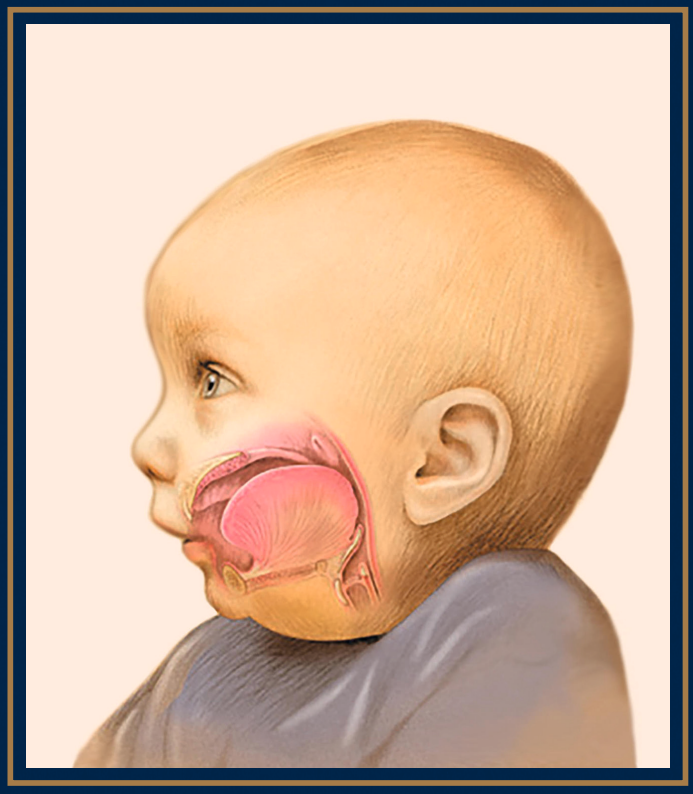
New perspectives in the treatment of patients with Robin sequence



Robrecht J.H. Logjes

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New perspectives in the treatment of patients with Robin sequence

New Perspectives in the Treatment of Patients with Robin Sequence

Nieuwe perspectieven in de behandeling van patiënten met Robin Sequentie
(met een samenvatting in het Nederlands)

Proefschrift

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For my family and friends

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1.

CHAPTER 1.
INTRODUCTION AND AIMS OF THIS THESIS

1.1 HISTORICAL BACKGROUND

Robin sequence refers to the triad of micrognathia, glossoptosis and upper airway obstruction in newborns. The French Stomatologist Dr. Pierre Robin was not the first to identify this craniofacial malformation in newborns (Figure 1). Previously, some cases were described by St. Hilaire in 1822, by Fairbain in 1846 and by Shukowsky in 1911 (Fairbairn 1846; Shukovsky 1911; St-Hilaire and Buchbinder 2000; Randall, Korgman, and Jahins 1965) However, the subsequent description in 1923 by Pierre Robin led to the introduction of the term "glossoptosis" (lazy tongue, a falling downward or backward of the tongue) and the concomitant dangers e.g. upper airway obstruction and feeding difficulties that can occur in affected patients (Robin 1923).

FIGURE 1: Dr. Pierre Robin
adapted from Apedipour 2017

Dr. Pierre Robin was born in 1867 and became a professor at the French School of Stomatology in Paris in 1899. In 1914, he became Editor of the periodical journal "*Revue de Stomatologie*" (Randall, Korgman, and Jahins 1965). In 1923 he published the first of approximately 17 reports on the problems of "glossoptosis", stating that glossoptosis and the concomitant respiratory and feeding problems could be treated with an orthodontic appliance that he called 'Monobloc' in children from the age of 3 years to adult age (Robin 1923; Randall, Korgman, and Jahins 1965). Robin published his first article on the "Monobloc" back in 1902, where he introduced this appliance to restore the normal relationship between the maxilla and mandibula in children (Robin 1923; 1934; Randall, Korgman, and Jahins 1965).

In a later publication, Dr. Pierre Robin reported the feeding difficulties typically presented by these patients and their failure to gain weight. He mentioned that patients with the described triad could have an associated cleft palate, because he observed a cleft palate in one of his patients. In addition, he believed that glossoptosis could be the cause of cyanosis and pulmonary infection. In severe cases he noted that death was unpreventable as he stated, *'I have never seen a child live more than 16 to 18 months who presented hypoplasia such as the lower maxilla was pushed more than 1 cm behind the upper'* (Robin 1934) (Figure 2).

The subsequent description in 1923 by Pierre Robin led to the eponymous definition (St-Hilaire and Buchbinder 2000). The craniofacial malformation was named Pierre Robin syndrome for nearly 50 years, before better understanding lead to the identification of multiple etiologies that could result in the same clinical findings, which does not occur in a syndrome (St-Hilaire and Buchbinder 2000). Instead of syndrome, the term "sequence" was suggested, because the micrognathia subsequently resulted in glossoptosis and upper airway obstruction. It became universally accepted that malformation should be named "Pierre Robin sequence" and that the prior anomaly, the micrognathia, is pathogenetically heterogeneous (Sadewitz 1992). In medicine, it is unusual to use the first name of the person after whom a condition is named. Therefore, when adhering to the purists, it seems obvious that the condition should be called "Robin sequence" (RS) (Breugem and Mink van der Molen 2009; Breugem and Courtemanche 2010; Breugem et al. 2016). However, heterogeneity in nomenclature and diagnosis remains, with the eponym "Pierre Robin sequence" used in the majority of recent published papers (van Nunen, van den Boogaard, and Breugem 2018). In 2016, an international clinical consensus was achieved regarding the three features (micrognathia, glossoptosis and upper airway obstruction) that should be included in the diagnosis of patients with RS (Breugem et al. 2016).

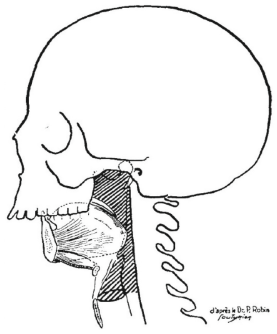

FIGURE 2
adapted from Robin 1934

1.2 CLINICAL PRESENTATION

Controversies considering the diagnosis of RS (and different definitions used) result in different data sources and methodology for the birth prevalence calculation of RS. It has been reported that birth prevalence can vary from 1 in 3.900 to 1 in 122.400 newborns, with a median incidence of 1 in 14.500 newborns (6.9 per 100.000) reported (Paes et al. 2015). The Dutch birth prevalence of RS is estimated to be 1 in 5.600 newborns (or 17.7 per 100,000), with a slight female predominance (Paes et al. 2015).

The micrognathia can be initiated by extrinsic, intrinsic, or neurologic/neuromuscular causes. These different etiologies produce heterogeneity in the RS phenotype; clinicians distinguish patients with syndromic RS (patients with an associated syndrome) and "RS-plus" (patients with additional malformations but without a genetically-confirmed syndrome) from those that only demonstrate the RS-triad without concomitant anomalies (isolated RS). Therefore, patients with RS represent a heterogeneous patient population with syndromic RS and/or RS plus in about 26% to 83% of cases (Sheffield et al. 1987; Sher 1992; Basart et al. 2015; Paes et al. 2015; Gomez-Ospina and Bernstein 2016).

The retropositioned tongue base or "lazy tongue" (glossoptosis) results in upper airway obstruction (UAO) and increased work of breathing. The comorbidities

secondary to the UAO include reflux, feeding difficulties, CO2 retention, failure to thrive, developmental delay, heart failure, brain damage, and sudden death (Hoffman, Kahn, and Seitchik 1965; Evans et al. 2011).

The clinical presentation in patients with RS can demonstrate a wide variation in the degree of UAO and clinicians mainly focus on these morbidities in the treatment of RS (van den Elzen et al. 2001; Butow, Hoogendijk, and Zwahlen 2009; Evans et al. 2011). However, RS has an associated mortality that ranges from 2% to 26% of cases (Costa et al. 2014). The prognosis for the patient with isolated RS is likely to be very different to an individual with RS as part of a complex syndrome.

The complex consequences of the congenital malformations in patients with RS require a multidisciplinary team of specialists to remedy the impaired airway and orognathic malfunction and to assure good long-term developmental outcomes far beyond infancy. This team of specialists might include molecular biologists, geneticists, embryologists, pediatricians, plastic and reconstructive surgeons, otolaryngologists, maxillofacial surgeons, dentists, orthodontists, psychologists and speech and languages pathologists (Cohen et al. 2017).

1.2.2 Upper airway obstruction and/or obstructive sleep apnea

While obstructive sleep apnea (OSA) is restricted to measuring airway obstruction occurring during sleep, UAO is defined as being independent of state (asleep or awake). The UAO and/or OSA not only exposes patients with RS to a risk of brain hypoxia but also of low psychomotor development, growth failure, pulmonary hypertension, hypercapnia, increased work of breathing and sleep disturbance. This can range from continuous respiratory distress while awake and asleep (as Randall reported an infant can literally exhaust himself to death unless the obstruction is relieved) to more subtle UAO/OSA in which findings may only be seen during sleeping, feeding or laying in supine position (Mackay 2011; Evans et al. 2011; Breugem et al. 2016). At all levels of UAO/OSA infants may be exposed to oxygen desaturation and sleep disruption which may contribute to neurocognitive impairment (Bass et al. 2004; Urschitz et al. 2004).

1.3 TREATMENT OF THE RS AIRWAY

1.3.1 Nonoperative interventions

In most patients with RS, the UAO/OSA is manageable by non-operative interventions that include prone/lateral positioning, supplemental oxygen, a nasopharyngeal airway, continuous positive airway pressure, and a pre-epiglottic baton plate. In those infants who fail non-operative strategies, surgical intervention may be indicated. Tongue-lip adhesion (TLA), subperiosteal release of the floor of the mouth, mandibular distraction osteogenesis (MDO), and tracheostomy are the most commonly described operations (van Lieshout et al. 2016; Almajed et al. 2017). These individual interventions have been well investigated; however, substantial variation among institutions exists for both the

evaluations employed and treatments provided. The measurements used for indications and outcome evaluations of all these different interventions are not standardized. Internationally accepted protocols for the investigation and management of UAO/OSA in RS are lacking (Van Lieshout et al. 2015; Resnick et al. 2019).

1.3.2 Tongue lip adhesion and mandibular distraction osteogenesis

When non-operative treatments fail to improve the UAO/OSA, the most common surgical procedures include TLA and MDO, and if used with the right indications, these could prevent the need for a tracheostomy (Bijnen et al. 2009; Flores et al. 2014; Resnick et al. 2019).

TLA, first advocated by Shukowsky in 1911, is usually performed in the first few weeks of life and involves surgically tethering the tongue forward to the lower lip, relieving the UAO/OSA in patients with RS (Shukovsky 1911). It relies on subsequent growth of the mandible in the first year of life and is usually reversed at the time of cleft palate repair, however, if UAO/OSA is persistent detachment can be performed at a later stage (Douglas 1946; Hoffman 2003; Bijnen et al. 2009; Viezel-Mathieu, Safran, and Gilardino 2016).

Distraction of the neonatal mandible was first introduced by McCarthy in 1992 after the development of a distraction technique by Ilizarov et al. in long tubular bones and first applied in dog mandibles by Snyder et al. (Ilizarov and Ledyaev 1992; Snyder et al. 1973; McCarthy et al. 1992). This technique directly treats and corrects the prior anomaly in patients with RS, the micrognathia, by performing an osteotomy of the mandible and gradually lengthen it by an internal or external distraction device. After a short waiting period, the mandibular segments are distracted from each other at a slow rate, and like in fracture healing, new bone tissue is formed. This is followed by a consolidation period for bone maturation (Breugem et al. 2012; Flores 2014).

1.4 CLEFT PALATE IN RS

As mentioned before, although it is not considered a prerequisite for the diagnosis, cleft palate is encountered in 90% of patients with RS (Evans et al. 2011; Breugem et al. 2016). Remarkably, relatively little has been reported on the surgical and speech outcomes of the cleft palate treatment that is associated with RS.

1.4.1 Embryology

In patients with a cleft palate, during embryological development the palatal shelves fail to fuse. The normal development of *the primary palate* begins in the region of the incisive foramen and moves anteriorly, including the anterior hard palate, alveolus and the middle portion of the lip. The development of the *secondary palate* is reverse and starts in the region of the incisive foramen and moves posteriorly including the

remainder of the hard palate, the complete soft palate and uvula (Sperber, Sperber, and Guttmann 2010; Peterson-Falzone et al. 2017)

In patients with a cleft palate without any other congenital anomalies, also referred to as "isolated cleft palate patients" (ICP), the etiology is thought to be multifactorial, including genetic and environmental causes that could influence the intrinsic growth and closure of the palatal shelves (Burg et al. 2016).

The exact etiology of the associated cleft palate in patients with RS is unknown but it is believed to have a relationship with the in-utero tongue position. The tongue is forced into a more posterior and superior position secondary to the micrognathia and blocking the palatal shelves to fuse (Figure 3). This can result in a wide U-shaped cleft palate (Hanson and Smith 1975; Resnick et al. 2018).

Patients with RS and a craniofacial syndromic diagnosis might have intrinsic developmental malformed palatal shelves and underlying intrinsic tissue characteristics that can affect the velopharyngeal mechanism, creating further challenges in cleft palate repair and subsequently achieving adequate speech outcomes (Patel et al. 2012; Basta et al. 2014).

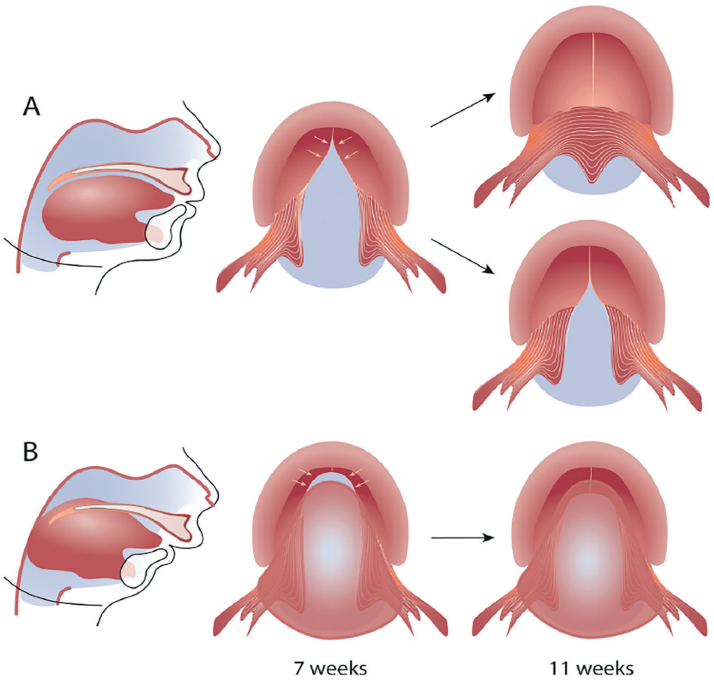

FIGURE 3: Etiology of cleft palate in RS.
Development of the typical wide (U-shaped) cleft palate, as often seen in Robin sequence. Example of normal palatal closure, or development of a cleft palate (A), and development of a cleft palate as seen in Robin sequence; Where micrognathia results in a posteriorly displaced tongue which is partially interposed between the closing lateral palatine shelves (B). Reprinted from PhD Thesis "Progress toward understanding Robin Sequence" with permission of Dr. E.C. Paes.

1.4.2 Velopharyngeal insufficiency

Patients with cleft palate will demonstrate signs of VPI when the cleft palate is unrepaired, but are also at risk for VPI postoperatively after cleft palate repair or a speech improving operation because of a lack of tissue/a short palate (Peterson-Falzone et al. 2017).

A part of this thesis will focus on clefts of the secondary palate, which results in an open communication between the oral and nasal cavity. Patients with a cleft of the secondary palate initially have difficulties with feeding and hearing and later speech development and possibly velopharyngeal insufficiency (VPI). In healthy patients the soft palate, also called *velum,* enables closure of the nasal cavity in relation to the oral and pharyngeal cavity during swallowing, feeding and speech. The soft palate muscles include the musculus tensor palatini muscle, palatopharyngeus muscle, levator veli palatini muscle, and the musculus uvulae (Huang, Lee, and Rajendran 1997; 1998) Patients with a cleft palate can suffer from VPI, which is a subcategory of velopharyngeal inadequacy. Inadequate velopharyngeal closure can have different causes including structural/anatomical causes (velopharyngeal insufficiency), neurological causes (also called velopharyngeal incompetency) and causes related to speech mislearning and articulatory etiologies (also called velopharyngeal mislearning).

1.4.3 Soft palate anatomy

The levator veli palatini muscle forms a muscular sling, suspending the soft palate from the cranial base. Its fibers occupy the middle 50 percent of the soft palate and are lying in transverse orientation (Boorman and Sommerlad 1985; Huang, Lee, and Rajendran 1998). The levator muscle is the prime mover in the soft palate component of velopharyngeal closure. The soft palate component of the palatopharyngeus consists of two heads clasping the levator muscle and inserting into the latter just short of the midline. Its pharyngeal component inserted into the superior constrictor muscle in the lateral and posterior pharyngeal walls. Together, these two muscles form a sphincter around the velopharyngeal port and are the pharyngeal component of velopharyngeal closure (Figure 4) (Boorman and Sommerlad 1985). The Passavant's ridge is thought to be a prominence of mucous tissue as result of contraction of the superior constrictor muscle during swallowing. Although it's existence and function are controversial, the soft palate might be in contact with the ridge during velopharyngeal closure (Calnan 1957).

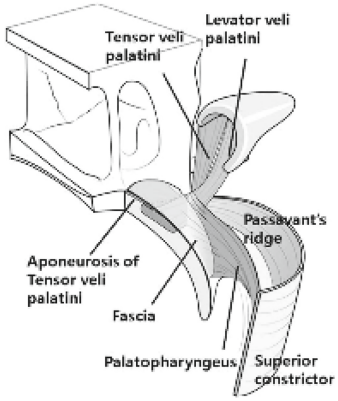

FIGURE 4: Anatomy of the soft palate muscles

1.4.4 Cleft palate repair

The primary goal of cleft palate repair is anatomical reconstruction of an intact palate to allow for development of normal speech while minimizing the risk of oronasal fistula and ensuring long-term harmonious facial growth (Timbang et al. 2014). Two major techniques

are used for cleft palate repair in current practice by cleft surgeons: the two flap technique with intravelar veloplasty also referred to as the "straight line technique" (including the Von Langenbeck palatoplasty, Veau-Wardill-Kilner pushback palatoplasty, and the Bardach two-flap palatoplasty) and the Furlow Z-plasty (Kriens 1969; Furlow 1986; Sommerlad 2003; Katzel et al. 2009; Jackson et al. 2013; Timbang et al. 2014; Stein et al. 2019).

1.4.4.1 Intravelar veloplasty

Patients with a cleft palate have an abnormal positioning of the levator veli palatini muscle that causes loss of integrity of the other soft palate tissues that is the primary cause of VPI and subsequent poor speech outcomes (Kriens 1969) . Therefore release and reorientation of the levator veli palatini muscle , also called the intravelar veloplasty is essential in cleft palate surgery and is an inherent component of the most commonly used straight line techniques (Kriens 1969; Sommerlad 2003; Timbang et al. 2014). Sommerlad advocates a radical muscle dissection of the levator veli palatini muscle for an adequate posterior reorientation (Sommerlad 2003).

1.4.4.2 Von Langenbeck straight line repair

The first straight line technique was described in 1861 by Bernard von Langenbeck who used mucoperiosteal flaps for the repair of the hard palate with anterior attachment of the mucoperiosteal flaps to the alveolar margin creating bipedicle flaps (Figure 5). The cleft edges are incised and if needed lateral incisions are applied. After the flaps are elevated from the hard palate, the soft palate muscles are dissected and followed by midline closure (Wallace 1987; Agrawal 2009). This technique aims to restore the normal anatomy of the levator veli palatini muscle and the palatopharyngeus muscle and results in midline scarring without lengthening of the soft palate (Huang, Lee, and Rajendran 1998; Timbang et al. 2014). This example of straight line technique is nowadays always combined with an intravelar veloplasty since the extent of retropositioning of the levator veli palatini muscle affects velopharyngeal function (Andrades et al. 2008). However, the extent of muscle dissection and reorientation can vary amongst cleft surgeons.

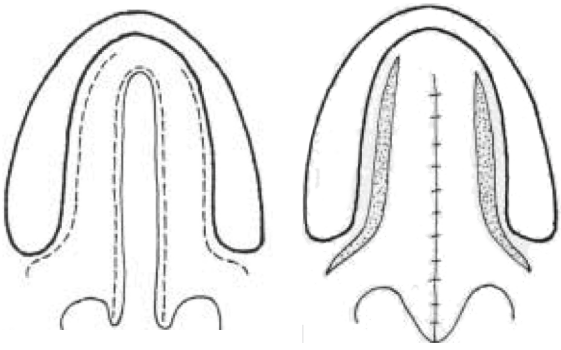

FIGURE 5: Von Langenbeck technique.

