 = soft palate and less than one-third of the hard palate, 3 = soft palate and greater than one-third but less than two-thirds of the hard palate, 4 = complete soft and hard palate to the incisive foramen); VPI, Velopharyngeal insufficiency; Secondary Furlow, Secondary double opposing Z-plasty to resolve velopharyngeal insufficiency.

statistical power to evaluate the association between the occurrence of fistula and other variables.

Speech Outcomes

When perceptual speech evaluation results were available at ≥4 years of age, speech outcome was included in our analysis. These data were available for 91 patients: 44 RS-patients (19 isolated, 25 syndromic) and 47 ICP-patients, with a median postoperative follow-up of 8.2 years (range: 0.8–19.5). Of the 44 RS-patients, all 18 patients who needed surgical airway intervention underwent a tongue-lip adhesion, except for 1 patient who had a tracheostomy. Twenty patients were excluded from evaluation because they had not reached the age of 4 years, and 45 patients were lost to follow-up before their speech evaluation at ≥4 years. No significant differences in underlying diagnosis of patients lost to follow-up were observed (Table 5). Two syndromic RS-patients were non-verbal due to cognitive language disorders and therefore excluded.

Velopharyngeal Insufficiency

No difference in VPI rates between the 2 cleft surgeons was observed (Table 2). VPI was diagnosed in significantly

Table 3. Reasons for CP Repair beyond 12 Months in Patients with RS (n = 32)

	RS Patients
Pulmonology clearance following polysomnogram	8
Cardiac anomalies requiring specific clearance by cardiology	2
Delayed due to surgery for other non-craniofacial comorbidities	4
Clearance after interdisciplinary evaluation, including clinical assessment of resolution of airway compromise and sufficient mandible growth	12
Initial presentation past 1 year of age or personal scheduling conflicts	6

Table 4. Characteristics of RS Patients

	No. Patients (%)
Total	75 (100)
Isolated RS	34 (45)
Syndromic RS	41 (55)
RS as part of a syndrome	16 (22)
Stickler syndrome	3
16p11.2 deletion syndrome	2
Marfan syndrome	1
Diastrophic dysplasia syndrome	1
Catel-Manzke syndrome	1
Caudal regression syndrome	1
Oromandibular limb hypogenesis syndrome	1
Van der Woude syndrome	1
Goltz–Gorlin syndrome	1
15q duplication syndrome	1
Spondyloepiphyseal dysplasia congenital	1
Femoral facial syndrome	1
Fetal alcohol syndrome	1
Other associated anomalies or chromosomal abnormalities	25 (33)

Syndromic RS, Robin sequence as part of a syndrome, or RS with a chromosomal abnormality or other congenital anomaly.

more RS-patients than ICP-patients (41% versus 17%; $P = 0.012$). All RS-patients diagnosed with VPI had SLIV and 2 ICP-patients with VPI had primary Furlow repair. Rates of VPI were similar for isolated RS and ICP (16% versus 17%; $P = 1.000$). In the RS-group, VPI was diagnosed significantly more often in syndromic RS than in isolated RS (60% versus 16%; $P = 0.005$) (Fig. 1).

The results of multivariable logistic regression analysis for VPI are demonstrated in Table 6. The presence of wide (≥10 mm) and severe (Jensen grade 3 or 4) CP anatomy was associated 8-fold greater odds for VPI (OR: 8.2, 95%CI: 1.3–54.0, $P = 0.028$). Syndromic RS, compared with isolated RS, had a non-significant odds ratio for VPI of 4.2 (95%CI: 0.9–19.8, $P = 0.072$). Age at repair, diagnosis of isolated RS (compared with ICP), and initial tongue-lip adhesion in RS-patients (compared with RS-patients without tongue-lip adhesion) were also not associated with VPI.

Table 5. Characteristics of Patients Lost to Follow-up for Speech Evaluation

	Patients Lost FU; No Appropriate Age (%)	Patients Included (%)	P
RS: ICP	7:13 (14:22)	44:47 (86:78)	0.278
	Lost FU before the Age of 4 Years (%)	Included (%)	P
RS: ICP	22:23 (33:33)	44:47 (67:67)	0.953
s-RS: i-RS	9:13 (27:41)	25:19 (73:59)	0.223
i-RS: ICP	13:23 (41:33)	19:47 (59:67)	0.506

s-RS, syndromic Robin sequence; i-RS, isolated Robin sequence; FU, follow-up.