1.4.4.3 Furlow technique

The Furlow Z-plasty was introduced as a new technique for cleft palate repair in 1986 (Figure 6) (Furlow 1986). Z-plasties are applied in the oral and nasal mucosa and the cleft margin forms the central limb of each Z-plasty. The soft palate muscles are incorporated on one side each of the oral and nasal Z-plasty and eventually reoriented in the transverse position (Furlow 1986; Agrawal 2009). This results in an overlap of the levator veli palatini and palatopharyngeus muscle across the midline that is anatomically abnormal (Huang, Lee, and Rajendran 1998). The hard palate is repaired by making an incision along the cleft margin, elevating the mucoperiosteum from the medial side and closing the cleft in two layers without making lateral incisions since this results in additional scarring that might affect maxillary growth (Furlow 1986; Agrawal 2009). The Furlow repair has the advantages of lengthening the soft palat and no overlap between the oral and nasal mucosal incisions (Timbang et al. 2014).

However this technique might be less favorable in wide clefts since it may result in excessive lateral tension, increasing the risk of fistula formation and causing an impairment of velar stretch capacity (Huang, Lee, and Rajendran 1998; Losken et al. 2011) However, a modification of the Furlow Z-plasty that includes lateral incisions of the Von Langenbeck type, makes a tension free closure in wide cleft palates possible (LaRossa et al. 2004; Jackson et al. 2013). More recent, the addition of buccal flaps to the Furlow repair obviates the need for relaxing incisions and allows the utilization of the Furlow repair in wide cleft palates (Mann et al. 2017).

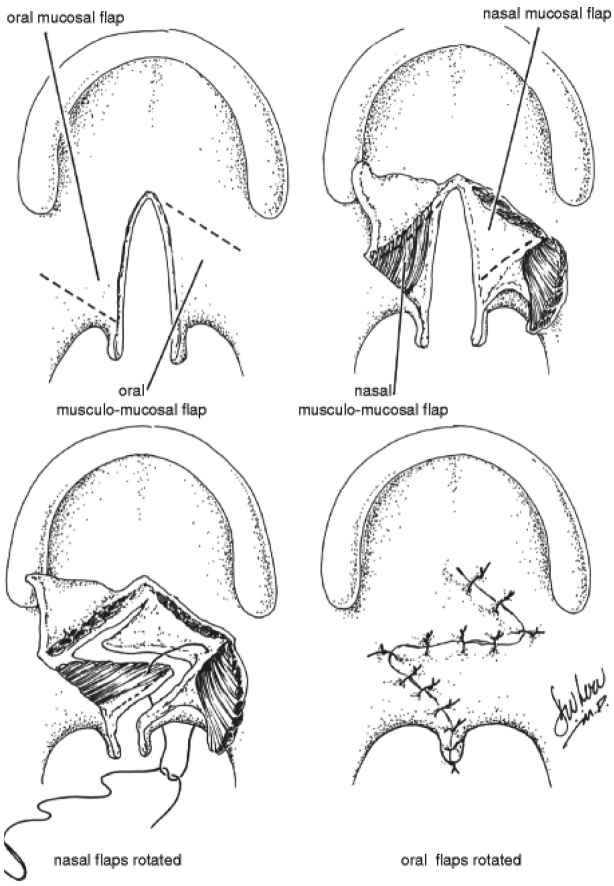

FIGURE 6: Furlow technique
adapted from Furlow 1986

1.4.4.4 Timing of cleft palate repair

To date, the optimal timing of palate closure remains a topic of discussion. Earlier closure of the soft and/or hard cleft palate results in earlier resolution of the feeding problems and improves speech outcomes. However, the iatrogenic scar tissue from cleft palate repair can result in maxillary growth abnormalities that can cause hypoplasia of the mid-face (Kappen et al. 2017, NVPC 2019). This can have an effect on the anterior-posterior relation of the mandible and the maxilla and on prominence of the nose. Lateral growth of the alveolar segments of the maxilla can also be impaired by hard palate closure, causing the molars to no longer align properly, resulting in a cross-bite. This midface hypoplasia is the biggest concern in patients with a cleft of the lip, alveolus and palate, however, also patients with only a cleft of the secondary palate including a portion of the hard palate, are at risk. Because of these reasons many centers used to perform cleft palate repair in two stages. The soft palate was repaired before 12 months and at later stage the hard palate was repaired (Kappen et al. 2017; NVPC 2019). But several studies demonstrated poor long-term speech outcomes after two staged repair and advocated a one stage repair of the soft and hard palate for improvement in long-term speech outcomes (Bardach, Morris, and Olin 1984; Holland et al. 2007; Kappen et al. 2017). In The Netherlands, all cleft teams repair the soft palate during the first year of life, with the majority performing the repair around nine months. Considering the hard palate there is significant variation ranging from 3 months to 12 years, with almost every team describing its own protocol (NVPC 2019). In the United States, a cleft palate should be repaired by the age of 18 months and preferably earlier when possible, without mentioning a distinction for hard and/or soft palate repair (ACPA 2017).

1.4.4.5 treatment of velopharyngeal insufficiency after cleft palate repair

Velopharyngeal function is very important for speech and language development, since all speech is produced with a closed velopharyngeal port, with the exception of three sounds in the English language (/m/, /n/, /ng/) (Perry 2011). Patients can demonstrate an impaired velopharyngeal function after cleft palate repair due to a structural tissue insufficiency, that results in hypernasality in speech or multiple articulations errors of consonants (John et al. 2006; Henningsson et al. 2008; Peterson-Falzone et al. 2017). These consonant errors can be categorized based on the nature of the error, primary in relation to the place of articulation in the oral cavity or pharynx. These articulation errors can be classified in four categories: anterior oral, posterior oral, nonoral (or so called maladaptive compensatory articulations) and passive (or so called audible nasal air emission/turbulence) (John et al. 2006; Peterson-Falzone et al. 2017). Perceptual speech evaluation is performed by a cleft speech pathologist as part of a multidisciplinary cleft team following cleft palate repair. Perceptual speech evaluation around the age of 4 years is used to diagnose VPI, when the phonologic development is completed (Meijer 2003; Vargervik, Oberoi, and Hoffman 2009) Besides hypernasality, passive and nonoral articulation errors are indicators directly related to VPI, while the anterior-oral and

posterior oral CTC in speech can also have other causes than VPI related to different oral morphology (John et al. 2006; Peterson-Falzone et al. 2017)

If perceptual speech evaluation suspects the presence of VPI this can be confirmed by a nasopharyngeal endoscopy and/or video fluoroscopy (Vargervik, Oberoi, and Hoffman 2009; Gart and Gosain 2014; Peterson-Falzone et al. 2017). Approximately 40% of the patients after cleft palate repair demonstrate VPI that needs secondary surgical intervention to resolve it (Gart and Gosain 2014).

1.4.5 Speech improving operations

In the surgical management for VPI there are 3 distinct categories are available: 1. palate re-repair with muscle repositioning that includes secondary intravelar veloplasty, secondary Furlow z-plasty and buccal myomucosal flaps, 2. pharyngoplasty procedures including pharyngeal flap or sphincter pharyngoplasty, and 3. posterior pharyngeal wall augmentation.

1.4.5.1 Secondary Furlow Z-plasty

The secondary Furlow Z-plasty lengthens the soft palate and can be applied as a secondary operation in all patients, regardless of whether or not an intravelar veloplasty is performed at time of cleft palate repair (Furlow 1986; Gart and Gosain 2014). Some authors describe the use of this technique even after a primary Furlow repair (Gosain, Chim, and Sweeney 2018). Moreover, this technique leaves several other surgical techniques available if VPI is not resolved and it has a low potential of causing airway obstruction and obstructive sleep apnea.

1.4.5.2 Bilateral myomucosal buccinator flaps

This relatively new technique is popularized by Mann and relies on adding new and good vascularized tissue from both sides into the palate for lengthening and to resolve VPI (Hill et al. 2004; Mann et al. 2011)

The junction of the hard and soft palate is first marked and divided, detaching the soft palate muscles and allowing them to move posteriorly towards the pharyngeal wall. The defect between the hard and soft palate that is created will be reconstructed by a sandwich of the bilateral buccinator flaps. The first flap raised is sutured with its mucosal surface upwards forming the new the nasal layer of the defect. The other flap is then raised and sutured with its mucosal surface down forming the new oral layer of the defect (Hill et al. 2004).

1.4.5.3 Posterior pharyngeal flap

The first operation to improve velopharyngeal function was reported by Passavant in 1865 and included an adhesion of the soft palate to the posterior pharyngeal wall, while in 1875 Shoenborn refined it to the pharyngeal flap operation that was later popularized by Padgett (Padgett 1930; Sloan 2000; Gart and Gosain 2014). Posterior pharyngeal flaps can be based inferiorly, laterally or most used superiorly (Figure 7). The flap is a permanent passive, central obturator of the velopharyngeal gap and relies on adequate lateral pharyngeal wall motion to close the lateral areas of the velopharyngeal gap

during function (Huang, Lee, and Rajendran 1998; Sloan 2000). Many modifications have been described throughout the years, e.g. the modified Honig velopharyngoplasty where palatal lengthening is achieved by a pushback in combination with a superior based pharyngeal flap (Mink van der Molen et al. 2009).

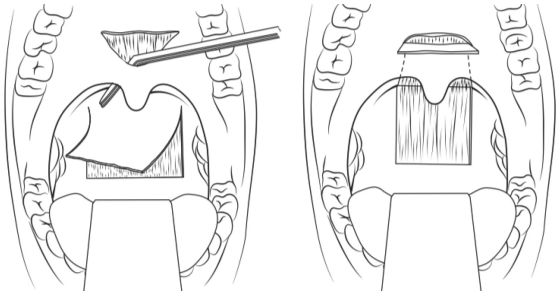

FIGURE 7: Superior pharyngeal flap technique.

1.4.5.4 Sphincter pharyngoplasty

The surgical concept of a dynamic sphincter pharyngoplasty to provide velopharyngeal closure was first introduced by Hynes in 1950 and others have proposed several subsequent anatomic alterations like the popular modification of Ortichochea (Figure 8) (Hynes 1950; Orticochea 1968). Superiorly based posterior tonsilar pillar flaps are created that include the palatopharyngeus muscle, and are transposed posteriorly and superiorly and inset in the pharyngeal walls. The extravelar part of the palatopharyngeus muscle is used to create thickness of the lateral and posterior pharyngeal walls that results in decrease of the velopharyngeal gap circumferentially (Huang, Lee, and Rajendran 1998; Sloan 2000; Gart and Gosain 2014).

There is a concern of airway obstruction and obstructive sleep apnea associated with posterior pharyngeal flap surgery. This has also been reported following sphincter pharyngoplasty, but may not be as frequent or severe as with posterior pharyngeal flap (Sloan 2000; Gart and Gosain 2014).

FIGURE 8: Sphincter pharyngoplasty Ortichochea's technique.

1.5 AIMS OF THIS THESIS

This thesis was initiated to provide better insight in different treatment aspects of patients with RS. Understanding of the etiology/pathogenesis and optimizing treatment modalities could facilitate improved counseling of involved physicians and could result in better management of education and expectations for patient with RS and their families.

To optimally diagnose, subsequently, treat and ultimately give a good outcome and prognosis to patients with RS, a thorough understanding of the embryology and pathogenesis is necessary. **Chapter 2** provides an update about our current understanding of the development of the mandible, tongue and palate and possible mechanisms involved in the development of RS. Special focus is given on the etiology of the primary anomaly (the micrognathia) with subsequent the cleft palate. These different etiologies of the RS phenotype are investigated based on embryologic, developmental and genetic mechanisms.

Although RS is a well-known phenomenon, it is still associated with considerable morbidity and even mortality. In **chapter 3** we try to gain greater insight into the mortality rate and the characteristics of deceased patients with RS in a cohort of 103 consecutive patients followed at the Wilhelmina Children's Hospital in Utrecht. In addition, associated cardiac and neurological anomalies in patients with RS are identified, together with other factors potentially associated with an increased mortality.

Identifying the optimal treatment for UAO/OSA in patients with RS is challenging due to substantial variability in presentation. Universal accepted protocols for the optimal treatment for UAO/OSA in patients with RS are lacking and objective assessments are not standardized. In **chapter 4** a systematic review is performed to investigate of the use of objective measurements from oximetry, polysomnography and blood gas in treatment indications and evaluations for UAO/OSA. This provides an initial step towards building evidence to guide clinical decision making in respiratory management for patients with RS.

In **chapter 5,** a recent article is discussed that assessed treatment success of their surgical intervention (neonatal mandibular distraction) in a comprehensive way and is an excellent example how future studies assessing UAO/OSA in patients with RS should be designed. However, for future studies to be able to compare outcome more comprehensively, we suggest in **chapter 5** several aspects that are still missing.

Patients with RS often have a cleft palate and need surgical repair of the soft palate musculature. Surgical techniques to obtain adequate soft palate repair elaborate on the muscle repair, however, there is little known regarding the innervation of these muscles. In the past cleft surgeons were focussing purely on the most perfect muscle reconstruction, however, for a dynamic repair anatomical insight in the nerves innervating the soft palate muscles is important. In **chapter 6** we focus on the recent advances in the understanding of the innervation of the levator veli palatini, palatopharyngeus and tensor veli palatini muscle. Improved anatomical insights into

the innervation of these muscles will likely allow improvements in cleft palate repair and subsequently decrease the incidence of VPI.

After surgical repair of a cleft palate a common complication is VPI. The bilateral myomucosal buccinator flap has become an important relatively new treatment option to resolve VPI. **Chapter 7** assesses the outcome of a new surgical technique that includes a levator veli palatini muscle repositioning and an oral Z-plasty in combination with a unilateral myomucosal buccinator flap, in 42 consecutive cleft palate patients treated and followed at the Wilhelmina Children's Hospital in Utrecht. In addition, several advantages and disadvantages of this new technique are investigated.

Whether treatment of cleft palate associated with RS should attain similar outcomes to ICP remains unknown. Patients with RS can present with additional features including different cleft palate etiology and anatomy, underlying syndromic diagnosis, a delayed repair due to airway concerns and neonatal airway interventions, that could all influence long-term speech outcomes. **Chapter 8** investigates long-term speech outcomes and identifies outcome predictors for VPI in all consecutive patients with RS and ICP treated and followed at the Craniofacial Center of the University of California San Francisco. The investigated protocol includes a one stage straight-line repair with intravelar veloplasty or Furlow Z-plasty depending on cleft palate and airway characteristics. In addition, the development of UAO/OSA after cleft palate repair, and the outcomes of a secondary Furlow Z-plasty and a tertiary sphincter pharyngoplasty to resolve VPI in patients with RS, are investigated.

TLA is one of the commonly used surgical treatments for UAO/OSA in patients with RS. The tongue is sutured to the lower lip and released after 9-12 months during cleft palate repair that could possibly influence later speech development. The purpose of **chapter 9** is to assess the effect of TLA on the long-term speech and articulation outcomes of patients with RS that underwent cleft palate repair by Von Langenbeck technique with intravelar veloplasty. These outcomes are compared to patients with RS and a cleft palate who required positioning alone and with patients with ICP who were all treated according the same protocol at the Amsterdam University Medical Center, location VUmc. The protocol included a separate closure of the anterior hard palate at a later stage, if cleft palate anatomy didn't allow one stage closure of the hard and soft palate around 12 months.

In addition to the traditional clinical evaluations, proxy and patient-reported outcomes are being increasingly acknowledged as useful in assessing the result of surgical interventions. Numerous studies have proven the efficacy of MDO or TLA in patients with RS, however, none has compared health-related quality of life outcomes. These patient and parents' perspective judgments could have a significant impact on deciding for either MDO or TLA as surgical treatment. In **chapter 10**, we report on health-related quality of life outcomes of these two surgical treatments by comparing two tertiary medical centers: The Wilhelmina Children's Hospital using MDO and the Amsterdam Medical Center Location VUmc using TLA.

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PART I

DIAGNOSTICS

2.

CHAPTER 2.

THE ONTOGENY OF ROBIN SEQUENCE

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ABSTRACT

The triad of micrognathia, glossoptosis and concomitant airway obstruction defined as "Robin sequence" (RS) is caused by oropharyngeal developmental events constrained by a reduced stomadeal space. This sequence of abnormal embryonic development also results in an anatomical configuration that might predispose the fetus to a cleft palate. RS is heterogeneous and many different etiologies have been described including syndromic, RS-plus, and isolated forms. For an optimal diagnosis, subsequent treatment and prognosis, a thorough understanding of the embryology and pathogenesis is necessary. This manuscript provides an update about our current understanding of the development of the mandible, tongue and palate and possible mechanisms involved in the development of RS. Additionally, we provide the reader with an up to date summary of the different etiologies of this phenotype and link this to the embryologic, developmental and genetic mechanisms.

INTRODUCTION

The triad of micrognathia, glossoptosis and concomitant neonatal airway obstruction, currently known as Robin sequence, was first described by St. Hilaire in 1822, by Fairbain in 1846 and by Shukowsky in 1911(Fairbairn, 1846; Randall, 1977; St-Hilaire & Buchbinder, 2000). The subsequent description in 1923 by the French Stomatologist Pierre Robin led to the eponymous definition of the condition (Robin, 1923). The condition was named Pierre Robin syndrome for nearly half a century, before better understanding lead to the identification of multiple etiologies that could result in the same clinical findings, which does not occur in a syndrome (St-Hilaire & Buchbinder, 2000). Instead of syndrome, the term "sequence" was introduced, since the micrognathia subsequently resulted in glossoptosis and upper airway obstruction. It became widely accepted that the condition should be called "Pierre Robin sequence" and that the prior anomaly, the mandibular growth restriction, is pathogenetically heterogeneous (Sadewitz, 1992). In current literature the disorder is most commonly described as "Robin sequence" (RS) (Breugem & Courtemanche, 2010; Breugem & Mink van der Molen, 2009). Recently, an international consensus was achieved regarding the three features (micrognathia, glossoptosis and upper airway obstruction) that should be included in the diagnosis of RS (Breugem et al., 2016).

RS has an incidence of 1 in 8,000-14,000 newborns (Bush & Williams, 1983; Printzlau & Andersen, 2004; Vatlach et al. 2014) and the majority of cases may be associated with a syndrome, a chromosomal abnormality, or other additional anomalies, but may also occur as an isolated entity (Breugem & Mink van der Molen, 2009; Holder-Espinasse et al., 2001; Izumi, Konczal, Mitchell, & Jones, 2012; Xu et al., 2016).

Symptoms of RS include varying degrees of upper airway obstruction and feeding problems, possibly leading to subsequent life-threatening respiratory and cardiac sequelae and failure to thrive when not adequately treated (Costa et al., 2014; Van den Elzen et al. 2001). Mortality rates of 1-26% have been described (Costa et al., 2014; Kaufman et al., 2016).

Numerous treatment options have been developed and vary according to severity. Conservative interventions such as prone- or side positioning techniques, placement of a nasopharyngeal airway or pre-epiglottic baton, and continuous positive airway pressure (CPAP), is primarily applied (Abel et al. 2012; Amaddeo et al., 2016; Buchenau et al., 2007; Evans et al., 2011; Poets & Bacher, 2011). However if these are unsuccessful, surgical management such as tongue-lip-adhesion (TLA), mandibular distraction osteogenesis (MDO), subperiosteal release of the floor of the mouth, or tracheostomy may be considered (Evans et al., 2011).

Since it is well known that the RS is not only pathogenetically heterogeneous, but also phenotypically heterogeneous, it is possible that defining the specific cause could influence the treatment approach or may at least influence the prognosis (Cohen, 1999). The complex consequences of the RS glossopalatognathic malformations require a team of specialists to remedy the impaired airway and orognathic malfunction. This

team of specialists might include molecular biologists, geneticists, embryologists, plastic surgeons, pediatricians, otolaryngologists, maxillofacial surgeons, dentists, orthodontists and speech pathologists. A better understanding of the etiopathogenesis and subsequent expectation of the potential mandibular development could result in better treatment for individual RS-patients.

It is important for all physicians involved in the care of children with RS to have a functional understanding of the embryology of RS. The aim of the current review is to focus on the embryology of the palate, mandible and the tongue. Moreover, information from molecular pathways and possible underlying syndrome diagnosis could improve our understanding of this phenomenon and will be discussed.

EMBRYOLOGY AND PRENATAL DEVELOPMENT

Much of what we currently know about the origins of RS is based upon work done in zebra fish and murine models (Bhatia et al., 2015; Ghassibe-Sabbagh et al., 2011; Gordon et al., 2014; Swindell et al., 2015; Tan et al. 2013; Yuan et al. 2012). While this information is important to identify the developmental mechanisms involved in RS, understanding normal human oral development is necessary to place these mechanistic insights into a clinically relevant perspective (Marques et al. 1998).

Mandibular development

During neural plate folding, cranial neural crest cells, which have the potential to differentiate into bones and connective tissue, will arise in the mid- and hindbrain regions and migrate ventrally to initiate the development of the first pharyngeal arch (which provides the embryonic maxillary and mandibular prominences) (Parada & Chai, 2015; Sperber et al. 2010d). Within the mandibular prominence, formation of the mandibular division of the trigeminal nerve is followed by the condensation of the ectomesenchyme, the multipotent cells derived from the cranial neural crest (Sperber et al. 2010b). The process of condensation brings skeletal precursors into close association, thereby increasing cell-cell signaling required to initiate chondrogenesis and forms a primordial anlage for the ensuing skeletal element of the mandible (Hall & Miyake, 2000) (Figure 1).

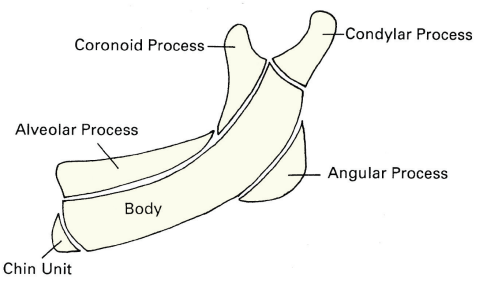

FIGURE 1: The mandible divided in skeletal units. Reprinted from the textbook Craniofacial Embryogenetics and Development, 2nd edition by G.H. Sperber, S.M. Sperber and G.D. Guttmann with permission of the publisher, People's Medical Publishing House—USA, Raleigh, North Carolina.

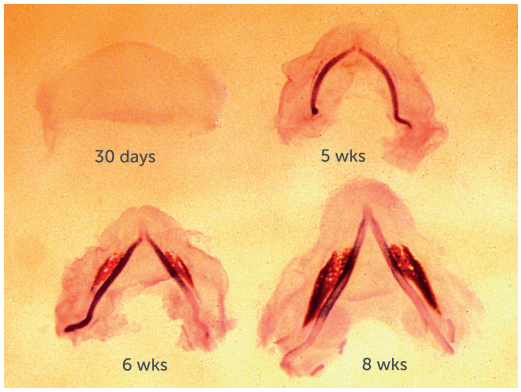

FIGURE 2: Intramembranous mandibular bone forming adjacent to Meckel's cartilage.
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The first skeletal element formed within the mandibular process is Meckel's cartilage, which becomes the fundamental morphogenetic template of the mandible (Amano et al., 2010; Lee et al., 2001; Lorentowicz-Zagalak et al. 2005; Radlanski et al., 2016). Subsequent interaction of the ectomesenchyme with the mandibular arch epithelium results in an osteogenic membrane between days 36 and 38 of development (Figure 2).

This osteogenic membrane lies lateral to the Meckel's cartilage, which forms between 41 and 45 days of development (Orliaguet et al. 1993). In the region of the bifurcation of the inferior alveolar nerve and artery into its mental and incisive branches, a single ossification center for each half of the mandible will develop in the sixth week post-conception (Sperber et al. 2010b). From here the process of intramembranous ossification, where the ectomesenchymal neural crest-derived osteoprogenitor cells differentiate directly into bone, results in formation of the mandibular ramus dorsally and the mandibular body ventrally. Eventually the bony tissue surrounds and invades the Meckel's cartilage in a proximal to distal direction and results in resorption of this cartilage skeleton dorsally from the mental foramen at the twenty-fourth week of development, while simultaneously intramembranous bony trabeculae are formed on the lateral side (Bender et al. 2018; Parada & Chai, 2015; Sperber et al., 2010b).

The mental and mandibular foramina, including the mandibular canal, are formed due to the prior presence of the inferior alveolar nerve and artery (Sperber et al., 2010b). At the site of the mandibular lingula this ossification process stops, although Meckel's cartilage persists and later forms the basis of two ear ossicles (the body and short crus of the incus, the head and neck of the malleus), the anterior ligament of the malleus and the sphenomandibular ligament (Amano et al., 2010; Bender et al., 2018; Sperber et al., 2010b; Sperber et al. 2010d). The only part of the mandible that directly derives from the Meckel's cartilage is the mental ossicle (Sperber et al., 2010d) (Figure 3).

Between the seventh and eight week post conception, the articular discs and presumptive condyle of the primitive temporomandibular joint arises, and by the eleventh week a recognizable joint capsule is formed (Merida-Velasco et al., 1999; Smartt et al. 2005). A secondary mandibular cartilage, which is dissociated from Meckel's cartilage, develops between the tenth and fourteenth week post conception

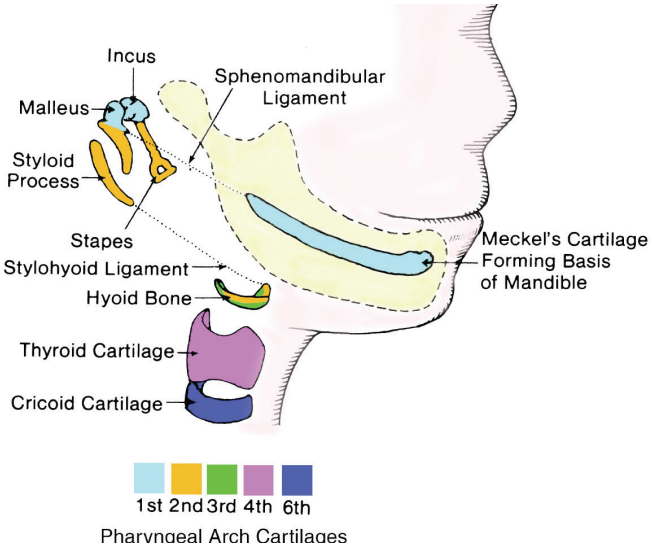

FIGURE 3: Derivatives of the pharyngeal arch cartilages.
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and results in the coronoid process and the head of the condyle. This secondary cartilage of the coronoid process assists in the development of the temporalis muscle and the additional intramembranous bone (Amano et al., 2010; Merida-Velasco et al., 1999; Sperber et al., 2010b). Secondary cartilage ossifies on both sides of the mental symphysis at seven months of development and within this fibrous tissue of the symphysis, mental ossicles arise which will assist the transformation from a syndesmosis into a synostosis in the first postnatal year (Sperber et al., 2010b). The secondary cartilage situated dorsal to the coronoid process is the precursor of the future condyle and arises at the tenth week post conception. These cartilage cells stimulate endochondral ossification of the condylar neck and are a stimulus for growth of the body and ramus of the mandible. Some of these cartilage cells will persist into adulthood, where they function as an articular surface in the temporomandibular joint or growth center for the mandibular condyle (Amano et al., 2010; Bender et al., 2018; Sperber et al., 2010b). After the development of these primary structures, the mandible will continue to grow, directly proportional to fetal weight and gestational age (Berraquero et al. 1995).

Development of the tongue

The tongue develops in the fourth week post conception from the first pharyngeal arch in the ventral wall of the pharynx. At the same time medially and caudally of these lingual swellings and cranially of the foramen cecum, the tuberculum impar is formed (Figure 4 & 5). These lingual swellings merge with each other and form the

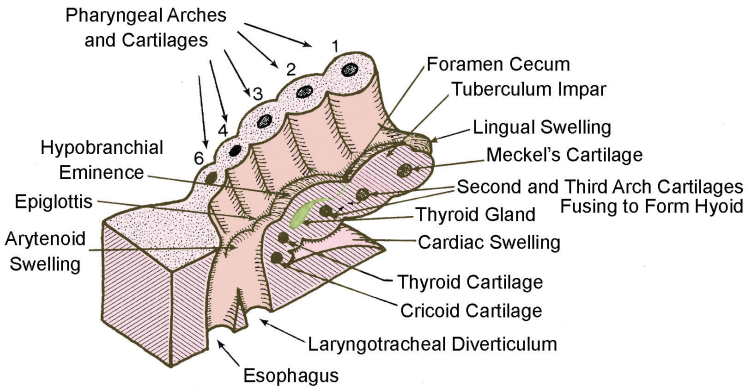

FIGURE 4: Tongue primordial arising in the ventral wall of the pharynx of a 4-week-old embryo.
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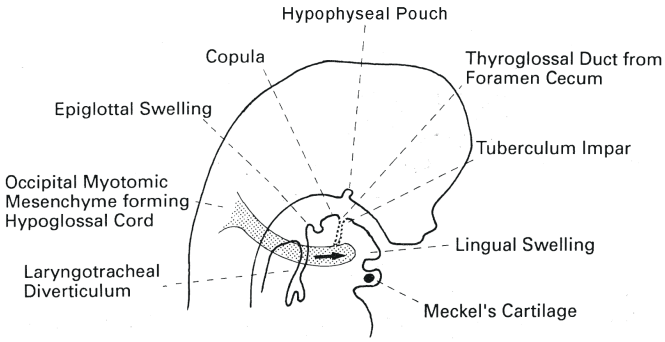

FIGURE 5: Paramedian section of a 5-week-old embryo illustrating the development of the ventral wall of the oropharynx and path of migration of the occipital somite myotomes forming the tongue muscles.
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anterior two thirds of the tongue, which is covered by ectodermally derived epithelium (Chen et al., 2009; Kulbersh & Wiatrak, 2015; Sperber et al. 2010c). The body of the tongue becomes separated from the oropharyngeal floor, except for the frenulum, by the degeneration of central cells, which results in the formation of a linguogingival groove. This process frees the body of the tongue and makes it highly mobile (Sperber et al., 2010c). The root of the tongue is formed by the copula and is covered by endodermally

derived mucosa of the second, third and fourth pharyngeal arches (Chen et al., 2009; Kulbersh & Wiatrak, 2015; Sperber et al., 2010c).

The copula originates from the ventral bases of second, third and fourth pharyngeal arches and is a large midventral prominence just behind the tuberculum impar (Chen et al., 2009; Sperber et al., 2010c). At the site of fusion of the body and the root of the tongue, a V-shaped sulcus terminalis is formed (Kulbersh & Wiatrak, 2015; Sperber et al., 2010c).

Eventually the tongue will grow rapidly and fill the whole stomodeal chamber, which will later develop into nasopharynx, oropharynx and mouth. Due to the growth of the stomodeal chamber and mandibular development, the tongue is able to descend relative to the roof of the chamber (Sperber et al., 2010c).

Palatal development

The secondary palate, which eventually divides the oral and nasal cavities into two independent chambers, originates as outgrowths from the oral surface of each of the maxillary processes known as the palatal shelves. The two palatal maxillary processes are initially located in a vertical position, with the tongue located between these two segments. Initial elongation of the palatal shelves is vertical, such that the growing edges of the shelves move parallel to each other towards the floor of the oral cavity. Oral volume increases as the elongation of the Meckel's cartilage and mandibular growth draws the tongue forward since the genioglossus muscle has its origin on the mental spine of the mandible and concomitant muscular development of the tongue converts it from a cylindrical to more flattened profile. Simultaneously, expansion of the tissue at the base of the palatal shelves due to changes in the extracellular matrix composition and cellular morphology generates a force, which pushes the tips of the shelves in a medial direction (Ferguson, 1978; Tang et al 2015; Yu et al. 2015). This tightly coordinated series of events allows the vertically orientated lateral palatal shelves to ascend to the level of the nasal septum and become horizontally opposite to each other (Price et al. 2016) (Figure 6).

The epithelium of both shelves makes their first contact at 8 weeks of development. This medial edge epithelium plays a key role in mediating the fusion of these lateral palatal shelves (Fitzpatrick et al.

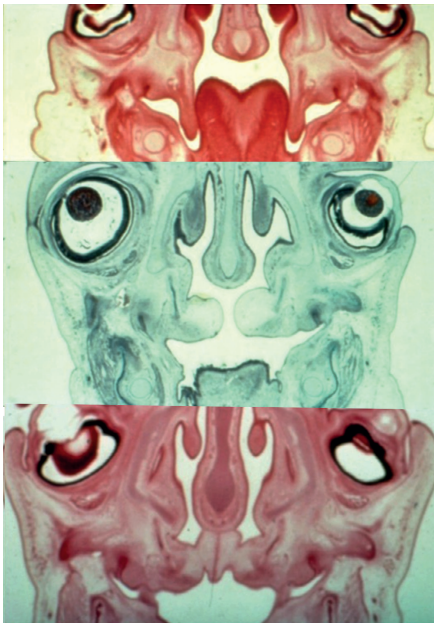

FIGURE 6: Stages of palatal development, elevation and fusion.
By kind permission of Dr. Virginia Diewert

1990; Proetzel et al., 1995; Smith et al. 2012; Tudela et al., 2002). By crucial processes of apoptosis and epitheliomesenchymal transformation this intervening epithelium gradually disappears, and a continuous structure is formed (Sperber et al. 2010a; Tan & Farlie, 2013). This process is initiated just behind the foramen incisivum and subsequently the secondary palate closes from anterior to dorsal. The palate subsequently develops as ectomesenchymal osteoprogenitors within the fused palatal shelves undergo intramembranous ossification (Smith et al., 2012; Sperber et al., 2010a). The primary palate, which is formed ventral to the foramen incisivum, is primarily derived from the frontonasal prominence and is not specifically involved in the pathogenesis of RS.

Except for the most posterior part of the palate, primary ossification centers of the maxillae and palatine bones form the hard palate (Ferguson, 1978; Sperber et al., 2010a). The soft palate derives from myogenic mesenchymal tissue of the first pharyngeal arch and fourth pharyngeal arch which respectively give rise to the tensor veli palatine muscle, innervated by the trigeminal nerve, and levator veli palatini, uvular and faucial pillar muscles innervated by the pharyngeal plexus and vagus nerve (Sperber et al., 2010a).

UNDERSTANDING THE PATHOPHYSIOLOGY OF ROBIN SEQUENCE

Although, RS is defined by a number of specific anatomical anomalies, there are many initiating events that could result in an RS-like phenotype. It is important to understand the range of known or suspected initiators since the prognosis for any particular individual will be greatly affected by the nature of the primary event responsible for restricting growth of the mandible.

It is imperative for clinicians to differentiate between RS-patients that have an identified underlying syndrome, from the isolated RS-group. The latter is characterized by RS-patients that only demonstrate the triad of micrognathia, glossoptosis and upper airway obstruction, without any concomitant anomalies. In addition, RS-patients that have additional anomalies or chromosomal defects but without a (yet) identified associated syndrome, are classified in the RS-plus group (Xu et al., 2016).

In RS it is believed that the reduced mandibular size can be the result of extrinsic abnormalities, intrinsic abnormalities or neurologic/neuromuscular abnormalities. During the first 6 weeks of development the fetal head is in a flexed position with the growing mandible close against the chest. The gradual extension of the head, until the 12th week of gestation, results in a normal outgrowth of the mandible. Head extension may be limited by oligohydramnios, multiple fetuses, uterine abnormalities, an abnormal embryonic implantation site, or unstretched uterine muscles within a small uterus, which could result in intrauterine restriction, possibly leading to micrognathia (Cohen, 1976; Mackay, 2011; Sadewitz, 1992). These can all be considered extrinsic causes of RS.

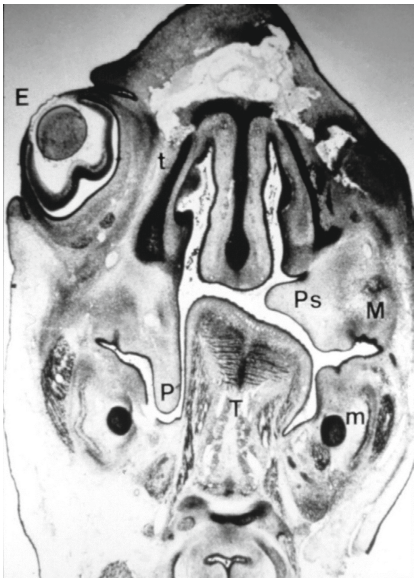

FIGURE 7: Tongue intervention in palatal shelf elevation.
E = eye; m = mandible, M = maxilla, P and Ps = Palatal shelf.

The intrinsic abnormalities include a range of known and unknown genetic influences which can result in syndromic, RS-plus or isolated forms, including syndromes like Treacher Collins syndrome, Stickler syndrome and many other syndromes which all result in a hypoplastic mandible due to Meckel's cartilage deficiencies (Sadewitz, 1992; Tan et al., 2013). The prognosis for the patient with isolated RS is likely to be very different to an individual with RS as part of a complex syndrome. On the other hand, understanding the underlying causes of syndromic RS might also provide clues for identifying novel etiologic mechanisms in isolated or RS-plus forms (Kaufman et al., 2016).

The ontogeny of the RS results from anomalies in the complex events of development of the palato-oropharyngeal area. The reduced size of the mandible that houses the tongue within its confines, results in the developing tongue being forced upwards and backwards into the now reduced stomadeal chamber concomitantly with growth of the embryonic palatal shelves (Figure 7).

The backward fall of the base of the tongue is termed glossoptosis, a characteristic of the RS (Schweiger et al. 2016). At this time, mouth opening is normally a factor in withdrawing the tongue from its interposition between the vertical palatal shelves.

This motor activity requires the gaping actions driven by the mylohyoid and digastric muscles attached to the Meckel's cartilage and innervated by the trigeminal nerve that may be compromised by any neuromotor deficiency.

Continued growth of the mandible and subsequent mandibular morphology is also influenced by functional stresses placed on the mandible by the adjacent soft tissue, such as the developing masticatory and pharyngeal muscles (Pfaff et al. 2014).

Indeed, several neurologic or neuromuscular abnormalities are associated with micrognathia and diagnosed in RS (Abadie et al. 2002; Baujat et al., 2001; Renault et al. 2000). Reported neuromuscular disorders associated with RS are Congenital Myotonic Dystrophy (DM1; OMIM #160900), Moebius syndrome (MB; OMIM 157900) and Carey-Fineman-Ziter syndrome (CFZ; OMIM 254940), characterized by Moebius sequence, RS and hypotonia (Tan et al., 2013). These examples suggest that in some cases RS may result from a primary neuromuscular deficit with the hypoplastic mandible resulting from a subsequent failure of reactive skeletal growth.

As mentioned before, due to the glossoptosis and failure of tongue withdrawal in RS, the elevated intruding tongue can intervene between the vertical palatal shelves, preventing their normal elevation and lead to the development of a usually U-shaped cleft palate (Evans et al., 2011; Hanson & Smith, 1975; Sperber et al., 2010a; Sperber et al. 2013) (Figure 8).

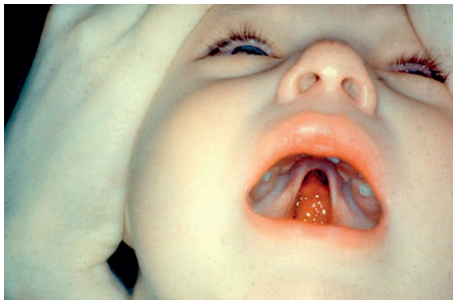

FIGURE 8: U-shaped cleft palate characteristic of Robin sequence

The risk of developing a cleft palate seems to be related to the length of the mandible, with a doubling of the risk of clefting per millimeter reduction in mandible size (Hermann et al. 2014). In addition, a relation between reduced mandibular length and impaired tooth development has been suggested, since tooth agenesis is significantly more frequent in patients with RS (Andersson et al., 2015; Antonarakis & Suri, 2014). Moreover, RS-patients with hypodontia and RS-patients without hypodontia, showed a different mandibular morphology, facial growth and long term dental arch length (Suri et al. 2006). However, the high incidence of tooth agenesis in RS may also indicate a related etiology. The tissues forming the tooth and lip/palate derive from the same facial prominences as the mandible, and related signaling pathways regulate the morphogenesis of both structures (Tan et al., 2013). Thus, a primary defect in pharyngeal arch or morphogenetic signaling could impact both mandibular growth and tooth development.

It would be desirable to make a prognosis and treatment approach in each RS-infant individually based on their etiology and genetic diagnosis. Since the high heterogeneity of RS, better understanding of the pathophysiology is crucial and should result in a more personalized treatment in every individual RS-infant. The increasing use of next-generation sequencing suggests a more etiological diagnosis in RS rather than a clinical diagnosis (Breugem et al., 2016). Subsequently, this could result in adjusting treatment protocols since treatment and prognosis for each individual RS-infant may differ. For example, up until now RS-infants are categorized by severity in order to determine the best treatment for respiratory distress in the neonatal period (Caouette-Laberge et al. 1994; Paes et al., 2015) This ranges from the RS-infant with respiratory distress that is manageable by previously described conservative options (prone and side positioning, nasopharyngeal airway and CPAP) to the RS-infant with severe respiratory distress that needs surgical treatment that includes traditional TLA or relatively new MDO (Abel et al., 2012; Evans et al., 2011; Poets & Bacher, 2011). Recently, an increasing number studies reported on the outcomes of these surgical techniques and systematic review of the literature suggested that MDO might be more effective in relieving the airway obstruction compared to TLA (Almajed et al., 2017). However, MDO is associated with potential complications and reports on long-term outcomes are limited (Paes et al., 2016). The association between the underlying etiological diagnosis and mandibular

morphology and eventual mandibular growth (catch-up growth), might influence the surgical airway management. There has been a lot of controversy about the so-called " catch-up growth" in RS-patients. However, it has been demonstrated that most RS-patients do not achieve full outgrowth compared to the normal, non-cleft population (Laitinen & Ranta, 1992; Suri et al. 2010). It is still unclear which RS-patients achieve normal outgrowth and which RS-patients do not. Patients with Treacher Collins syndrome for instance, are notoriously known for their small mandibles. A recent study demonstrated with 30 cephalometric measurements that Treacher Collins patients are significantly different from normative data (Esenlik et al. 2017). Another study reported on the comparison of craniofacial characteristics (assessed by lateral cephalograms) between 22q11.2 deletion syndrome and Stickler syndrome, both with or without RS. When comparing the 22q11.2 deletion patients with versus without RS, no significant difference was observed for any of the 50 measurements. This suggests that the RS-features in the 22q11.2 deletion syndrome may be the result of hypotonia rather than any craniofacial or physical obstruction of the airway. The comparison of Stickler syndrome plus RS versus 22q11.2 deletion plus RS demonstrated two skeletal and eight airway measures to be significantly different. The authors state that Stickler and 22q11.2 deletion syndrome are similar in craniofacial morphology but demonstrate marked differences in pharyngeal and airway morphology (Glander & Cisneros, 1992). These cephalometric differences clearly indicate the necessity to differentiate between the different genetic diagnosis of patients with RS.