Speech Operations

Secondary Furlow to resolve VPI was performed in 16 RS-patients (36%), at a median age of 6.2 years (range: 2.3–11.1), versus 4 ICP-patients (9%), at a median age of 3.5 years (range: 3.1–7.1), $P = 0.002$. All patients who underwent secondary Furlow had primary SLIV. The rate of secondary Furlow did not differ significantly for isolated RS versus ICP (16% versus 9%, $P = 0.401$). Thirteen syndromic RS-patients (52%) versus 3 isolated RS-patients (16%) underwent secondary Furlow ($P = 0.025$) (Fig. 1).

Figure 2 illustrates the secondary and tertiary speech operations to resolve VPI. Secondary Furlow was planned for 2 of the 16 RS-patients at time of this analysis. After secondary Furlow, 9 RS-patients (64%, 6 syndromic and 3 isolated) had complete resolution of their VPI. The remaining 5 patients (36%), all syndromic, had some level of persistent VPI, 2 of whom underwent a sphincter pharyngoplasty at 7.0 and 10.5 years; another patient had a sphincter pharyngoplasty planned. After sphincter pharyngoplasty, both syndromic RS-patients had complete resolution of VPI. Four ICP-patients (9%) underwent secondary Furlow for the treatment of VPI. Of these, 1 patient underwent a pharyngeal flap with pushback at 3.9 years that resulted in complete resolution of VPI.

Cleft Speech Characteristics

The aggregate of all speech evaluations showed significantly higher rates of audible NAE/T and MCA-errors for RS-patients than for ICP-patients ($P = 0.009$ and $P = 0.001$, respectively, Table 7). There were no MCA-errors in ICP-patients. At the latest speech evaluation, the only significant difference between RS and ICP-patients was the MCA-errors. At the latest speech evaluation, the rate of audible NAE/T was significantly higher in syndromic RS than in isolated RS ($P = 0.016$).

Airway

None of the RS-patients developed acute respiratory distress following repair. In follow-up, 8 RS-patients (17%), 6 of whom were syndromic, had OSA confirmed by polysomnography at a median age of 4.8 years (range: 2.9–6.3 years) versus 1 ICP-patient (2%) at 10.3 years, $P = 0.031$. All 8 RS-patients with OSA had primary SLIV. After successful OSA treatment, 3 RS-patients underwent secondary Furlow for VPI.

Table 6. Multivariable Logistic Regression Analysis for Variables Associated with RS to Predict Velopharyngeal Insufficiency (n = 91 patients)

Variables	OR	95% CI	P
Age (mo)	1.01	0.92–1.10	0.895
Surgical airway intervention			
RS without TLA	Ref		
RS with TLA	1.30	0.28–6.05	0.741
Diagnosis			
Isolated cleft palate	Ref		
Isolated RS	0.58	0.11–2.96	0.511
Isolated RS	Ref		
Syndromic RS	4.17	0.88–19.84	0.072
Composite CP anatomy			
Width 1,2 & Jensen 1,2	Ref		
Width 1,2 & Jensen 3,4	4.25	0.59–30.67	0.152
Width 3,4 & Jensen 1,2	0.86	0.02–33.21	0.936
Width 3,4 & Jensen 3,4	8.24	1.26–54.02	0.028

The goodness of fit of our multivariable logistic regression model was assessed by the Area under the Receiver Operating Characteristic Curve (AUROC). This number is a measure of our model's separability between the patients with the outcome no VPI and outcome VPI and can range from 0.5 (no separation capacity) to 1.0 (perfect separation capacity). The AUROC of our model was 0.79. The use of SLIV or Furlow repair was determined by our surgical protocol of using SLIV in wider and more severe CPs. Therefore, this variable was the consequence of the variable "composite CP anatomy" (in statistics called "a mediator") and not included in this analysis.
OR, Odds ratio; CI, Confidence interval; VPI, Velopharyngeal insufficiency; TLA, tongue-lip adhesion; Ref, Reference; Jensen cleft classification (1 = soft palate only, 2 = soft palate and less than one-third of the hard palate, 3 = soft palate and greater than one-third but less than two-thirds of the hard palate, 4 = complete soft and hard palate to the incisive foramen); width of the CP [1 = narrow (<5 mm), 2 = medium (≥5 mm and <10 mm), 3 = wide (≥10 mm and ≤14 mm), 4 = extremely wide (≥15 mm)].