Only one report compared mandibular size and position in patients with RS based on the underlying diagnosis, and subsequently suggests a different treatment approach in airway management. An isolated RS-group was compared with a syndromic RS-group including 4 common syndromic types of RS: Stickler syndrome, 22q11.2 deletion syndrome, Treacher Collins syndrome, and hemifacial microsomia. Mandibular length was significantly shorter in the syndromic RS group compared to the isolated RS-group. The authors implicate a "thoughtful approach" for respiratory distress in RS. Stickler and 22q11.2 deletion syndrome patients are likely to demonstrate similar mandibular morphology compared to isolated RS-patients (Rogers et al. 2009). This might advocated for conservative airway management with a nasopharyngeal airway or the use of TLA when facing severe respiratory distress in these RS-subgroups. The mandible in Treacher Collins and hemifacial microsomia was not expected to normalize, which suggests that these syndromic RS-patients are suitable candidates for MDO (Anderson et al. 2004; Rogers et al., 2009). However, RS is a very heterogeneous phenomenon and more insight in the genetic causes will likely provide more information about the pathophysiology of RS.

GENETIC PERSPECTIVE

An overview of the identified genes, gene functions & expressions and phenotypes associated with Robin sequence are demonstrated in Table 1. Candidate genes associated with Robin sequence based on animal models are presented in Table 2.

Developmental gene networks in relation to underlying diagnoses

Craniofacial and tooth development is tightly controlled by the interaction of numerous signaling gene pathways (Bush & Jiang, 2012; Depew et al. 2005; Parada & Chai, 2015; Sheehan-Rooney et al. 2013).

The *Dlx* (distal-less homeobox) gene family gene family is essential for the development, patterning and morphogenesis of the pharyngeal arches forming a nested gene expression code analogous to the Hox-code (Depew et al., 2005). The *Dlx5 and 6* genes constitute a major difference between the development of the maxilla and mandible (Parada & Chai, 2015). Interestingly, studies in *Dlx5/6*$^{-/-}$ mice demonstrated an agenesis of Meckel's cartilage and abnormal morphology of the mandible with the mandibular skeletal structures transformed into maxillae-like structures.

The identification of a mutation in *DLX6* in a Nova Scotia Duck Tolling Retriever (NSDTR) dog breed, characterized by CP palate and micrognathia, similar to RS, support the role of *DLX6* in the etiology of RS phenotype (Wolf et al., 2014) (Table 2). Subsequent analysis of *DLX5* and *DLX6* in patients with RS revealed a mutation within a highly conserved and functional region of *DLX5*, suggesting the DLX5 gene might be involved in RS in humans (Wolf et al., 2014).

It has been demonstrated that *Dlx6* acts as a downstream effector of endothelin receptor type A (*Ednra)* signaling in the mouse. In *Ednra*–/– embryos, lower jaw structures undergo a homeotic transformation into maxillary-like structures (Ruest et al. 2005; Ruest et al. 2004). Recently, Gordon et al. identified *EDNRA* as the causative gene for mandibulofacial dysostosis with alopecia syndrome (MFDA, OMIM #616367) involving mandibular hypoplasia, micrognathia, cleft palate and glossoptosis (Gordon et al., 2015). Interestingly, *Ednra* signaling is stimulated by endothelin 1 (Edn1), expressed in the overlying pharyngeal arch ectoderm (Clouthier et al., 2013). The *EDN1 gene* has been identified as the causative gene for recessive auriculocondylar syndrome (OMIM #615706) and dominant isolated question-mark ears (OMIM #612798) (Gordon et al., 2013), which can present with features of RS, like micrognathia and glossoptosis (Basart et al., 2015). Clouthier et al. reported that several familial cases of auriculocondylar syndrome were very mildly affected and may present with isolated micrognathia, suggesting that some sporadic cases of more frequent mandibular dysplasias such as RS may actually have an underlying genetic cause in common with that of auriculocondylar syndrome (Clouthier et al., 2013).

It also has been demonstrated that EDN1 is also necessary for *Hand2* expression in the pharyngeal arch (Sasaki et al. 2013; Tamura et al. 2014). *Hand2* is expressed in the first pharyngeal arch and plays a role in the dorsoventral/proximodistal pattern

of the mandibular arch, but also initiates tongue morphogenesis (Barron et al., 2011; Parada & Chai, 2015; Tamura et al., 2014; Yanagisawa et al. 2003). In humans, the *HAND2* gene resides at chromosome 4q. The clinical spectrum of 4q deletions is variable but commonly includes developmental delay, facial dysmorphic features, RS, and abnormalities of the cardiovascular, musculoskeletal and gastrointestinal systems. These patients with a 4q deletion suggest that the *HAND2* gene might also be causative for mandibular hypoplasia and RS in humans (Strehle et al., 2012).

Cartilage and skeletal development

During the earliest stages of mandibular morphogenesis, skeletal development starts with the formation of the rod-shaped Meckel's cartilage, by condensation of the cranial neural crest cell-derived mesenchyme (Radlanski et al., 2016). The Sox9 transcription factor has been shown to be essential for multiple steps in the chondrogenesis pathway from initiation of condensation through to control of extracellular matrix gene expression. (Barna & Niswander, 2007; Jakobsen et al., 2007; Oh et al., 2014). In mice, conditional loss of *Sox9* in neural crest cells result in complete absence of Meckel's cartilage. Furthermore, Sox9-null neural crest cells are unable to contribute to chondrogenic mesenchymal condensations. This disruption results in a diminished template of cartilage for the subsequent intramembranous osteogenesis that provides for the bony development of the mandible (Figure 2). The small mandible subsequently leads to the retruded tongue, obstructing the oropharyngeal airway similar to RS (Mori-Akiyama et al. 2003).

TABLE 1: Identified genes, gene functions & expressions and phenotypes associated with Robin sequence.

Gene	Gene MIM	Chromo-some location	Inheri-tance	Gene function	Gene expression	Condition	Pheno-type MIM	Synonym	Main features
Collagen or bone development									
TGDS	616146	13q32.1	AD	Proteoglycan synthesis or sulfation	Cartilage	Catel-Manzke syndrome	616145	PIERRE ROBIN SYNDROME WITH HYPERPHALANGY AND CLINODACTYLY	Robin Sequence with hyperphalangy and clinodactyly.
COL11A1	120280	1p21.1	AD	Fibril-forming collagen	Mainly in cartilage extracellular matrix.	Marshall syndrome	154780	MARSHALL SYNDROME	Chondrodysplasia, midfacial hypoplasia, high myopia, and sensorineural hearingloss.
COL11A1	120280	1p21.1	AD	Fibril-forming collagen	Mainly in cartilage extracellular matrix.	Stickler syndrome, type II	604841	STICKLER SYNDROME, VITREOUS TYPE 2	Stickler syndrome with congenital nonprogressive myopia of a high degree and abnormal vitreous architecture.
COL11A2	120290	6p21.32	AD	Fibril-forming collagen	Mainly in cartilage extracellular matrix.	Weissenbacher-Zweymuller syndrome	277610	PIERRE ROBIN SYNDROME WITH FETAL CHONDRO-DYSPLASIA	Neonatal micrognathia and rhizomelic chondrodysplasia with dumbbell-shaped femora and humeri, and regression of bone changes and normal growth in later years, myopia.
COL11A2	120290	6p21.32	AD	Fibril-forming collagen	Mainly in cartilage extracellular matrix.	Stickler syndrome, type III	184840	STICKLER SYNDROME, NONOCULAR TYPE	Stickler syndrome without ocular phenotype.

TABLE 1: Continued

Gene	Gene MIM	Chromosome location	Inheritance	Gene function	Gene expression	Condition	Phenotype MIM	Synonym	Main features
COL11A2	120290	6p21.32	AD	Fibril-forming collagen	Mainly in cartilage extracellular matrix.	Otospondylomegaepiphyseal dysplasia	215150	CHONDRODYSTROPHY WITH SENSORINEURAL DEAFNESS	Sensorineural hearing loss, enlarged epiphyses, disproportionate shortness of the limbs, abnormalities in vertebral bodies, and typical facial features.
COL2A1	120140	12q13.11	AD	Fibril-forming collagen	Mainly in the cartilage extracellular matrix.	Kniest dysplasia	156550	KNIEST DYSPLASIA	Short stature, round face with central depression, prominent eyes, enlargement and stiffness of joints, contractures of fingers, normal head circumference, bell-shaped chest, and myopia.
COL2A1	120140	12q13.11	AD	Fibril-forming collagen	Mainly in the cartilage extracellular matrix.	Stickler syndrome, type I	108300	STICKLER SYNDROME, TYPE I	Characterized by ocular, auditory, skeletal, and orofacial abnormalities.
SLC26A2	606718	5q32	AR	Sulphate transporter; Proteoglycans sulfation and matrix organization.	Cartilage; involved in endochondral bone formation.	Diastrophic dysplasia	222600	DIASTROPHIC DYSPLASIA	Skeletal dysplasia with scoliosis, a form of clubbed foot bilaterally, malformed pinnae with calcification of the cartilage, premature calcification of the costal cartilages, and cleft palate in some cases. Particularly characteristic is the 'hitchhiker' thumb due to deformity of the first metacarpal.

TABLE 1: Continued

Gene	Gene MIM	Chromosome location	Inheritance	Gene function	Gene expression	Condition	Phenotype MIM	Synonym	Main features
SLC26A2	606718	5q32	AR	Sulphate transporter; Proteoglycans sulfation and matrix organization.	Cartilage; involved in endochondral bone formation.	Intermediate Phenotype Between Diastrophic Dysplasia and Recessive Multiple Epiphyseal Dysplasia			Robin sequence, mild shortening of upper and lower limbs, brachymetacarpalia/tarsalia, additional and accelerated carpal ossification.
AMER1	300647	Xq11.2	XLD	Interacts with beta-cateninin the wnt-signaling; involved in osteoblast activation, inhibition of osteoclast differentiation or redirection of pluripotential stem cell.	Mouse homolog of AMER1 expressed in developing skeleton and skull, thymus and pulmonary bronchioles.	Osteopathia striata with cranial sclerosis	300373	OSTEOPATHIA STRIATA WITH CRANIAL SCLEROSIS	Sclerosing bone dysplasia that presents in females with macrocephaly, cleft palate, mild learning disabilities, sclerosis of the long bones and skull, and longitudinal striations visible on radiographs of the long bones, pelvis, and scapulae. In males, the disorder is usually associated with fetal or neonatal lethality.
SOX9	608160	17q24.3	AD	COL2A1 is a candidate regulatory target of SOX9.	Expressed during chondrocyte differentiation and upregulated in male and down regulated in female genital ridges during sex differentiation.	Robin sequence	261800	ROBIN SEQUENCE	Isolated Robin sequence.

TABLE 1: Continued

Gene	Gene MIM	Chromosome location	Inheritance	Gene function	Gene expression	Condition	Phenotype MIM	Synonym	Main features
Metabolic disorder									
COG1	606973	17q25.1	-	Subunit of the COG (conserved oligomeric Golgi) complex. Key determinants of Golgi apparatus structure and its capacity for intracellular transport and glycoprotein modification.	Trophoblast, brain, skeletal muscle, testis, bone.	Cerebrocosto-mandibular syndrome/ Congenital disorder of glycosylation, type IIg	611209	RIB GAP DEFECTS WITH MICROGNATHIA	Severe micrognathia/ Robin sequence, osteopenia, rib defects (rib gaps), mental retardation, growth retardation, vertebral anomalies, microcephaly.
PGM1	171900	1p31.3	AR	Enzyme participating in both the breakdown and synthesis of glucose.	Trophoblast, neuron, skeletal muscle, bone, testis, liver, eye.	Congenital disorder of glycosylation, type It	614921	PHOSPHOGLUCO-MUTASES (PGM1)	Cleft lip and bifid uvula, hepatopathy, intermittent hypoglycemia, short stature, hypotonia, mental retardation, exercise intolerance, coagulation disorders, and immunodeficiency Less common features include rhabdomyolysis, dilated cardiomyopathy, and hypogonadotropic hypogonadism.
Neuromuscular Disorder									
DMPK	605377	19q13.32	AD	Non-receptor serine/ threonine protein kinase necessary for the maintenance of skeletal muscle structure and function; May play a role in myocyte differentiation and survival.	Expressed in many tissues including heart, skeletal muscle, liver and brain.	Congenital Myotonic Dystrophy	160900	STEINERT DISEASE	Hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; intellectual disability is common.

TABLE 1: Continued

Gene	Gene MIM	Chromo-some location	Inheri-tance	Gene function	Gene expression	Condition	Pheno-type MIM	Synonym	Main features
Unknown	Unknown	Unknown	AR (probably)	Unknown	Unknown	Carey-Fineman-Ziter syndrome	254940	MYOPATHY, CONGENITAL NONPRO-GRESSIVE, WITH MOEBIUS SEQUENCE AND ROBIN SEQUENCE	Craniofacial anomalies, micro-gnathia, Moebius sequence, generalized myopathy, relative macrocephaly, and developmental delay. Additional features scoliosis, talipes equinovarus, and a nonspecific primary myopathy as important manifestations of the disorder.
PLXND1	604282	3q22.1	AD	Important role in cell-cell signalling, and in regulating the migration of a wide spectrum of cell types.	Detected at low levels in heart, placenta, lung, skeletal muscle, kidney, thymus and liver. Detected at very low levels in brain, colon, spleen, small intestine and peripheral blood leukocytes.	Moebius syndrome	157900	MOEBIUS SEQUENCE	Congenital facial palsy with impairment of ocular abduction. The facial nerve (CN VII) and abducens nerve (CN VI) are most frequently involved, but other cranial nerves may be involved as well. Other variable features include orofacial dysmorphism, limb malformations and ental retardation.
REV3L	602776	6q21	AD	Interacts with MAD2L2 to form the error prone DNA polymerase zeta involved in translesion DNA synthesis.	Expressed in the developing embryonic mouse brain around mid-gestation.	Moebius syndrome	157900	MOEBIUS SEQUENCE	Congenital facial palsy with impairment of ocular abduction. The facial nerve (CN VII) and abducens nerve (CN VI) are most frequently involved, but other cranial nerves may be involved as well. Other variable features include orofacial dysmorphism, limb malformations and mental retardation.

TABLE 1: Continued

Gene	Gene MIM	Chromosome location	Inheritance	Gene function	Gene expression	Condition	Phenotype MIM	Synonym	Main features
Neural crest development									
TBX1/del 22q11.2	602054	22q11.21	AD	Transcription factors involved in regulation of developmental processes.	Mouse Tbx1 expressed in pharyngeal arches, pouches, and otic vesicle, vertebral column and tooth bud. Role neural crest developmental field is suggested.	Chromosome 22q11.2 deletion syndrome	192430/ 188400	CHROMOSOME 22q11.2 DELETION SYNDROME VELOCARDIO-FACIAL SYNDROME DIGEORGE SYNDROME	Cleft palate, cardiac anomalies, typical facies, and learning disabilities
TCOF1	606847	5q32	AD	Involved in ribosomal biogenesis; Essential for survival and migration of craniofacial neural crest cells.	TCOF1 protein is active during early embryonic development in structures that become bones and other tissues in the face.	Treacher Collins syndrome	154500	MANDIBULO-FACIAL DYSOSTOSIS	Antimongoloid slant of the eyes, coloboma of the lower eyelid, micrognathia, microtia and other deformity of the ears, hypoplastic zygomatic arches, and macrostomia. Conductive hearing loss and cleft palate are often present.
POLR1D	613715	13q12.2	AD	Encode RNA polymerases I and III involved in ribosome biosynthesis.	POLR1C plays a role in expression of TCOF1	Treacher Collins syndrome 2	613717	TREACHER COLLINS SYNDROME 2	Antimongoloid slant of the eyes, coloboma of the lower eyelid, micrognathia, microtia and other deformity of the ears, hypoplastic zygomatic arches, and macrostomia. Conductive hearing loss and cleft palate are often present.

TABLE 1: Continued

Gene	Gene MIM	Chromosome location	Inheritance	Gene function	Gene expression	Condition	Phenotype MIM	Synonym	Main features
POLR1C	610060	6p21.1	AD	Involved in ribosome biosynthesis.	POLR1D plays a role in expression of TCOF1	Treacher Collins syndrome 3	248390	MANDIBULOFACIAL DYSOSTOSIS, TREACHER COLLINS TYPE, AUTOSOMAL RECESSIVE	Antimongoloid slant of the eyes, coloboma of the lower eyelid, micrognathia, microtia and other deformity of the ears, hypoplastic zygomatic arches, and macrostomia. Conductive hearing loss and cleft palate are often present.
DHODH	126064	16q22.2	AR	Catalyses the fourth enzymatic step in de novo pyrimidine biosynthesis.	Neural crest cells	Miller syndrome	263750	POSTAXIAL ACROFACIAL DYSOSTOSIS	Micrognathia, cleft lip and/or palate, hypoplasia or aplasia of the postaxial elements of the limbs, coloboma of the eyelids, and supernumerary nipples .
Pharyngeal arches development									
GNAI3	139370	1p13.3	AD	Functions downstream of the EDNRA; crucial role in pharyngeal arch patterning.	Mandibular domain of the first arch.	Auriculocondylar syndrome 1	602483	QUESTION MARK EARS SYNDROME	Malformed ears (question mark ears), prominent cheeks, microstomia, abnormal temporomandibular joint, and mandibular condyle hypoplasia.
PLCB4	600810	20p12.	AR, AD	Functions downstream of the EDNRA; crucial role in pharyngeal arch patterning.	Mandibular domain of the first arch.	Auriculocondylar syndrome 2	614669	AURICULOCONDYLAR SYNDROME 2	Malformed ears (question mark ears), prominent cheeks, microstomia, abnormal temporomandibular joint, and mandibular condyle hypoplasia.

TABLE 1: Continued

Gene	Gene MIM	Chromosome location	Inheritance	Gene function	Gene expression	Condition	Phenotype MIM	Synonym	Main features
EDN1	131240	6p24.1	AR	Neural crest cell development within the first and second pharyngeal arches.	Edn1 is expressed from the epithelium of the mandibular prominence of the first and Caudal Pharyngeal Arch	Auriculocondylar syndrome -3	615706	AURICULOCONDYLAR SYNDROME 3	Malformed ears (question mark ears), prominent cheeks, microstomia, abnormal temporomandibular joint, and mandibular condyle hypoplasia.
Transcriptional defects									
SATB2	608148	2q33.1	AD	Participates in transcription regulation and chromatin remodelling; mouse Satb2 binds to Hoxa2; inhibitor of bone formation and regulator of branchial arch patterning.	Expression in brain, craniofacial tissues, including the palatal shelves, tongue, and mandible. Kidney, thymus and testis	Glass syndrome	612313	CHROMOSOME 2q32-q33 DELETION SYNDROME	Intellectual disability of variable severity and dysmorphic facial features, including micrognathia, downslanting palpebral fissures, cleft palate, and crowded teeth.
RNA related									
EFTUD2	603892	17q21.31	AD	Highly conserved spliceosomal GTPase.	Mesenchyme of limb buds and lung buds, trachea and oesophagus, mandibular mesenchyme, ventricular zone cells of the forebrain, epithelium of the otic vesicle.	Mandibulofacial dysostosis, Guion-Almeida type	610536	GROWTH AND MENTAL RETARDATION, MANDIBULOFACIAL DYSOSTOSIS, MICROCEPHALY, AND CLEFT PALATE	Progressive microcephaly, midface and malar hypoplasia, micrognathia, microtia, dysplastic ears, preauricular skin tags, cleft palate, global developmental delay, and speech delay. Additional features are choanal atresia resulting in respiratory difficulties and conductive hearing loss.

TABLE 1: Continued

Gene	Gene MIM	Chromosome location	Inheritance	Gene function	Gene expression	Condition	Phenotype MIM	Synonym	Main features
SNRPB	182282	20p13	AR, AD	Required for cell division.	Various tissues, including osteoblasts and chondrocytes.	Cerebrocostomandibular syndrome	117650	RIB GAP DEFECTS WITH MICROGNATHIA	Severe micrognathia, rib gap defects, and mental retardation
SF3B4	605593	1q21.2	AD	Role in mRNA splicing.	Optic eminence, optic vesicle, hindbrain and somites.	Acrofacial dysostosis 1, Nager type	154400	ACROFACIAL DYSOSTOSIS 1, NAGER TYPE	Downslanted palpebral fissures, hypoplasia of the lower lid eyelashes, midface retrusion, and micrognathia and limbanomalies (consisting absence of radius, radioulnar synostosis, and hypoplasia or absence of the thumbs).
RBM10	300080	Xp11.23	AD	RNA binding motif (RBM) family.	First and second branchial arch, developing limb buds, and the tailbud.	TARP syndrome	311900	TALIPES EQUINOVARUS, ATRIAL SEPTAL DEFECT, ROBIN SEQUENCE, AND PERSISTENCE OF LEFT SUPERIOR VENA CAVA	Talipes equinovarus, atrial septal defect, Robin sequence, and persistence of left superior vena cava.
EIF4A3	608546	17q25.3	AR	Involved in RNA metabolism.	Pharyngeal arches, highest expression in heart, brain, placenta, lung, liver, skeletal muscle, kidney, and thymus.	Richieri-Costa-Pereira syndrome	268305	ROBIN SEQUENCE WITH CLEFT MANDIBLE AND LIMB ANOMALIES	Robin sequence with cleft mandible and limb anomalies.

MIM: Mendelian Inheritance in Man, AD: Autosomal Dominant, AR: Autosomal Recessive, CN: Cranial nerve, RNA: Ribonucleic Acid, DNA: Deoxyribonucleic acid

In humans, intragenic mutations in *SOX9* leads to the semi-lethal skeletal dysplasia Campomelic Dysplasia (CD; OMIM #114290), characterized by RS, shortening and anterior bowing of the long bones (campomelia), a bell-shaped chest with eleven pair ribs, scoliosis, narrow iliac wings, ossification delay of pubis and cervical vertebrae and club feet (Foster et al., 1994; Houston et al., 1983; Wagner et al., 1994). *SOX9* mutations with residual function of the SOX9 protein has been associated with an attenuated form known as acampomelic campomelic dysplasia, without bending of the long bones, but with micro- and/or retrognathia, glossoptosis and cleft palate (Gopakumar et al., 2014; Staffler et al., 2010). Disruption of putative regulatory elements upstream of SOX9 has been reported in patients with Campomelic dysplasia and acampomelic campomelic dysplasia, but also in patients with isolated RS (Benko et al., 2009; Castori et al., 2016; Gordon et al., 2014). There appears to be a correlation with increased distance of the disruption from *SOX9* and the severity of the phenotypes with the most distant disruptions associated with RS (Gordon et al., 2009; Selvi & Mukunda-Priyanka, 2013; Rainger et al., 2014). While, the full implications of these distant chromosomal anomalies for skeletal development are unclear, identification of a 17q24 chromosomal anomaly in an individual with non-syndromic RS should prompt a close examination for additional skeletal features.

The nearest gene located upstream of *SOX9* is the potassium channel *KCNJ2*. Mutations in this gene are responsible for Andersen-Tawil syndrome (OMIM #170390) characterized by periodic paralysis, cardiac arrhythmias, short stature scoliosis and distinctive dysmorphic facial features, including hypoplastic mandible and in some cases cleft palate (Plaster et al., 2001). Interestingly, *KCJN2* is expressed in facial primordia and was shown to be important for patterning of craniofacial genes and facial development as well as for in vitro muscle differentiation (Hinard et al. 2008). Whether abnormal muscle development results in the mandibular hypoplasia and cleft palate in patients with the Andersen-Tawil syndrome remains to be elucidated but this data is supportive of a potential role for KCNJ2 mis-regulation in the etiology of RS associated with 17q24 anomalies.

Mutations in the SOX9-regulated collagen genes *COL2A1*, *COL11A1* and *COL11A2* are associated with respectively Stickler syndrome type 1 (OMIM #108300), type 2 (OMIM #604841) and type 3 (OMIM #184840) and reported as a common cause of RS (Basart et al., 2015; Izumi et al., 2012). Stickler syndrome is characterized by ocular findings, mainly myopia, mild spondyloepiphyseal dysplasia, and early-onset osteoarthritis and is the syndrome most commonly associated with RS, consistent with a Meckel's cartilage-based etiology.

SOX9 also plays a role in regulating the expression of the *SATB2* gene, by binding a cis- regulatory element (CRE) upstream of *SATB2* (Rainger et al., 2014) Interestingly, loss of function mutations in *SATB2* leads to micrognathia and cleft palate in both mice and human (Britanova et al., 2006; Rainger et al., 2014). *SATB2* is a nuclear matrix protein with a central role in the transcriptional network that regulates craniofacial pattern by chromatin remodeling and transcriptional regulation of transcription factors

involved in osteoblasts differentiation (Dobreva et al., 2006; Leoyklang et al., 2013). Mouse studies showed that *Satb2* is expressed in the developing jaw and loss of *Satb2* leads to apoptosis in the distal jaw mesenchyme. It is suggested that Satb2 is required for survival of distal jaw precursors (Fish, 2016). In humans, chromosome 2q32-q33 deletions and translocations, including the SATB2 gene, as well as mutations in the coding region of SATB2 or in the CRE's upstream of SATB2 cause a recognizable syndromic form of RS, associated with intellectual disability, cleft palate, micrognathia, small mouth, arachnodactyly and facial dimorphisms (OMIM #612313) (Docker et al., 2014; Rainger et al., 2014).

In addition to collagens, proteoglycans are the main components of cartilage (Parada & Chai, 2015). Defects in proteoglycan generation and processing are associated with a number of conditions that feature RS.

The *SLC26A2* gene encodes a widely distributed sulfate/chloride antiporter required for proteoglycan sulfation. *Slc26a2* mutant mice studies confirmed a dramatic decrease in sulfated proteoglycans, but also alterations in the organization of type II and type X collagen fibers, and premature onset of mineralization of the cartilage of the growth plates (Cornaglia et al. 2009). The identification of compound heterozygous *SLC26A2* mutation in two sisters with RS and mild limb shortening, accelerated carpal ossification, and multiple epiphyseal dysplasia, supports the hypothesis that a proteoglycan sulfation defect, might be an underlying mechanism in the etiology in RS (Zechi-Ceide et al. 2013). Mutation of SLC26A2 is also associated with a spectrum of autosomal recessive chondrodysplasias, the most common of these, diastrophic dysplasia (DTD; OMIM # 222600), has been reported as an RS-associated skeletal dysplasia (Tan et al., 2013).

Similarly, mutations in the *IMPAD1* gene, involved in proteoglycan sulfation, result in the GPAPP type of chondrodysplasia with joint dislocations (OMIM #614078). The two patients reported with this diagnosis presented with severe growth retardation with short and abnormal extremities, RS, knee hyperlaxity and abnormally shaped phalanges due to accessory hand bones (Nizon et al., 2012). The features in these patients show a clear overlap with Catel-Manzke syndrome (CATMANS; OMIM #616145), characterized by RS combined with a unique form of bilateral hyperphalangy, causing a clinodactyly of the index finger resulting from mutation of the TGDS gene, which has also been linked to proteoglycan synthesis and sulfation (Ehmke et al., 2014).

TABLE 2. Candidate genes associated with Robin sequence based on animal models

Study	Gene	Gene MIM	Chromo-some location	Type of animal model	Gene function	Association with Robin sequence
Sheehan-Rooney et al. 2013	HAND2	602407	4q34.1	Zebrafish	Essential for cardiac morphogenesis, required for vascular development limb development and involved in the development of branchial arches	Plays a role in appropriate expression of SATB2
Rainger et al. 2014 Ghassibe-Sabbagh et al. 2011	FAF1*	604460	1p23.3	Mice Zebrafish	Initiate FAS-induced apoptosis	Plays a role in regulation of cranial neural crest differentiation. Expression of cartilage-specific markers SOX9A and COL2A1
Swindell et al. 2015 Yuan et al. 2012	CRISPLD2	612434	16q24.1	Zebrafish	Promotes matrix assembly. Binds to heparin, dermatan sulphate and chondroitin sulphate	Plays a role modulating the migration, differentiation, and/or survival of neural crest cells
Wolf et al. 2014 Rieder et al. 2012	DLX6	600030	7q21.3	NSDTR dog breed	Sequence-specific DNA binding, transcription factor activity, sequence-specific DNA binding	Plays a role in regulating mandibular specification
Ling et al. 2017	WNT9A	602863	1q42.13	Zebrafish	Probable developmental protein; May be a signalling molecule which affects the development of discrete regions of tissues	Plays a role in regulating Meckel's cartilage maturation and endochondral ossification
Zhang et al. 2011	FUZ	610622	19q13.33	Mice	Probable planar cell polarity effector involved in cilium biogenesis; May regulate protein and membrane transport to the cilium; May regulate the morphogenesis of hair follicles which depends on functional primary cilia (by similarity)	Plays a role in the negative feedback loop controlling Wnt/β-catenin signaling. Associated with a hyperplastic malformed Meckel's cartilage
Parada et al. 2015 Koczkowska et al. 2017	MAPK1	176948	22q11.22	Mice	MAP kinase signaling cascade, involved in eukaryotic signal transduction: transmission of extracellular signals to cytoplasmic and nuclear effectors MAP kinase signaling cascade MAP kinase signaling cascade MAP kinase signaling cascade MAP kinase signaling cascade	Plays a role in osteogenic differentiation of neural crest cells
Duan et al. 2016	VEGFA	192240	6p21.1	Mice	Induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces permeabilization of blood vessels	Plays a role in optimal intramembranous ossification of mandibular bones

TABLE 2: Continued

Study	Gene	Gene MIM	Chromosome location	Type of animal model	Gene function	Association with Robin sequence
Ansari et al. 2014	PHAX	604924	5q23.2	Mice	RNA binding	Plays a role in the development of pharyngeal arches
Huang et al. 2016	SOX11	600898	2p25.2	Mice	Multiple developmental processes, including regulatory network for corticospinal neuronsmultiple developmental processes critical components of a regulatory network controlling the identity and connectivity of corticospinal neurons regulatory network controlling the identity and connectivity of corticospinal neurons. regulatory network controlling the identity and connectivity of corticospinal neurons regulatory network controlling the identity and connectivity of corticospinal neurons regulatory network controlling the identity and connectivity of corticospinal neurons	Plays a role in cell proliferation of developing mandibular mesenchyme via Cyclin D1
Kouskoura et al. 2016	BMP7	112267	20q13.31	Mice	Part of the transforming growth factor-beta superfamily of regulatory molecules and induces osteogenic transformation in osteoblastic cells	Plays a role in chondrogenesis in Meckel's cartilage and rostral process formation, that could result in disturbances in the attachment sites and the morphology of the genioglossus muscle

NSDTR: Nova Scotia Duck Tolling Retriever, MIM: Mendelian Inheritance in Man.
* The involvement of FAF1 in Robin sequence is uncertain. Rainger et al. reported that in the single family described by Ghassibe-Sabbagh et al., while one of the translocation breakpoints fell in FAF1, the other one fell upstream of SATB2.

Defects in ubiquitous cellular processes resulting in RS-related conditions

There is a growing number of craniofacial syndromes and congenital anomalies resulting from mutations in apparently fundamental cellular systems which might be predicted to have a global impact yet result in specific craniofacial and related defects.

The otopalatodigital (OPD) spectrum syndromes arise due to gain-of-function mutations of *FLNA* (Clark et al. 2009; Robertson, 2007). FLNA crosslinks cytoskeletal actin into a three dimensional network to stabilize the cytoskeleton, but also interacts with many signaling molecules to regulate changes in cell shape, migration, growth and cell differentiation (Clark et al., 2009; Nakamura et al. 2011; Song et al., 2016). OPD2 (OMIM 304120) often involves a cleft palate and micrognathia as well as a severe skeletal dysplasia raising the possibility of a phenotypic overlap with RS (Robertson, 2007).

Cerebrocostomandibular syndrome (CCMS; OMIM #117650) is characterized by RS and posterior rib defects, ranging from rib gaps to complete absence of ossification (Lehalle et al., 2015). The identification of CDG type II with a mutation in *COG1 (*component of oligomeric golgi complex 1, involved in glycosylation) in patients with RS and features resembling cerebrocostomandibular syndrome revealed that a metabolic disorder might also be the underlying cause of RS (Zeevaert et al., 2009). Curiously, CCMS is also caused by mutation in *SNRPB*, encoding the small nuclear ribonucleoprotein polypeptides B and B1 and a core component of the spliceosome required for processing of pre-mRNA into the mature mRNA form in all cells (Bacrot et al., 2015).

Other mandibular facial dysostosis disorders associated with RS caused by mutations in genes involved in spliceosome function are: Mandibulofacial dysostosis, Guion-Almeida type (MFDGA, OMIM #610536) associated with mutation in *EFTUD2*; Nager type of acrofacial dysostosis (AGD1, OMIM #154400) by mutations in *SF3B4;* Richieri-Costa – Pereira syndrome (RCPS; # MIM 268305) caused by mutations in *EIF4A3*. Similarly, TARP syndrome (TRPS, OMIM 311900, characterized by RS, talipes equinovarus, atrial septal defect and persistence of left superior vena cava) has been shown to result from mutation of *RBM10*, which associates with the spliceosomal complex and regulates alternative splicing of the pre-mRNA by enhanced exon skipping (Wang et al., 2013).

The most frequent mandibulofacial dystosis syndrome Treacher-Collins syndrome (TCS; #OMIM 154500) is caused by mutations in *TCOF1, POLR1D or POLR1C,* which are involved in ribosome biogenesis. The ribosome is a sub-cellular organelle required for synthesis of proteins and is required by all cells, yet mutation of *TCOF1* results in widespread death of cranial neural crest cells required to construct the facial skeleton (Dixon et al., 2006). The presentation of Treacher Collins syndrome is highly variable and a small mandible, cleft palate and respiratory obstruction can be interpreted as RS.

Furthermore, mutations in *DHODH,* encoding an enzyme required for de novo pyrimidine biosynthesis, cause postaxial acrofacial dysostosis (POADS; OMIM #263750), also known as Miller syndrome. Miller syndrome is a rare autosomal recessive disorder characterized clinically by severe micrognathia, cleft lip and/or palate,

hypoplasia or aplasia of the postaxial elements of the limbs, coloboma of the eyelids and supernumerary nipples (Rainger et al., 2012). Pyrimidine synthesis is essential for RNA and DNA production and protein synthesis and is therefore crucial for growth and development.

Interestingly, a deletion on chromosome 22q11.2 is believed to be one of the most frequent associated syndromes in RS, with reported frequencies up to 13% in the RS-population (Shprintzen, 1988). Mutations in the *TBX1*-gene disturb normal migration of the cervical neural crest cells into the derivatives of the pharyngeal arches and cause the phenotypes Velocardiofacial syndrome (OMIM #192430) and DiGeorge syndrome (OMIM #188400). However, two recent studies that investigated large cohorts of RS-patients on genetic diagnosis reported low frequencies of 22q11.2 deletions (1.5% and 1%), indicating the importance of genetic re-evaluation of syndromic, isolated and RS-plus patients (Basart et al., 2015; Gomez-Ospina & Bernstein, 2016).

Despite the tissue-specific nature of these craniofacial defects and syndromic forms of RS, they appear to result from defects in fundamental and essential processes such as DNA, RNA and protein synthesis and regulation of gene expression. Thus, while these syndromic forms of RS present with an array of additional features, one might hypothesize that the mechanisms underlying these syndromic presentations may also play a role in cases of isolated or RS-plus patients.

CONCLUSION

The advent of exome sequencing approaches to gene identification for genetic diseases continues to produce a wealth of new data on the etiology of craniofacial dysmorphology. In the wake of this new knowledge it is important to review our current understanding of the embryology and development of the mandible, tongue and palate and to facilitate identification of possible mechanisms involved in the development of RS. Both the primary skeletal origin of RS resulting in a hypoplastic mandible and the hypoplastic mandible due to extrinsic abnormalities are widely accepted in most RS-patients. However, oropharyngeal hypotonia, caused by a dysfunction of the brainstem or other structures, might also result in a hypoplastic mandible. More research of the neurological anomalies in RS-patients would be useful. Additionally, the genetic aberrations associated with RS are diverse, and demonstrate the numerous pathways and mechanisms, which may result in the same developmental outcome. Focusing more on the etiological diagnosis should eventually result in a more personalized approach in each individual RS-patient. While there have been a number of recent molecular diagnoses regarding syndromic forms of RS, progress with isolated and RS-plus forms remains limited. It is hoped that revisiting the developmental anatomy in the context of these new genetic findings will prompt further consideration of the etiology of the isolated and RS-plus manifestation in RS.

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CHAPTER 3.
MORTALITY IN ROBIN SEQUENCE

Identification of risk factors

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ABSTRACT

Introduction: Although Robin sequence (RS) is a well-known phenomenon, it is still associated with considerable morbidity and even mortality. The purpose of this study was to gain greater insight into the mortality rate and identify risk factors associated with mortality in RS.

Methods: We retrospectively reviewed all RS-infants followed at the Wilhelmina Children's Hospital from 1995 to 2016. Outcome measurements were death and causes of death.

Results: The authors identified 103 consecutive RS-infants with a median follow up of 8.6 years (range: 0.1 - 21.9 years). Ten of the 103 infants (10%) died at a median age of 0.8 years (range: 0.1 – 5.9 years). Nine of these ten infants (90%) were diagnosed with an associated syndrome. Of these, seven infants died of respiratory insufficiency due to various causes (two related to upper airway obstruction). The other two syndromic RS-infants died of arrhythmia due to hypernatremia and of West-syndrome with status epilepticus. One isolated RS-infant died of brain ischemia after MDO-surgery.

Cardiac anomalies were observed in 41% and neurological anomalies in 36%. The presence of a neurological anomaly was associated with a mortality rate of 40% versus 7% in infants with no neurological anomaly ($p = 0.016$), with an odds ratio of 8.3 (95% CI: 1.4-49.0) for neurological anomaly versus no neurological anomaly. Mortality was 15% in infants with syndromic RS versus 2% in infants with isolated RS ($p = 0.044$). Mortality was not significantly associated with the presence of a cardiac anomaly, surgical treatment for severe respiratory distress in the neonatal period or prematurity.

Conclusion: RS represents a heterogeneous patient population and is associated with a high level of underlying syndromes. The present study reports a mortality rate of 10% significantly associated with syndromic RS and the presence of neurological anomalies. A multidisciplinary approach in all infants born with RS, including genetic testing and examination of neurological anomalies in a standardized way, is crucial to identify infants with underlying syndromes potentially associated with increased mortality.

INTRODUCTION

Robin sequence (RS) was first described by the French stomatologist Pierre Robin in 1923 and is characterized by the triad of micrognathia, subsequently leading to glossoptosis and varying degrees of upper airway obstruction (Robin 1923). RS is a congenital condition occurring in approximately 1 in 5600-8000 live births (Vatlach et al. 2014; Paes et al. 2015). Recently, an international consensus was achieved regarding the three distinguishing characteristics (micrognathia, glossoptosis and upper airway obstruction) that should be included in the diagnosis of RS in newborns. Cleft palate is frequently encountered, but is not considered a prerequisite for the diagnosis (Breugem et al. 2016). RS-infants represent a heterogeneous patient population because RS might be an isolated condition or be part of a syndrome (in about 26% to 83% of cases) (Paes et al. 2015; Shprintzen 1992; Sheffield et al. 1987; Sher 1992). Clinicians mainly focus on the morbidities of RS, which include respiratory complications due to upper airway obstruction, feeding problems, a related failure to thrive, and the associated cleft palate problems, when present (Evans et al. 2011; Butow et al. 2009; van den Elzen et al. 2001). Reported mortality rates in RS vary from 2% to 26% (Sheffield et al. 1987; van den Elzen et al. 2001; van Nunen et al. 2014; Costa et al. 2014; Dykes et al. 1985; Jolleys 1966; Caouette-Laberge et al. 1994; Smith and Senders 2006; Holder-Espinasse et al. 2001; Bush and Williams 1983; Evans et al. 2006; Williams et al. 1981). Upper airway management plays a central role in the treatment of RS. Treatment of the tongue-based respiratory obstruction minimizes the risk of hypoxic cerebral injury and repeated (aspiration) pneumonia (Douglas 1946; Hoffman et al. 1965; Parsons and Smith 1982). Nonsurgical interventions include positional change, the nasopharyngeal airway, continuous positive airway pressure, and the palatal plate (Evans et al. 2011; Mondini et al. 2009; Bacher et al. 2011). However, when facing severe respiratory distress, surgical procedures are applicable, such as mandibular distraction osteogenesis (MDO), tongue-lip adhesion (TLA), subperiosteal release of the floor of the mouth, and tracheotomy (Bijnen, et al. 2004; Glynn et al. 2011; Breugem et al. 2008; Burstein and Williams 2005).

Limited information is available in the literature concerning the mortality in RS. Recently, Costa et al. demonstrated that mortality in RS is not always directly related to tongue-based respiratory obstruction. Cardiac and neurological anomalies were found to be associated with significantly increased mortality (Costa et al. 2014). A better understanding of the mortality in RS and its relationship with cardiac and neurological anomalies might improve the multidisciplinary treatment of this complex congenital disorder.

The primary aim of this study was to gain greater insight into the mortality rate and characteristics of the deceased RS-infants. The secondary aims were to identify the associated cardiac and neurological anomalies in RS and to identify factors potentially associated with an increased mortality in RS-infants.

MATERIAL AND METHODS

In this retrospective cohort study, we included all infants that were admitted to the Wilhelmina Children's Hospital and diagnosed with RS from 1995 to 2016. The study was approved by the medical ethical board (13-557/C). RS was defined as micrognathia, glossoptosis and upper airway obstruction, with or without the presence of cleft palate. The Dutch Cleft Registry, managed by the Dutch Association for Cleft Palate and Craniofacial Anomalies, was used for patient identification and supplemented with information for infants that underwent surgery related to RS. Medical records of all RS-infants were reviewed and analyzed in January 2017.

Patient characteristics that were obtained included age, sex, gestational age, type of cleft palate, type of syndrome, and treatment for upper airway obstruction in the neonatal period. Variables included syndromic RS (RS as part of a syndrome or RS with other associated anomalies/chromosomal defects) or isolated RS, prematurity (defined as gestational age < 37 weeks), cardiac anomalies, neurological anomalies, and surgical treatment for severe respiratory distress in the neonatal period.

The primary observational outcome measurements of this study were death and causes of death. Subsequently, associated cardiac and neurological anomalies were analyzed. All RS-infants underwent a physical examination by a pediatrician. When physical examination suspected any anomalies, extensive examination was performed. Extensive cardiac examination included assessment by electrocardiography and echocardiography, and extensive neurological examination included assessment by brain Magnetic Resonance Imaging (MRI) and echoencephalography.