DISCUSSION

In this study of long-term speech outcomes for patients with RCP, the length of follow-up (median over 8 years) enabled definitive comparison of speech outcomes between RS-patients and ICP-patients, and assessment of improvement over time. The importance of long-term comparison is emphasized by the relatively advanced age of RS-patients who underwent secondary Furlow or sphincter pharyngoplasty (median age of 6.2 and 8.8 years, respectively).

The findings of this study support the premise that the anatomy of RCP differs from that of ICP, and are compatible with existing hypotheses of different cleft etiology. We found, in agreement with others, that the Veau classification alone is insufficient to describe RCP because within the same Veau classification, clefts can still range largely in width.[25] Evaluation of anterior-to-posterior and side-to-side dimension demonstrated a wider and more severe CP in RS, supporting previous descriptions.[18,26] This accurate anatomic description permitted evaluation of an association with long-term speech outcomes.

Prior studies have performed multivariable analyses to predict VPI outcomes in cleft lip and/or CP patients and demonstrated cleft width to be an independent predictor.[27–33] However, in this study, we considered several previously untested variables for possible effects on VPI outcomes, including different etiology and anatomy, underlying syndromic diagnosis, delayed repair, and neonatal airway interventions. Prior reports did not include multivariable regression analysis to identify predictors for VPI in RS.