Genetic work-up in all infants included standard clinical examination by a geneticist, and additional testing by karyotyping and FISH for a 22q11.2 deletion. Array-CGH and next-generation sequencing were performed from 2008 and 2012, respectively, if an associated syndrome was suspected. Additionally, a recent re-evaluation of the initial genetic diagnoses was performed in our cohort (Basart et al. 2015). We defined isolated RS in infants with a normal clinical examination, negative results from previously described tests, and a normal development. Normal development was assessed by using the Van Wiechen Scheme, that is the Dutch equivalent of the Bayley Scales of Infant Development. Statistical analysis was performed by using the Chi-Square Test and Fisher's Exact tests in IBM SPSS Statistics 24.0 (IBM Inc., NY, USA). A p-value of < 0.05 was considered to be significant.

RESULTS

Patient characteristics

At our institution, 103 consecutive infants were diagnosed with RS in the 22-year study period (1995-2016). The median follow-up period was 8.6 years (range: 0.1 - 21.9 years). Table 1 shows the baseline characteristics of all the RS-patients: isolated RS, 42%;

TABLE 1: Baseline characteristics of RS-infants followed at the Wilhelmina Children's Hospital 1995-2016

Infants	Number of infants (%)	Female	Male	Gestational age (weeks)	Presence of CP (%)	CP-type
Total	103 (100%)	54	49	39.4 (range 30.9-42.0)	101 (98%)	I (4); II (20); III (57); IV (20)
Isolated RS	43 (42%)	25	18	39.1 (range 32.3- 42.0)	42	I (0); II (8); III (24); IV (10)
Syndromic RS	60 (58%)	29	31	38.9 (range 30.9-42.0)	59	I (4); II (12); III (33); IV (10)
RS as part of a syndrome	39 (38%)					
Stickler Syndrome	16					
Treacher-Collins Syndrome	2					
Spondyloepiphyseal Dysplasia Congenita	2					
4q deletion Syndrome	1					
Auriculo-Condylar Syndrome	1					
Carey-Fineman-Ziter Syndrome	1					
EEC Syndrome	1					
Worster-Drought Syndrome	1					
Klinefelter Syndrome	1					
Cerebro-Costo-Mandibular Syndrome	1					
Catel-Manzke Syndrome	1					
Yunis-Varon Syndrome	1					
Van der Woude Syndrome	1					
Osteopathia Striata with Cranial Sclerosis	1					
Hyperphosphatasia Mental Retardation Syndrome 1	1					
Hemifacial Microsomia	1					
Sotos Syndrome	1					
CHARGE-Syndrome	1					
Unknown Syndrome	4					
Other associated abnormalities or chromosomal abnormalities	21 (20%)					

RS: Robin sequence, **Syndromic RS:** RS as part of a syndrome or RS with other associated anomalies/chromosomal defects, **CHARGE-Syndrome:** Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital abnormality and Ear abnormality syndrome, **EEC syndrome:** Ectrodactyly Ectodermal Dysplasia Cleft Lip/Palate syndrome, **CP:** cleft palate, **CP-type, modified "Jensen et al. classification" (Jensen et al. 1988):** I, submucosal cleft or bifid uvula; II, soft palate; III, soft palate and part of hard palate; IV, soft palate and hard palate up to incisive foramen.

syndromic RS, 58% (20% RS with other associated anomalies/chromosomal defects and 38% RS as part of a syndrome); median gestational age, 39.4 weeks (range: 30.9-42.0 weeks); prematurity, 13%; presence of cleft palate, 98%. Surgical treatment for severe respiratory distress in the neonatal period was required in 35% of the infants (21 MDO's, five TLA's, seven tracheotomies, one MDO and later stage tracheotomy, one TLA and later stage tracheotomy, and one tracheotomy resolved by MDO).

Mortality

Ten of the 103 infants (10%) died at a median age of 0.8 years (range: 0.1 – 5.9 years). One other infant was unvaccinated due to the parents' religious belief and died of Haemophilus influenzae type B septic meningitis. Since this death was totally unrelated to RS, this infant was excluded from the analysis. The characteristics of the ten deceased RS-infants are listed in Table 2. An even distribution of deaths was observed in our study period (1995-2016). Five females and five males died. Seven infants died of respiratory insufficiency due to various causes (two of viral pneumonia, one of aspiration pneumonia, one of pneumosepsis, two of airway obstruction problems, and one of muscle weakness). The other three infants died of arrhythmia due to hypernatremia of 167 mmol/L with urosepsis (n = 1), West-syndrome with status epilepticus (n = 1), and brain ischemia after MDO-surgery (n = 1). Nine infants had syndromic RS, and one infant had no diagnosed syndrome or other associated anomalies/chromosomal defects. This isolated RS-infant died of brain ischemia due to a major complication of persistent low blood pressure during MDO-surgery.

Extensive cardiac and neurological examination

In 41 infants (40%) extensive cardiac examination was performed, including 27 assessments by electrocardiography and 31 assessments by echocardiography. Extensive neurological examination was done in 42 infants (41%), of which 15 had a brain MRI and 35 an echoencephalography. The group of 41 infants that underwent extensive cardiac examination consisted of both syndromic (76%) and isolated (24%) RS-infants. The 42 infants that had extensive neurological examination, also included both syndromic (69%) and isolated (31%) RS-infants. When looking at the total syndromic RS-group (n = 60), in only 52% and 48% extensive cardiac and neurological examination was performed, respectively.

Anomalies and risk groups

All anomalies diagnosed by extensive cardiac and neurological examination are listed in Table 3. Seventeen infants (41%) were diagnosed with cardiac anomalies, of which the ventricular septum defect (n = 10) was observed most frequently. Neurological anomalies were diagnosed in 15 infants (36%), and a hypoplastic corpus callosum (n = 5) was found most frequently. Extensive examination by electrocardiography did not reveal any anomalies.

TABLE 2: Characteristics of the deceased RS-infants followed at the Wilhelmina Children's Hospital 1995-2016

Infant & Year of birth	Sex	Age at death (years)	Isolated/ Syndromic	Syndrome	Cause of death	Cardiac-Neuro-logical analysis	Surgery	Anomalies
I - 1995	F	5.9	Syndromic	Karyotype 46, XX, 8p+	Respiratory insufficiency after viral pneumonia in combination with Reye's syndrome.	No	Yes	-	* Grade IIa left ventricular bleeding, severe periventricular flaring and dysplastic corpus callosum
II - 1996	M	0.7	Syndromic	CHARGE-syndrome	Respiratory insufficiency after viral pneumonia with CHARGE association.	Yes	Yes	-	* Atrioventricular septal defect, patent ductus arteriosus, and right ventricular hypertrophy
III - 1999	F	0.8	Syndromic	4q- syndrome	Arrhythmia due to hypernatremia of 167 mmol/L and urosepsis.	Yes	Yes	TLA	* Bilateral germinolytic cysts and cavum septum pellucidum * Aortic stenosis with coarctation of the aorta, multiple ventricular septal defects and left ventricular hypertrophy
IV - 2001	M	0.1	Syndromic	Spondyloepiphyseal Dysplasia Congenita Syndrome	Respiratory insufficiency after aspiration pneumonia.	No	No	-	
V - 2003	F	2.8	Syndromic	Unknown syndrome: Microcephaly, blindness, severe psychomotor retardation and epilepsy	Respiratory insufficiency after pneumosepsis, palliative treatment. History of gastroesophageal reflux with aspirations, causing recurrent airway problems.	Yes	Yes	-	* Hypoplastic corpus callosum, septum pellucidum agenesis, lenticulostriatal vasculopathy, ventricular system left > right and periventricular noduli suspected for a neuronal migration disorder
VI - 2004	F	2.7	Syndromic	Hyperphosphatasia with Mental Retardation Syndrome 1	West Syndrome with status epilepticus.	Yes	Yes	-	* Hypoplastic corpus callosum * Ventricular septal defect

TABLE 2: Continued.

Infant & Year of birth	Sex	Age at death (years)	Isolated/ Syndromic	Syndrome	Cause of death	Cardiac-Neuro-logical analysis		Surgery	Anomalies
VII - 2009	M	0.2	Syndromic	Yunis Varon Syndrome	Respiratory insufficiency after persistent upper airway obstruction that showed no improvement after TLA. Palliative treatment since persistent respiratory problems, severe dysphagia and other complex anomalies.	Yes	Yes	TLA	* Hypoplastic pons and vermis, partial agenesis of the corpus callosum * Hypoplastic left ventricle complex, coarctation of the aorta, aberrant right subclavian arteries, persistent left superior vena cava, atrial septal defect, and patent ductus arteriosus
VIII - 2010	F	0.1	Isolated	-	Post MDO-surgery severe convulsions. Brain ischemia due to low blood pressure moments during surgery and possible preoperative hypoxic moments due to RS.	Yes	Yes	MDO	
IX - 2011	M	3	Syndromic	Treacher Collins Syndrome	Respiratory insufficiency caused by upper airway obstruction (mucus), reanimation with post anoxic brain injury and brain herniation. History of multiple hospital admissions due to aspirations and respiratory problems.	Yes	No	MDO	
X - 2013	M	0.2	Syndromic	Carey-Fineman-Ziter Syndrome	Respiratory insufficiency due to muscle weakness that required persistent ventilation. Palliative treatment.	Yes	Yes	MDO	* Brainstem calcifications (associated with Carey-Fineman-Ziter Syndrome)

M: Male, **F:** Female, **RS:** Robin Sequence, **Syndromic RS:** RS as part of a syndrome or RS with other associated anomalies/chromosomal defects, **MDO:** Mandibular distraction osteogenesis, **TLA:** Tongue-lip adhesion, **CHARGE-Syndrome:** Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital abnormality, and Ear abnormality syndrome.
Note: 70% of all the deceased RS-infants underwent both extensive cardiac and neurological examination.

The presence of a neurological anomaly was associated with a mortality rate of 40% versus 7% in infants with no neurological anomaly (p = 0.016). The odds ratio for mortality was 8.3 (95%CI: 1.4-49.0) for neurological anomaly versus no neurological anomaly. The mortality rate was 15% in infants with syndromic RS versus 2% in infants with isolated RS (p = 0.044). The other variables did not demonstrate a statistically significant association with mortality: the presence of a cardiac anomaly was associated with a mortality rate of 24% versus 17% in infants with no cardiac anomaly (p = 0.698), surgical treatment for severe respiratory distress with 14% versus 8% for noninvasive treatment (p = 0.318), and premature birth with 2% versus 8% for full-term birth (p = 0.621).

TABLE 3: Identified anomalies of the RS-infants followed at the Wilhelmina Children's Hospital 1995-2016

Anomaly	No.
Cardiac (41% of analyzed RS-infants*)	**34**
Ventricular septal defect	10
Patent foramen ovale	5
Patent ductus arteriosus	3
Coarctation of the aorta	2
Bicuspid aortic valve	2
Right ventricular hypertrophy	2
Atrial septal defect	1
Atrioventricular septal defect	1
Left non-compaction ventricular cardiomyopathy	1
Aberrant right subclavian arteries	1
Persistent left superior vena cava	1
Supravalvular pulmonary stenosis	1
Pulmonic stenosis	1
Left pulmonary artery stenosis	1
Left ventricular hypertrophy	1
Hypoplastic left ventricle	1
Neurologic (36% of analyzed RS-infants*)	**30**
Hypoplastic corpus callosum	5
Cavum septum pellucidum	4
Asymmetric ventricular system	3
Hypoplastic pons	3
Bilateral germinolytic cysts	2
Hypoplastic vermis	2
Cyst	2
Grade IIa ventricular bleeding	1
Bilateral thalamic densities	1
Cavum vergae	1
Lenticulostriatal vasculopathy	1
Periventricular noduli suspected for neuronal migration disorder	1
Bilateral frontal and left periventricular aspecific white matter abnormalities	1
Typical leukomalacia abnormalities	1
Colpocephaly	1
Brainstem calcifications (associated with Carey-Fineman-Ziter Syndrome)	1

RS: Robin sequence
*Note: Some RS-infants had multiple anomalies

DISCUSSION

This retrospective study of a large cohort of RS-infants provides new insight into the mortality of RS and the associated risk factors. We report a mortality rate of 10% in RS-infants, and mortality significantly associated with the presence of neurological anomalies and with the diagnosis of syndromic RS. Mortality was not significantly associated with the presence of a cardiac anomaly, surgical treatment for severe respiratory distress in the neonatal period, or prematurity.

Our reported mortality rate is in line with the previously described mortality rates in RS-infants, which range from 2% to 26% (van den Elzen et al. 2001; van Nunen et al. 2014; Costa et al. 2014; Dykes et al. 1985; Sheffield et al. 1987; Jolleys 1966; Caouette-Laberge, Bayet, and Larocque 1994; Smith and Senders 2006; Holder-Espinasse et al. 2001; Bush and Williams 1983; Evans et al. 2006; Williams et al. 1981)], although it was higher than we expected when the study was initiated. Our group of deceased infants consists of a highly heterogeneous group (Table 2). Costa et al. reported in their cohort of 181 RS-infants (the largest cohort available) a higher mortality rate of 17%, and in their series only syndromic RS-infants died ($p = 0.002$) (Costa et al. 2014). In our cohort nine syndromic RS-infants and one isolated RS-infant died, and we observed a significant association between syndromic RS and mortality ($p = 0.044$). The death of this isolated RS-infant should be discussed. Sadly, this infant developed severe convulsions post-MDO-surgery, and a CT-scan of the brain demonstrated severe lesions of ischemia. The brain ischemia was interpreted by the low blood pressure moments during MDO-surgery in combination with the preoperative hypoxic moments due to RS. This emphasizes the fragility of RS in relationship to anesthesia and surgical interventions. Moreover, a complete genetic workup was not made for this infant, and it is possible that, with time, these genetic investigations could have revealed a possible genetic cause or syndrome. Furthermore, a recent study by Basart et al. emphasized the importance of repeated genetic evaluation. After re-evaluation, 25% of patients had a new genetic diagnosis (Basart et al. 2015). Subsequently, with a more universally accepted minimum "norm" of gene-analysis performed by the clinical geneticist, especially since the introduction of the next-generation sequencing, more infants could be diagnosed with an additional genetic condition (Breugem et al. 2016).

In our heterogeneous group of deceased infants, we could identify seven infants that died of respiratory insufficiency due to different causes (two of viral pneumonia, one of aspiration pneumonia, one of pneumosepsis, two of airway obstruction problems, and of muscle weakness). All these seven infants had syndromic RS, and a wide range of age-at-death was observed (0.1-5.9 years). This indicates that clinicians should be more aware of respiratory problems in syndromic RS-infants, also after the first year of life. This is in line with Van Lieshout et al., who reported that, between the age of 1 and 18 years, almost one out of four RS-infants continues to have respiratory problems. Additionally, RS-infants who need respiratory support early after birth are at risk of continuing or re-developing obstructive sleep apnea after the age of 1 year (van Lieshout

et al. 2016). In our study, we could relate the cause of respiratory insufficiency to upper airway obstruction in only two infants (VII and IX). In the other infants (I, V, X), the respiratory distress might be related to a neurological cause, based on the presence of their neurological anomalies. This might result in pharyngo-laryngeal dyscoordination that could predispose these infants to the risk of respiratory insufficiency.

This study has several limitations that should be discussed. First, we experienced an important variability in follow-up time ranging from 0.1 years to 21.9 years, with a median of 8.6 years. The lower range of our follow-up time is explained by the RS-infants in our cohort that died at a very young age.

Second, the present study only identified two RS-infants without the presence of a cleft palate. The recent international consensus on the diagnosis of RS states that cleft palate is not mandatory for the diagnosis of RS, although it is present in about 90% of RS-infants (Breugem et al. 2016). However, a report in 2009 demonstrated that there was no uniformity among clinicians in the Netherlands involved in craniofacial care in defining RS and the inclusion of cleft palate as part of the sequence (Breugem and Mink van der Molen 2009). It is possible that, in our study period, infants without the presence of cleft palate were not identified as RS at our institution. This would explain the high incidence of cleft palate (98%) in our RS-cohort.

Third, having a neurological anomaly and an associated syndrome might be confounding variables. In the future, larger RS-cohorts are necessary to make a distinction between these variables.

Lastly, not all infants had the same cardiac and neurological workup; this is because extensive cardiac and neurological examination were only performed, when physical examination suspected any anomalies. This diagnostic workup remained unchanged over the study period and resulted in extensive cardiac and neurologic examinations of 40% and 41% of our infants, respectively. Our findings of 41% cardiac and 36% neurological anomalies are higher compared to other studies (Costa et al. 2014; Pearl 1982; Rozendaal et al. 2012; Williams et al. 1981; Monroe and Ogo 1972). However, the criteria for performing extensive cardiac or neurological examination in these studies were not specified. Previously reported cardiac anomalies in RS-infants range from 7% to 31%, and neurologic anomalies were observed in 25% (Costa et al. 2014; Pearl 1982; Rozendaal et al. 2012; Williams et al. 1981; Monroe and Ogo 1972). Extensive examination was performed in only a subgroup of our RS-infants, which was suspected for anomalies after physical examination; these infants were also more likely to have anomalies, which could explain our higher incidence of anomalies. On the other hand, we cannot exclude all cardiac and neurological anomalies in our cohort since, of the syndromic RS-infants, only 52% and 48% had extensive cardiac and neurological examinations, respectively. By analyzing all of the different anomalies, we could only identify the ventricular septum defect and the hypoplastic corpus callosum as frequently associated anomalies in RS. The other identified anomalies were diverse and indicated the heterogeneity of RS.

However, in our institution, physical examination combined with extensive neurological examination could identify a group of RS-infants that had increased mortality; 40% in RS-infants with a neurological anomaly ($p = 0.016$). This is in line with the findings of Costa et al. who reported cardiac and neurological anomalies significantly associated with an increased mortality rate (Costa et al. 2014). Interestingly, extensive cardiac and neurological examination was not only performed in the syndromic RS-infants. The pediatrician's physical examination resulted in extensive cardiac and neurological examination in 24% and 31% of the isolated RS-infants. The demonstrated significant association between the presence of neurological anomalies and an increased mortality rate advocates that all RS-infants should be investigated for the presence of anomalies.

CONCLUSION

RS-infants represent a heterogeneous population and is associated with a high level of underlying syndromes. The present study reports a mortality rate of 10%, which was significantly associated with syndromic RS and the presence of neurological anomalies. A multidisciplinary approach in all infants born with RS, including genetic testing and examination of neurological anomalies in a standardized way, is crucial to identify infants with underlying syndromes potentially associated with increased mortality. We suggest future prospective multicenter studies that extensively examine the possible genetic diagnosis and congenital anomalies in a standardized way in infants with RS.

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4.

CHAPTER 4

OBJECTIVE MEASUREMENTS FOR UPPER AIRWAY OBSTRUCTION IN INFANTS WITH ROBIN SEQUENCE: WHAT ARE WE MEASURING?

A systematic review

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ABSTRACT

Study objectives: Identifying optimal treatment for infants with Robin sequence (RS) is challenging due to substantial variability in the presentation of upper airway obstruction (UAO) in this population. Objective assessments of UAO and treatments are not standardized. A systematic review of objective measures of UAO was conducted as step towards evidence based clinical decision making for RS.

Methods: A literature search was performed in Pubmed and Embase databases (1990-2020) following PRISMA-guidelines. Articles reporting on RS and UAO-treatment were included if the following objective measures were studied: oximetry, polysomnography and blood gas. Quality was appraised by methodological index for non-randomized studies (MINORS, range: 0-24).

Results: A total of 91 articles met inclusion criteria. Mean MINORS-score was 7.1 (range:3-14). Polysomnography was most frequently used (76%) followed by oximetry (20%) and blood gas (11%). Sleep position of the infant was reported in 35% of studies, with supine position most frequently, and monitoring time in 42%, including overnight recordings in more than half. Of 71 studies that evaluated UAO-interventions, the majority used polysomnography (90%), of which 61% did not specify the polysomnography technique. Reported polysomnography metrics included oxygen saturation (61%), apnea-hypopnea index (52%), carbon dioxide levels (31%), obstructive-apnea-hypopnea index (27%), and oxygen-desaturation-index (16%). Only 42 studies reported indications for UAO-intervention, with oximetry and polysomnography thresholds used equally (both 40%). In total, 34 distinct indications for treatment were identified.

Conclusions: This systematic review demonstrates a lack of standardization, interpretation and reporting of assessment and treatment indications for UAO in RS. An international, multidisciplinary consensus protocol is needed to guide clinicians on optimal UAO assessment in RS.

INTRODUCTION

Robin sequence (RS) is diagnosed in infants born with micrognathia, glossoptosis and varying degrees of upper airway obstruction (UAO) (Robin 1923). This craniofacial anomaly is the result of a sequence of disturbances to embryonic development that is believed to begin with mandibular hypoplasia. Micrognathia can be initiated by extrinsic, intrinsic, or neurologic/neuromuscular causes (Robin 1923; St-Hilaire and Buchbinder 2000; Tan et al. 2013; Logjes et al. 2018). These differing etiologies may explain the heterogeneity of the RS phenotype. Clinicians distinguish infants with syndromic RS and "RS-plus" (RS with additional malformations but without a genetically-confirmed syndrome) from those without concomitant anomalies (isolated RS). A U-shaped cleft palate is a common finding in affected infants, but is not required to make the diagnosis of RS (Logjes et al. 2018; Tan et al. 2013; St-Hilaire and Buchbinder 2000).