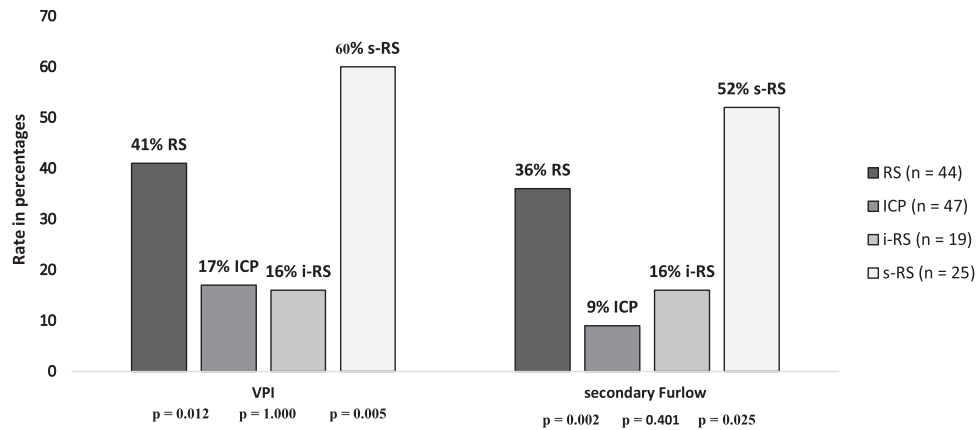
Fig. 1. Rate of VPI and secondary Furlow to resolve VPI in the RS group (n = 44) versus the ICP group (n = 47), and subgroups isolated RS (n = 19) and syndromic RS (n = 25). i-RS, Isolated RS; s-RS, syndromic RS. VPI was diagnosed in 41% of the RS group (n = 18) versus 17% of the ICP group (n = 8), *P = 0.012*. Secondary Furlow for treatment of VPI was performed in 36% of the RS group (n = 16) versus in 9% of the ICP group (n = 4), *P = 0.002*. VPI was observed in 16% of the isolated RS group (n = 3) versus 17% of the ICP group (n = 8), *P = 1.000* and secondary Furlow for treatment of VPI was performed in 16% of the isolated RS group (n = 3) versus 9% of the ICP-group (n = 4), *P = 0.401*. Within the RS group, VPI was found in 60% of syndromic RS patients (n = 15) versus 16% of isolated RS patients (n = 3, *P = 0.005*) and secondary Furlow for treatment of VPI was performed in 52% of the syndromic RS group (n = 13) versus 16% of the isolated RS group (n = 3, *P = 0.025*).
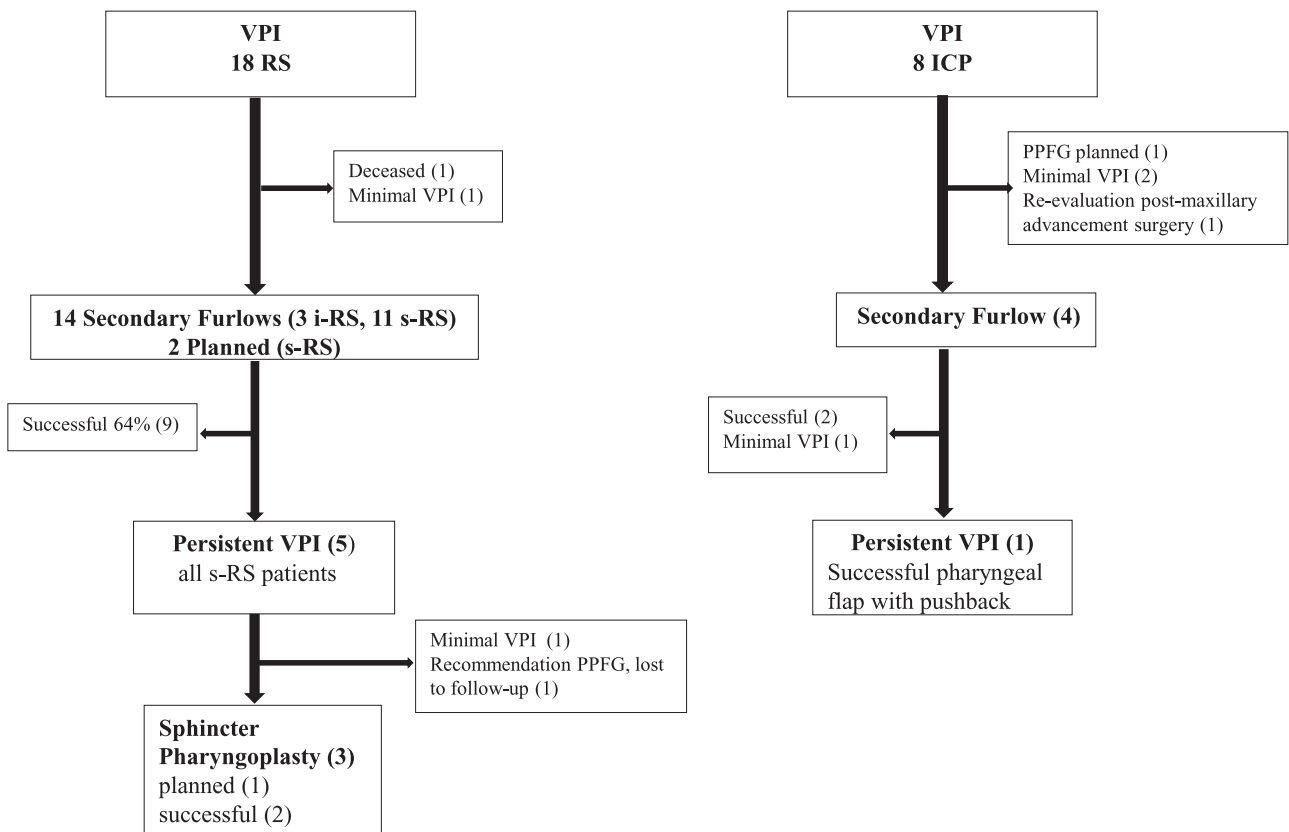

Fig. 2. Speech operations to resolve velopharyngeal insufficiency. i-RS, Isolated RS; s-RS, syndromic RS; VPI, velopharyngeal insufficiency; PPFG, posterior pharyngeal fat grafting; Minimal VPI, velopharyngeal insufficiency without personal or social consequences; Successful: complete resolution of velopharyngeal insufficiency.