Because of variable degrees of breathing and feeding problems and the associated high mortality, pediatricians acknowledge that early diagnosis of RS is important (Breugem et al. 2016; Evans et al. 2011). Infants with RS can experience hypoxia and are at risk of increased work of breathing, sleep disturbance, hypercapnia, pulmonary hypertension, growth failure and abnormal psychomotor development. Infants may be exposed to oxygen desaturation and sleep disruption which are hypothesized to contribute to neurocognitive impairment (Bass et al. 2004; Urschitz et al. 2004). These breathing difficulties can range from continuous respiratory distress while awake and asleep necessitating immediate intervention to subtle UAO that becomes apparent only when sleeping, feeding or while in the supine position (Mackay 2011; Evans et al. 2011; Breugem et al. 2016).

In most infants with RS, UAO can be managed conservatively. Non-operative interventions include prone/lateral positioning, insertion of a nasopharyngeal airway (NPA), supplemental oxygen therapy, high flow nasal oxygen therapy, continuous or bilevel positive airway pressure (CPAP or BIPAP), and insertion of an oral appliance (pre-epiglottic baton plate, PEBP). When non-operative treatments do not achieve respiratory stability, surgical interventions such as tongue-lip adhesion (TLA), subperiosteal release of the floor of the mouth, mandibular distraction osteogenesis (MDO), or tracheostomy could be considered (van Lieshout et al. 2016; Almajed et al. 2017). These interventions have been investigated comprehensively; however, evaluations and metrics utilized to determine threshold for treatment and to assess treatment outcomes are not standardized (van Lieshout et al. 2016; Almajed et al. 2017).

Substantial variation among institutions exists for both the evaluations employed and treatments provided. Internationally accepted protocols for the investigation and management of UAO in RS are lacking (van Lieshout et al. 2015; Resnick et al. 2018). A standardized, evidence-based approach to the assessment and treatment of UAO in infants with RS is needed. Such a protocol has the potential to guide clinicians in the timing of evaluations and indications for escalating respiratory support, and to facilitate

treatment comparisons across centers to improve treatment outcomes. Creation of a universal and evidence-based approach starts by standardizing the measurements used by clinicians to measure UAO, inform treatment decisions and evaluate outcomes.

The purpose of this review was to investigate the use of objective measurements of UAO in the management of infants with RS. The measurements reviewed were selected by an international multidisciplinary RS consensus workgroup that included pediatricians, sleep specialists and surgeons. The review focused on how objective measurements of oximetry, polysomnography (PSG), and blood gas determinations are used and interpreted as indications for treatment and evaluation of outcomes for infants with RS.

METHODS

This systematic review was performed according to PRISMA guidelines. A literature search was performed using Pubmed and Embase databases (Figure 1 online supplement (OS)), date 4-2-2020). We limited the search to publications published from 1990 onwards, anticipating limited reports prior to this date. In- and exclusion criteria are listed in Figure 1 OS.

Two authors (RL, NC) independently assessed all studies' full text after title abstract screening, and consensus was reached for all included studies.

The following data were extracted: publication year, country, study design, type of intervention, number of patients, mean age at intervention/admission, type of measurement, values and indices extracted from these measurements for UAO evaluation, values and indices used as indication/threshold for UAO intervention, number of patients with pre-intervention PSG, PSG type, monitoring time of continuous oximetry and/or PSG, position during oximetry and/or PSG, and presence and timing of post-intervention and/or multiple follow-up PSGs.

Study quality was appraised with the Methodological Index for Non-Randomized Studies (Slim et al. 2003). MINORS includes a 12-item checklist. Each item is scored 0 (not reported), 1 (reported, but inadequate) or 2 (reported and/or adequate). The maximum score is 16 for non-comparative studies and 24 for comparative studies.

For this review, UAO was defined as being independent of state (asleep or awake), while obstructive sleep apnea (OSA) was restricted to data measuring airway obstruction occurring during sleep.

RESULTS

After removal of duplicates, 1123 articles were identified for title/abstract screening (figure 1 OS). Subsequently, 319 articles were selected for full text review. Of these, 62 articles were excluded due to lack of objective measurements reporting or due to lack of actual measurement data.

Ninety-one studies were included in the final sample:1 randomized controlled trial, 7 prospective and 83 retrospective studies. The mean MINORS score was 7.1 (range: 3-14) (characteristics are presented in Table 1 OS).

Fifty-two studies (57%) reported on surgical interventions for UAO only, 22 studies (24%) on non-operative interventions for UAO only, and 17 studies (19%) reported on a combination of surgical and non-operative interventions as part of a treatment algorithm.

The most common objective assessment used was PSG (76%,69/91), followed by oximetry (20%,18/91), and blood gas analysis (11%,10/91). Among studies reporting the use of PSG, 36% (25/69) reported the PSG-technique. A minority of studies (35%,32/91) reported infant's position during assessment, with the supine position most frequently reported (47%), followed by prone position (22%;Table 1 OS, Figure 1). All reported recordings were performed in a hospital. The duration of recording was reported in 38 studies (42%) of which the majority reported an overnight period (58%,22/38) (Table 1 OS).

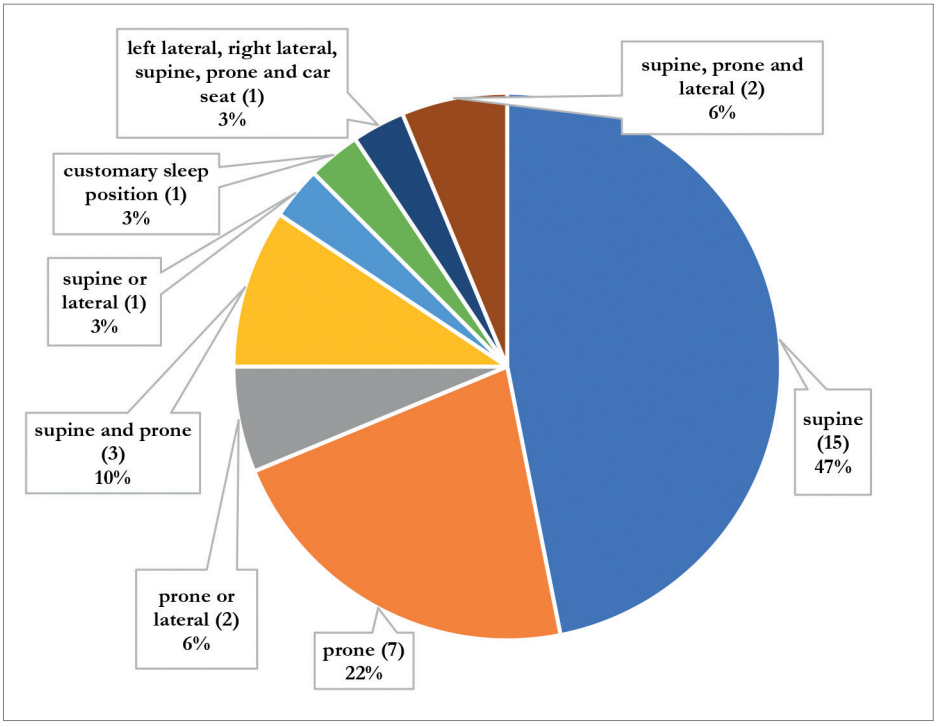

FIGURE 1. Different positions of the infant reported in studies (n = 32)

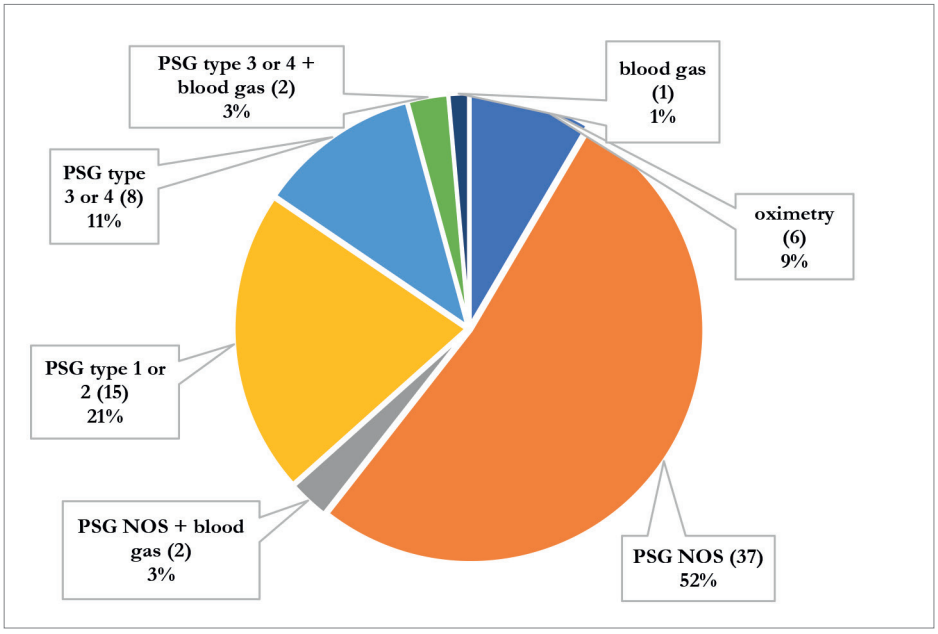

FIGURE 2. Objective measurements used in all evaluation studies (n = 71)
PSG: polysomnography, **PSG NOS:** polysomnography not other specified
Types of PSG are categorized according to the American Academy of Sleep Medicine (AASM)

1. Treatment evaluation studies

Evaluations of UAO treatments were reported in 71 studies, which included 2391 infants: oximetry only (6), PSG (60), PSG and blood gas analysis (4), and 1 blood gas analysis only (1) (Table 1 OS and Figure 2). Seventy-nine percent (56/71) of the evaluation studies reported both pre- and post-intervention data, with threshold for treatment indicated in 31% (22/71) (Table 1 OS).

1.1 Evaluation by oximetry only

Objective measurements by oximetry were reported in 6 studies that included 358 infants with RS: 5 pre- and post-intervention and 1 only pre-intervention. Oximetry type, specifics and recording duration varied. In 1 study, oximetry was part of an apnea monitor, while in 3 studies oximetry was specified as continuous pulse oximetry monitoring. Values extracted from oximetry included mean/median oxygen saturation levels (4), percent of time spent at each O_2 saturation level (1) and O_2 saturation >90% as binary variable (1). Two of the six studies reported on the position of the infant during oximetry: one reported the lateral or prone position and the other supine position.

TABLE 1: Characteristics of studies with treatment evaluation of OSA interventions by polysomnography

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Surgical interventions					
Konofaos et al. 2019	MDO	PSG (NOS)	supine	-	(1) severe upper airway obstruction that was not adequately managed with conservative therapy, (2) O2 saturation <80% while lying supine; (3) AHI ≥ 20 and (4) poor weight gain.
Zhang et al. 2019	MDO	Oximetry	-	-	Clusters of desaturation with at least 3 dips <80%
Ching et al. 2015	MDO	PSG type 1/2 (MPAS)	left lateral, right lateral, supine, and prone position and in a car seat (if available)	-	AHI > 5
Tahiri et al. 2015	MDO	PSG (NOS)	-	-	AHI >20 or significant CO2 retention (NS) & no central sleep apnea present
Greathouse et al. 2015	MDO/TLA	PSG (NOS)	-	-	AHI> 20 or CO2 retention with abnormal PSG (NS) or worsening of clinical status after exclusion of other sources of airway obstruction
Flores et al. 2015	MDO	PSG (NOS)	-	-	AHI >20 or significant CO2 retention (NS) & no central sleep apnea.
Tholpady et al. 2015	MDO	PSG (NOS)	-	-	AHI >20 or significant CO2 retention (NS) & failure of nonoperative interventions
Flores et al. 2014	MDO/TLA	PSG (NOS)	-	-	MDO: AHI ≥ 20 or significant CO2 retention (NS); absence of other significant airway anomalies as demonstrated by laryngoscopy/bronchoscopy; and absence of temporomandibular joint abnormality
Murage et al. 2014	MDO	PSG (NOS)	-	-	AHI >20 or significant CO2 retention (NS) & no central sleep apnea

TABLE 1. Continued.

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Surgical interventions					
Dong et al. 2014	mandibular traction	oximetry	lateral or prone	24 h	mean O2 saturation < 90% (24h) in the lateral/prone position, or if O2 saturation decreased continuously due to dyspnoea during the monitoring period and manual intervention/rescue was required
Breugem et al. 2012	MDO	oximetry	-	12 h	O2 saturation < 90% for>5% of 12h
Sesenna et al. 2012	MDO	oximetry, respiratory rates	-	-	repeated apneic episodes with severe desaturation (70%) and respiratory rate higer than 60/min
Baciliero et al. 2011	mandibular traction	oximetry	-	24 h	Desaturation (during the following activities of early life: sleeping, feeding, or wakefullness): O2 saturation <90% for ≥ 5% observation time (neonates at least 24h, children during sleep) or single recorded value of O2 saturationof <80%.
Kolstad et al. 2011	MDO	CO2 measurement (NOS)	-	-	Severe obstruction: persistent pCO2 >50 mm Hg or a life-threatening event related to upper airway compromise
Miloro et al. 2010	MDO	oximetry	-	-	frequent apneic episodes with O2 saturation < 70% on room air with repeat apnea monitor triggering
Shen et al. 2009	MDO	oximetry	prone	-	O2 saturation of about 40% in prone position
Breugem et al. 2008	SPRFM	oximetry	-	24 h	O2 saturation < 93% for > 95% per 24h, elevated CO2 retention levels (NS)
Denny 2004	MDO	oximetry from PSG (NOS)	-	-	repeated O2 desaturations < 80% & no spontaneous correction, abnormal PSG (NS)
Morovic et al. 2000	MDO	PSG (NOS)	-	12 h	AHI > 20 & O2 saturation < 80% during or within 12h after examination.

TABLE 1. Continued.

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Surgical interventions					
Gilhooly et al. 1993	TLA	oximetry from PSG (NOS)	prone position except when feeding and other nursing care	-	significant episode of airway obstruction: an event lasting 15 seconds or more during sleep or quiet activitity or shorter episodes of obstruction associated with a decrease in heartrate to < 80 beats per minute and/or a drop in O2 saturation to < 85%
Conservative interventions					
Wiechers et al. 2019	PEBP	PSG type 3 (CRSS)	supine	evening, minimum 8h	MOAI > 3
Müller-Hagendorn et al. 2017	PEBP	PSG type 3 (sleep study)	supine	evening, minimum 8h	MOAI > 3
Poets et al. 2017	PEBP	PSG type 3 (CRSS)	supine	evening, minimum 8h	MOAI > 3
Amaddeo et al. 2016	CPAP	PSG type 3/4 (PG)	prone	daytime nap PG (NS)	AHI >10 and/or minimal O2 saturation <90% and/or tcpCO2 >50 mmHg and/or ODI >15 events/h
Albino et al. 2016	Supplemental O2 (= nasal canula/ NPA/intubation)	oximetry from PSG (NOS)	prone	-	persistent episodes of respiratory distress: 10% O2 desaturation ≥10 seconds at rest, while sleeping, or during feeding.
Bacher et al. 2011	PEBP	PSG type 3 (PG)	supine	evening, minimum 8h	MOAI > 3, contraindication: OSA-related severe hypoxemia, defined as 3 or more desaturation events to < 60% O2 saturation
Leboulanger et al. 2010 ***	NRS: continuous positive airway pressure or noninvasive positive pressure ventilation/ (TRACH)	PSG type 4 (PS)	-	-	tcpCO2 of > 50 mmHg for >10 consecutive minutes and/ or > 10% of sleep time despite positioning measures and exclusive nasogastric tube feeding. For some patients NRS was initiated in the PICU because they not able to breath spontaneously without a pharyngeal tube for >30 minutes without profound decreases in pulse O2 saturation (<80%) and hypercapnia (PtcCO2 of > 60 mm Hg).

TABLE 1. Continued.

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Surgical interventions					
de Buys Roessingh et al. 2007	(PP)*/NPA	oximetry, blood gas	supine (slowly lowering the child while sleeping into supine position, repeated while bottle feeding)	-	persistent desaturation < 90% with clinical evidence of respiratory distress or CO2 retention as evidenced by a base excess of > 6.5
Anderson et al. 2007	NPA	oximetry	supine (gently lowered into a supine position while sleeping, if no obstruction occurs this was repeated while bottle feeding).	24-36 h	O2 saturation < 90% for > 5% (period: 24 to 36h) or intermittent deeper episodes of desaturation < 80%.
Buchenau et al., 2007	PEBP	PSG type 3 (CRSS)	supine	evening, minimum 8h	MOAI > 3, contraindication: additional major malformations (eg, congenital heart disease), a concomitant upper or lower respiratory tract infection, or severe UAO-related hypoxemia (ie, > 3 desaturations to < 60% O2 saturation)
Wagener et al. 2002	NPA	oximetry	supine (gently lowered into a supine position while sleeping, if no obstruction occurs this was repeated while bottle feeding).	24-36 h	O2 saturations <90% for > 5% of the time (period of 24 to 36h) or deep desaturations < 80%
Combination of surgical and conservative interventions					
Runyan et al. 2018	(PP)/MDO/ (TRACH)*	PSG (NOS)	-	-	Surgical intervention should be considered at an OI >20 (combined with other examination findings)
Li et al. 2017	(PP)*/ TLA/ MDO/FMR/ TRACH	oximetry	prone	-	Surgical intervention for patients with ongoing desaturations with PP (part of treatment algorithm). Patients were defined as having desaturations if any single recorded hospital O2 saturation was < 80% or if more than 1 hospital oxygen saturation was < 90%

TABLE 1. Continued.

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Surgical interventions					
Paes et al. 2015	PP/NPA/TLA/ MDO/TRACH	oximetry, TcpCO2 (Tosca®), blood gas	prone or lateral	-	Moderate/severe UAO (as part of treatment algorithm): 1. O2 saturations of <90 % for >5 % of the monitored time and/or any single desaturation <80% 2. Blood gas analysis revealing respiratory acidosis (pCO2 > 50 mmHg, HCO3 > 30 mmHg) or tcpCO2 > 50 mmHg during >25 % of the TST.
Salmen et al. 2015	(PP)*/NPA/ TRACH	oximetry	-	-	Severe RS: recurrent crises of pallor and/or cyanosis and/ or apnea, intercostal and supraclavicular retractions, O2 saturation < 90% with an O2 requirement to improve this condition & severe feeding difficulties for which feeding tubes were necessary.
Abel et al. 2013	(PP)/NPA/ (TRACH)*	oximetry from PSG (NOS)	-	overnight	NPA: If the PSG indicated moderate or severe obstruction (If the child was clinically severely obstructed on admission, an NPA was inserted without a pre-intervention sleep study). Moderate UAO: a set of at least three clusters of desaturations with at least 3 dips < 85% (but not < 80%). Severe UAO for a set of at least three clusters of desaturations with at least 3 dips < 80%.
Glynn et al. 2011	(PP)/NPA/ (TRACH)*	oximetry	supine (gently lowered into a supine position while sleeping, if no obstruction occurs this was repeated while bottle feeding).	24-36 h	O2 saturations < 90% for >5% of the time (24–36h)
Pradel et al. 2009	(PP or SP/palatal plate)*/mandibular traction	oximetry, blood gas	-	-	pCO2 > 60 mmHg, pH < 7.2 and O2 saturations < 85%

TABLE 1. Continued.

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Surgical interventions					
Schaefer et al. 2004	(PP)*/MDO/TLA/ TRACH	oximetry from PSG (NOS)	-	12 h	Patients are defined as having desaturations (part of treatment algorithm): if any single O2 saturation value is < 80 % or if O2 saturation values < 90 % for 5% or more of the monitored time (minimum of 12h for neonates or during sleep for older children). Patients without evidence of desaturation undergo further monitoring with a sleep study (continuous monitoring of O2 saturation, etpCO2 levels, and electroencephalographic output)
Marques et al. 2001	(NPA)*/TLA/ TRACH	oximetry	supine	-	Unable to maintain O2 saturation >90% with NPA in situ and unimproved oral accceptance of food
Caouette-Laberge et al. 1994	(PP/NPA)*/ SPRFM	blood gas	-	-	pO2 <60mmHg or a pCO2 > 50 mmHg
Augarten et al. 1990	(PP)*/TLA	blood gas, respiratory rates	prone	-	Fail of following criteria: Respiratory rate <60 + pCO2 <60 mmHg + pO2 >65 mmHg (BLOODGAS)+ oxygen requirement <60%

Consv.: conservatively, **SP:** side positioning, **PP:** prone positioning, **PEBP:** pre-epiglottic baton plate/Tubingen plate, **BIPAP:** bilevel positive airway pressure, **CPAP:** continuous positive airway pressure, **PAP:** noninvasive positive airway pressure, **NIV:** noninvasive ventilatory support (both CPAP or BIPAP), **NRS:** noninvasive respiratory support (both CPAP and PAP), **NPA:** nasopharyngeal airway/tube, **MDO:** mandibular distraction osteogenesis, **FEMOD:** fast early mandibular osteogenesis distraction, **TLA:** tongue-lip adhesion, **SPRFM:** subperiosteal release of the floor of the mouth, **SGP:** supraglottoplasty, **TRACH:** tracheostomy, **m:** months **h:** hours, **NS:** not specified, **post.:** post intervention not specified, **MPAS:** multi positional airway study, **CRS:** cardiorespiratory study, **CRSS:** cardiorespiratory sleep study, **PG:** polygraphic study, **PS:** physiologic study, **PSG:** polysomnography, **AASM:** American Academy of Sleep Medicine, **AHI:** apnea/hypopnea index, **OAHI:** obstructive apnea/hypopnea index, **MOAI:** mixed obstructive apnea index, **OAI:** obstructive apneas index, **CAI:** central apnea index, **MAI:** mixed apnea index, **AI:** apnea index, **HI:** hypopneas index, **RDI:** respiratory disturbance index , **SW:** slow wave, **REM:** rapid eye movement sleep, **ODI:** oxygen desaturation index, TST: total sleep time, **DI85:** desaturation index, defined as events <85% O2 desaturation, per hour TST, **DI80:** desaturation index, defined as events <80% O2 desaturation, per hour TST, **O2:** oxygen, **CO2:** carbon dioxide, **tcpCO2:** transcutaneous pCO2, **etpCO2:** end tidal pCO2

1.2 Evaluation by polysomnography

Objective measurements assessed by some form of PSG were reported in 64 studies: 51 reported both pre- and post-intervention, 11 only pre- or during intervention and 2 only post-intervention (Table 1). The PSG-technique was not specified in 61% (39/64), referred to as "PSG not other specified" (NOS). The remaining studies provided detailed information on PSG-technique that allowed categorization according to the American Academy of Sleep Medicine (AASM): PSG type 1 or 2 in 23% (15/64) and PSG type 3 or 4 in 16% (10/64).