Table 7. Rates of VPI, Secondary Furlow, and Cleft Speech Characteristics in the Aggregate of All Speech Evaluations and at the Latest Speech Evaluation

Patients	RS (%)	ICP (%)	P	s-RS (%)	i-RS (%)	P	i-RS (%)	ICP (%)	P
VPI	18 (41)	8 (17)	0.012	15 (60)	3 (16)	0.005	3 (16)	8 (17)	1.000
Secondary Furlow	16 (36)	4 (9)	0.002	13 (52)	3 (16)	0.025	3 (16)	4 (9)	0.401
Cleft speech characteristics in the aggregate of all speech evaluations									
Hypernasality	15 (34)	8 (17)	0.061	12 (48)	3 (16)	0.052	3 (16)	8 (17)	1.000
NAE/T	25 (57)	14 (30)	0.009	17 (68)	8 (42)	0.086	8 (42)	14 (30)	0.336
MCA	9 (21)	0 (0)	0.001	5 (20)	4 (21)	1.000	4 (21)	0 (0)	0.005
Cleft speech characteristics at the latest speech evaluation									
Hypernasality	3 (8)	5 (11)	0.721	3 (14)	0 (0)	0.233	0 (0)	5 (11)	0.311
NAE/T	12 (30)	10 (21)	0.351	10 (48)	2 (11)	0.016	2 (11)	10 (21)	0.484
MCA	4 (10)	0 (0)	0.041	2 (10)	2 (11)	1.000	2 (11)	0 (0)	0.080

To compare long-term outcomes between groups and to determine improvement in follow-up, the presence of cleft speech characteristics was assessed in the aggregate of all speech evaluations and at the latest speech evaluation. For the latter, both patients who underwent a secondary or third speech operation and patients who did not were included. Four RS patients were excluded from the analysis at the latest speech evaluation because at the time of the latest evaluation, 2 had a planned secondary Furlow, 1 had a planned sphincter pharyngoplasty, and 1 had a planned secondary Furlow, but died during the follow-up period.

s-RS, syndromic Robin sequence; i-RS, isolated Robin sequence; VPI, velopharyngeal insufficiency; Secondary Furlow, secondary double opposing Z-plasty to resolve VPI; NAE, audible nasal air emission; T, turbulence.

Reported VPI rates in RS range from 0% to 58%.[5–8,13–20] Our rate of 41% is in accordance with rates recently reported by Morice et al (36%), by Stransky et al (47%), and by Hardwicke et al (42%).[7,8,16] Hardwicke et al, who matched their RS-group with an ICP group for sex, age at repair, and cleft severity based on the LAHSAL-classification, observed significantly higher VPI rates in RS, concluding that other factors in RS might result in poorer speech outcomes.[8] But cleft width was not included and may be independently responsible for VPI in RS, as in non-RS cleft patients.[27–33] This latter conclusion is supported by our multivariable logistic regression analysis, which identified a wider and a more severe CP anatomy associated with VPI, when underlying diagnosis, age at repair, and tongue-lip adhesion were controlled for.

Our observation of similar VPI rates in isolated RS compared with ICP suggests that inherent differences in cleft etiology or anatomy are similarly treatable with existing surgical techniques. Several studies that compared isolated RS versus ICP supported this conclusion,[6,13,15] whereas 2 studies made contrary observations of higher VPI rates in isolated RS versus ICP.[5,7] This discrepancy is possibly related to our higher rate of identification of additional anomalies or syndromes, as discussed below. The findings of our study, including non-significant odds (0.6, 95%CI: 0.11–2.96, P = 0.511) in isolated RS compared with ICP in our multivariable logistic regression analysis, lead us to conclude that similar VPI outcomes should be expected in isolated RS compared with ICP.

Recently, an increasing number of RS-associated syndromes have been identified and a better understanding of RS-patients with additional anomalies (RS-plus) is emerging.[9,34,35] As in our study, 2 prior studies found significantly higher VPI rates in syndromic RS compared with isolated RS.[14,16] In one of them, velar musculature was assessed both clinically and by EMG to identify intrinsic velar causes of VPI that were non-cleft related. Phonological outcomes did not correlate with velar muscle function.[16] In our multivariable analysis, the odds of VPI for syndromic RS were increased (4.2) compared with those for isolated RS, but the difference was not quite statistically significant (95%CI: 0.88–19.84, P = 0.072). The

heterogeneity of associated syndromes makes this area of research challenging. Speech in syndromic RS should preferably be investigated in future studies by differentiation into groups based on etiology.[9] However, the results of our protocol demonstrate that the secondary Furlow and sphincter pharyngoplasty are suitable procedures to achieve VPI resolution in syndromic RS.

Tongue-lip adhesion in RS-patients for respiratory distress in the neonatal period was not related to VPI in our study, which is in accordance with the findings of Stransky et al.[7] We used mandible distraction as a primary surgical treatment more recently, and future studies will evaluate long-term speech outcomes after mandible distraction.

No MCA-errors were observed in our ICP-group. In contrast to audible NAE/T, which are obligatory and directly related to VPI, the MCA-errors are learned in response to VPI and may remain after additional speech operations. In RS-patients, oral morphology, related to reduced oro-pharyngeal space by a retruded jaw and posterior tongue rest posture, may predispose patients to MCA-errors. Hardwicke et al found significantly higher rates of posterior oral and nonoral cleft speech characteristics in RS.[8] The more widely used term "MCA-errors" is synonymous with those authors' "nonoral cleft speech characteristics," making their findings in line with our study.

None of our patients experienced early postoperative respiratory distress requiring intervention, in contrast to other studies reporting respiratory difficulties following CP repair in RS.[19,36–38] The safety of our protocol may relate to later surgical timing in RS, choice of surgical technique, and to adequate interdisciplinary airway assessment before repair using polysomnography when needed. With respect to surgical technique, tendency to use SLIV in RS is emphasized because it reduces the risk of worsening airway compromise as opposed to primary Furlow repair, in which greater lengthening, thickening, and more posterior position of the velum occurs. We found that secondary Furlow is an effective option for lengthening the soft palate and resolving VPI at a later stage, when the airway is larger and risk of obstruction is less. In a recent study, secondary Furlow appeared to have the least impact on

the airway. Although preoperative polysomnography was not done, those authors found that the percentage of patients diagnosed with OSA by polysomnography postoperatively was 25% versus 56% for sphincter pharyngoplasty and 78% for pharyngeal flap.[39] Another study found that of the 7 isolated RS-patients that underwent a superiorly based pharyngeal flap for VPI, 6 developed OSA and subsequently required flap take-down.[40] Apart from the effect of secondary speech operations on the RS airway, our follow-up data on OSA, together those from another study,[41] indicate the importance of continued monitoring of at-risk RS-patients beyond infancy.

The limitations of our study include those typical of retrospective design. Although we were able to accurately recover the majority of relevant data from records, in several instances, data values were missing or patients were lost to follow-up. For speech evaluation, among patients lost to follow-up, we found no variables significantly associated with loss to follow-up, suggesting a low risk of selection bias that cannot be completely ruled out. With respect to perceptual speech evaluation, although calculation of the inter- and intra-rater reliability was not possible in this study, these are related potential confounders that were minimized by assessment using two senior craniofacial speech pathologists over the total study period. Despite these limitations, we believe this study provides valuable and unique insights into speech outcomes in RS-patients.

CONCLUSIONS

Patients with RS have features that necessitate individualized treatment protocols and that could possibly affect surgical and speech outcomes compared with ICP-patients. Patients with RS have wider and more severe CP anatomy and airway compromise that resulted in delayed repair and greater use of straight line repair with intravelar veloplasty. Despite different CP etiology and the presence of several other RS- associated variables, our findings demonstrate that CP anatomy is the only independent variable predictive of VPI in RS-patients compared with ICP-patients. Age at repair, syndromic RS compared with isolated RS, isolated RS compared with ICP, and initial tongue-lip adhesion in RS are not predictive. Patients with isolated RS attain similar VPI outcomes compared with ICP-patients, though patients with syndromic RS require secondary Furlow procedures more often to resolve VPI than patients with isolated RS. Utilizing the Furlow as secondary procedure results in normal velopharyngeal function in the majority of RS-patients and the avoidance of obstructive speech operations. This work will improve preoperative predictability of speech outcomes after CP repair for patients with RS and their families.

Jason H. Pomerantz, MD
Division of Plastic and Reconstructive Surgery
Department of Surgery
University of California San Francisco
505 Parnassus Ave
San Francisco, CA 94143
E-mail: Jason.Pomerantz@ucsf.edu

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