A total of 2008 infants with RS were included in these studies and, of these, 1699 (85%) underwent a pre-intervention PSG. This discrepancy is not fully explained by the intubated infant being unable to undergo a pre-intervention polysomnography; in some studies, this difference was explained by the lack of available PSG data, while others did not further specify the reason for lack of pre-intervention data. In half of the studies including post-intervention PSG (53%,28/53) the time of measurement was not specified.

Oxygen saturation

Oxygen saturations assessed by oximetry as part of PSG were reported in 39 studies (61%,39/64). The most common metric reported was lowest/minimum/nadir oxygen saturation (62%,24/39), followed by mean oxygen saturation (41%,16/39), percent time with oxygen saturation <90% (31%,12/39), and percent time with oxygen saturation >96% (8%,3/39 studies). Other oximetry values from PSG (percent of time with oxygen saturation <80%, <85% or <89%, oxygen saturation <80% and baseline oxygen saturations) were each used in a single study (Table 1).

Respiratory event indices

The most frequently reported respiratory event index was the apnea-hypopnea index (AHI;52%, 33/64), followed by obstructive apnea-hypopnea index (OAHI;27%, 17/64); oxygen desaturation index (16%,10/64), specified as desaturation index to 80% in 5 studies and desaturation index to 85% in 1 study; central apnea index (13%,8/64); mixed-obstructive apnea index (MOAI, 9%, 6/64); respiratory disturbance index (8%,5/64); obstructive apnea index (6%,4/64); hypopnea index and sleep efficiency (each5%,3/64); and apnea index (3%,2/64).

Measures of sleep disturbance were included in a small proportion of studies, including arousal index in 11% (7/64) and percent of total sleep time characterized as rapid eye movement sleep in 8% (5/64).

2. Studies with indications for intervention

Objective indications/thresholds for intervention were reported in 42 studies (Table 2, Figure 2). Of these, 22 studies (52%) also used objective measurements for treatment evaluation (Table 1 OS), while the remaining 20 studies only reported on indications/thresholds for intervention. Objective measurements for treatment indications/thresholds varied substantially (Table 2, Figure 2). The most common objective measurements reported were oximetry (40%,17/42) and any form of PSG (40%,17/42, specified according to AASM criteria as PSG NOS in 9 studies, PSG type 3 or 4 in 7 studies and PSG type 1 or 2 in 1 study), followed by blood gas analysis and oximetry from PSG NOS (12%,5/42 each). Of the studies that used oximetry or oximetry from PSG, the most common threshold reported was oxygen saturation <90% for >5% of the monitoring period (32%,7/22). Of the studies that used any form of PSG, the most common threshold reported was an AHI>20 (41%,7/17) to indicate surgical treatment, followed by MOAI>3 (29%,5/17) to indicate treatment with a PEBP. A single objective metric was used to define a treatment threshold for 55% (23/42) of studies, including oxygen saturation in 11, respiratory events (AHI, MOAI) in 10, and blood gas and tcpCO_2 in 1 study each. An additional 19% (8/42) of studies used multiple objective metrics to define treatment thresholds, with the remaining studies using a combination of objective and subjective criteria (26%,11/42). Twenty studies reported position and 6 listed feeding as part of their threshold definition. In total, 34 different definitions for treatment threshold were identified (Table 2).

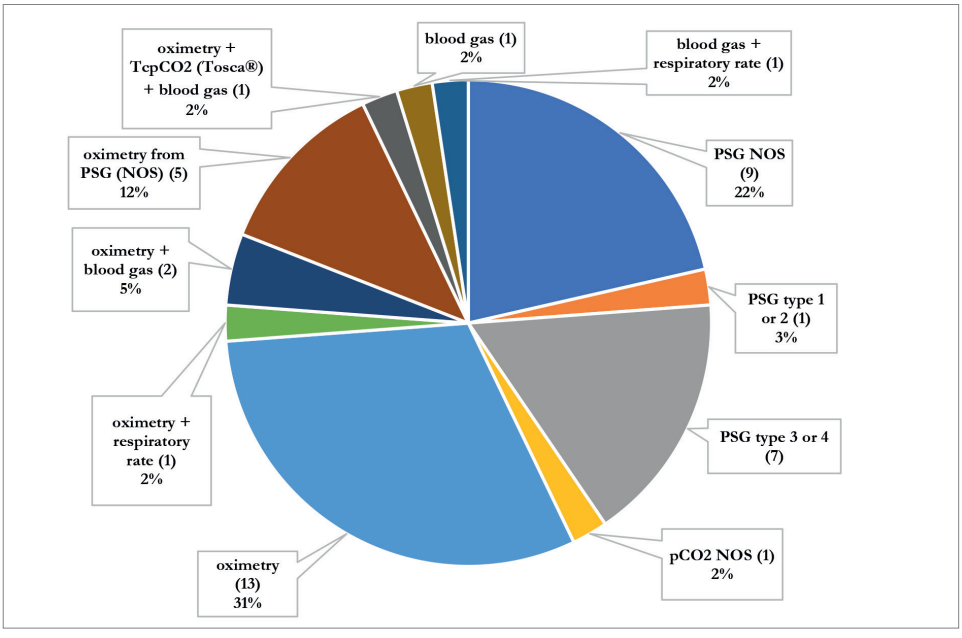

FIGURE 3. Objective measurements used in all indications/threshold studies (n = 42)
PSG: polysomnography, **PSG NOS:** polysomnography not other specified
Types of PSG are categorized according to the American Academy of Sleep Medicine (AASM)

TABLE 2: Characteristics of studies reporting on treatment indicators/thresholds for OSA interventions

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Surgical interventions					
Konofaos et al. 2019	MDO	PSG (NOS)	supine	-	(1) severe upper airway obstruction that was not adequately managed with conservative therapy, (2) O2 saturation <80% while lying supine; (3) AHI ≥ 20 and (4) poor weight gain.
Zhang et al. 2019	MDO	Oximetry	-	-	Clusters of desaturation with at least 3 dips <80%
Ching et al. 2015	MDO	PSG type 1/2 (MPAS)	left lateral, right lateral, supine, and prone position and in a car seat (if available)	-	AHI > 5
Tahiri et al. 2015	MDO	PSG (NOS)	-	-	AHI >20 or significant CO2 retention (NS) & no central sleep apnea present
Greathouse et al. 2015	MDO/TLA	PSG (NOS)	-	-	AHI> 20 or CO2 retention with abnormal PSG (NS) or worsening of clinical status after exclusion of other sources of airway obstruction
Flores et al. 2015	MDO	PSG (NOS)	-	-	AHI >20 or significant CO2 retention (NS) & no central sleep apnea.
Tholpady et al. 2015	MDO	PSG (NOS)	-	-	AHI >20 or significant CO2 retention (NS) & failure of nonoperative interventions
Flores et al. 2014	MDO/TLA	PSG (NOS)	-	-	MDO: AHI ≥ 20 or significant CO2 retention (NS); absence of other significant airway anomalies as demonstrated by laryngoscopy/bronchoscopy; and absence of temporomandibular joint abnormality
Murage et al. 2014	MDO	PSG (NOS)	-	-	AHI >20 or significant CO2 retention (NS) & no central sleep apnea
Dong et al. 2014	mandibular traction	oximetry	lateral or prone	24 h	mean O2 saturation < 90% (24h) in the lateral/prone position, or if O2 saturation decreased continuously due to dyspnoea during the monitoring period and manual intervention/rescue was required

TABLE 2: Continued.

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Breugem et al. 2012	MDO	oximetry	-	12 h	O2 saturation < 90% for>5% of 12h
Sesenna et al. 2012	MDO	oximetry, respiratory rates	-	-	repeated apneic episodes with severe desaturation (70%) and respiratory rate higer than 60/min
Baciliero et al. 2011	mandibular traction	oximetry	-	24 h	Desaturation (during the following activities of early life: sleeping, feeding, or wakefullness): O2 saturation <90% for ≥ 5% observation time (neonates at least 24h, children during sleep) or single recorded value of O2 saturationof <80%.
Kolstad et al. 2011	MDO	CO2 measurement (NOS)	-	-	Severe obstruction: persistent pCO2 >50 mm Hg or a life-threatening event related to upper airway compromise
Miloro et al. 2010	MDO	oximetry	-	-	frequent apneic episodes with O2 saturation < 70% on room air with repeat apnea monitor triggering
Shen et al. 2009	MDO	oximetry	prone	-	O2 saturation of about 40% in prone position
Breugem et al. 2008	SPRFM	oximetry	-	24 h	O2 saturation < 93% for > 95% per 24h, elevated CO2 retention levels (NS)
Denny 2004	MDO	oximetry from PSG (NOS)	-	-	repeated O2 desaturations < 80% & no spontaneous correction, abnormal PSG (NS)
Morovic et al. 2000	MDO	PSG (NOS)	-	12 h	AHI > 20 & O2 saturation < 80% during or within 12h after examination.
Gilhooly et al. 1993	TLA	oximetry from PSG (NOS)	prone position except when feeding and other nursing care	-	significant episode of airway obstruction: an event lasting 15 seconds or more during sleep or quiet activitity or shorter episodes of obstruction associated with a decrease in heartrate to < 80 beats per minute and/or a drop in O2 saturation to < 85%
Conservative interventions					
Wiechers et al. 2019	PEBP	PSG type 3 (CRSS)	supine	evening, minimum 8h	MOAI > 3

TABLE 2: Continued.

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Müller-Hagendorn et al. 2017	PEBP	PSG type 3 (sleep study)	supine	evening, minimum 8h	MOAI > 3
Poets et al. 2017	PEBP	PSG type 3 (CRSS)	supine	evening, minimum 8h	MOAI > 3
Amaddeo et al. 2016	CPAP	PSG type 3/4 (PG)	prone	daytime nap PG (NS)	AHI >10 and/or minimal O2 saturation <90% and/or tcpCO2 >50 mmHg and/or ODI >15 events/h
Albino et al. 2016	Supplemental O2 (= nasal canula/NPA/ intubation)	oximetry from PSG (NOS)	prone	-	persistent episodes of respiratory distress: 10% O2 desaturation ≥10 seconds at rest, while sleeping, or during feeding.
Bacher et al. 2011	PEBP	PSG type 3 (PG)	supine	evening, minimum 8h	MOAI > 3, contraindication: OSA-related severe hypoxemia, defined as 3 or more desaturation events to < 60% O2 saturation
Leboulanger et al. 2010 ***	NRS: continuous positive airway pressure or noninvasive positive pressure ventilation/ (TRACH)	PSG type 4 (PS)	-	-	tcpCO2 of > 50 mmHg for >10 consecutive minutes and/or > 10% of sleep time despite positioning measures and exclusive nasogastric tube feeding. For some patients NRS was initiated in the PICU because they not able to breath spontaneously without a pharyngeal tube for >30 minutes without profound decreases in pulse O2 saturation (<80%) and hypercapnia (PtcCO2 of > 60 mm Hg).
de Buys Roessingh et al. 2007	(PP)*/NPA	oximetry, blood gas	supine (slowly lowering the child while sleeping into supine position, repeated while bottle feeding)	-	persistent desaturation < 90% with clinical evidence of respiratory distress or CO2 retention as evidenced by a base excess of > 6.5
Anderson et al. 2007	NPA	oximetry	supine (gently lowered into a supine position while sleeping, if no obstruction occurs this was repeated while bottle feeding).	24-36 h	O2 saturation < 90% for > 5% (period: 24 to 36h) or intermittent deeper episodes of desaturation < 80%.
Buchenau et al., 2007	PEBP	PSG type 3 (CRSS)	supine	evening, minimum 8h	MOAI > 3, contraindication: additional major malformations (eg, congenital heart disease), a concomitant upper or lower respiratory tract infection, or severe UAO-related hypoxemia (ie, > 3 desaturations to < 60% O2 saturation)

TABLE 2: Continued.

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Wagener et al. 2002	NPA	oximetry	supine (gently lowered into a supine position while sleeping, if no obstruction occurs this was repeated while bottle feeding).	24-36 h	O2 saturations <90% for > 5% of the time (period of 24 to 36h) or deep desaturations < 80%
Combination of surgical and conservative interventions					
Runyan et al. 2018	(PP)/MDO/ (TRACH)*	PSG (NOS)	-	-	Surgical intervention should be considered at an OI >20 (combined with other examination findings)
Li et al. 2017	(PP)*/ TLA/MDO/ FMR/TRACH	oximetry	prone	-	Surgical intervention for patients with ongoing desaturations with PP (part of treatment algorithm). Patients were defined as having desaturations if any single recorded hospital O2 saturation was < 80% or if more than 1 hospital oxygen saturation was < 90%
Paes et al. 2015	PP/NPA/TLA/ MDO/TRACH	oximetry, TcpCO2 (Tosca®), blood gas	prone or lateral	-	Moderate/severe UAO (as part of treatment algorithm): 1. O2 saturations of <90 % for >5 % of the monitored time and/or any single desaturation <80% 2. Blood gas analysis revealing respiratory acidosis (pCO2 > 50 mmHg, HCO3 > 30 mmHg) or tcpCO2 > 50 mmHg during >25 % of the TST.
Salmen et al. 2015	(PP)*/NPA/TRACH	oximetry	-	-	Severe RS: recurrent crises of pallor and/or cyanosis and/or apnea, intercostal and supraclavicular retractions, O2 saturation < 90% with an O2 requirement to improve this condition & severe feeding difficulties for which feeding tubes were necessary.
Abel et al. 2013	(PP)/NPA/ (TRACH)*	oximetry from PSG (NOS)	-	overnight	NPA: If the PSG indicated moderate or severe obstruction (If the child was clinically severely obstructed on admission, an NPA was inserted without a pre-intervention sleep study). Moderate UAO: a set of at least three clusters of desaturations with at least 3 dips < 85% (but not < 80%). Severe UAO for a set of at least three clusters of desaturations with at least 3 dips < 80%.

TABLE 2: Continued.

Study	intervention	objective measurements	position of the infant	monitoring time	indication/threshold
Glynn et al. 2011	(PP)/NPA/ (TRACH)*	oximetry	supine (gently lowered into a supine position while sleeping, if no obstruction occurs this was repeated while bottle feeding).	24-36 h	O2 saturations < 90% for >5% of the time (24–36h)
Pradel et al. 2009	(PP or SP/palatal plate)*/mandibular traction	oximetry, blood gas	-	-	pCO2 > 60 mmHg, pH < 7.2 and O2 saturations < 85%
Schaefer et al. 2004	(PP)*/MDO/TLA/ TRACH	oximetry from PSG (NOS)	-	12 h	Patients are defined as having desaturations (part of treatment algorithm): if any single O2 saturation value is < 80 % or if O2 saturation values < 90 % for 5% or more of the monitored time (minimum of 12h for neonates or during sleep for older children). Patients without evidence of desaturation undergo further monitoring with a sleep study (continuous monitoring of O2 saturation, etpCO2 levels, and electroencephalographic output)
Marques et al. 2001	(NPA)*/TLA/ TRACH	oximetry	supine	-	Unable to maintain O2 saturation >90% with NPA in situ and unimproved oral accceptance of food
Caouette-Laberge et al. 1994	(PP/NPA)*/SPRFM	blood gas	-	-	pO2 <60mmHg or a pCO2 > 50 mmHg
Augarten et al. 1990	(PP)*/TLA	blood gas, respiratory rates	prone	-	Fail of following criteria: Respiratory rate <60 + pCO2 <60 mmHg + pO2 >65 mmHg (BLOODGAS)+ oxygen requirement <60%

PP: prone positioning, **SP:** side positioning, **PEBP:** pre-epiglottic baton plate/Tubingen plate, **CPAP:** continuous positive airway pressure, **PAP:** noninvasive positive airway pressure, **NRS:** noninvasive respiratory support (both CPAP and PAP), **NPA:** nasopharyngeal airway/tube, **MDO:** mandibular distraction osteogenesis, **TLA:** tongue-lip adhesion, **SPRFM:** subperiosteal release of the floor of the mouth, **TRACH:** tracheostomy, **h:** hours, **NS:** not specified, **MPAS:** multi positional airway study, **CRSS:** cardiorespiratory sleep study, **PG:** polygraphic study, **PS:** physiologic study, **PSG:** polysomnography, **AASM:** American Academy of Sleep Medicine, **AHI:** apnea/hypopnea index, **MOAI:** mixed obstructive apnea index, **ODI:** oxygen desaturation index, **O2:** oxygen, **CO2:** carbon dioxide, **tcpCO2:** transcutaneous pCO2, **etpCO2:** end tidal pCO2.

* if multiple interventions were reported in a study, but indication/threshold was only reported for one certain intervention, the other interventions are demonstrated between brackets.

*** different monitoring time (not specified) for treatment threshold compared to monitoring time for treatment evaluation

DISCUSSION

This report provides the first systematic review of the objective assessment of UAO in infants with RS. The results highlight considerable variability in the objective measures used to assess UAO, and in the interpretation of these measures. PSG was the most commonly used measurement, but PSG type and interpretation of results varied. Although oximetry was less commonly used as an evaluation measure, parameters from oximetry were frequently used to define treatment thresholds for UAO interventions. The overall quality of the evidence to support treatment decision making for infants with RS and UAO remains low. This is emphasized by the need to exclude 19% (62/319) of selected full text articles due to the lack of any objective measurement or actual data (Figure 1 OS).

Objective assessments of UAO, both before and after interventions, are essential to the evaluation of infants with RS and to assessing the impact of interventions, especially given the high rate of additional anomalies in RS and an associated mortality of 10–17% (Costa et al. 2014; Logjes, Haasnoot, et al. 2018). Of the included treatment evaluation studies, 21% (15/71) did not report both pre- and post-intervention data.

While availability of tests understandably varies due to resource availability, the stark lack of objective assessments and standard reporting of measures is disappointing. Measurement of airway compromise is necessary because the absence of clinical respiratory distress or snoring does not indicate the absence of airway obstruction. The latter cannot be well characterized by clinical assessment alone, and the spectrum of airway obstruction in infants with RS is broad (Anderson et al. 2011; MacLean et al. 2012; Cielo et al. 2016; Manica et al. 2018). The nature and severity of UAO may also change with growth or intervention (Wilson et al. 2000; Lee et al. 2015). Therefore, objective assessment of UAO is essential to the evaluation of infants with RS and in assessing the impact of interventions. Quantifying UAO also allows for an objective comparison of treatment modalities and builds an evidence-base to assist clinicians treating UAO in infants with RS (Almajed et al. 2017). The present study may serve as a starting point for future consensus recommendations for the objective measurement of UAO in infants with RS.

While the need for objective measurement of UAO in infants with RS is apparent, we recognize that objective assessments and treatment cutoffs will vary in the absence of prospective, controlled studies of airway treatment outcomes. We do not yet know which objective criteria should be prioritized; PSG, which identifies OSA and hypoventilation but does not expose other consequences of UAO, is most commonly reported in RS. Type I sleep studies or full PSG is the reference standard for diagnosing OSA in children (Marcus et al. 2012; Pamula et al. 2017; Gruber et al. 2014; Kaditis et al. 2016; 2017; Zancanella et al. 2014). This includes observed continuous overnight measurements of sleep and respiratory parameters with recommended signals of electroencephalography, electrooculography and electromyography to measure sleep, and arterial oxygen saturation, a measure of carbon dioxide (transcutaneous or end tidal), nasal pressure

and oronasal airflow, abdominal and thoracic wall movements to measure breathing, with the additional recording of body position and video monitoring (Berry et al. 2012). Type 2 studies are similar to type 1 studies but unattended. Type 3 and 4 studies are limited to cardiopulmonary parameters and do not include sleep parameters, with type 4 studies measuring only 1 or 2 parameters, typically oxygen saturation and heart rate.

While a type 1 PSG for the assessment of OSA is recommended in several guidelines (Marcus et al. 2012; Pamula et al. 2017; Gruber et al. 2014), infants are considered to be a complex population compared to children and, therefore, excluded from consideration in all but one OSA guideline (Kaditis et al. 2017). This, in addition to limited or no PSG access in many areas (Kaditis et al. 2016; Katz et al. 2014) and UAO in infants with RS occurring both asleep and awake, may account for the use of alternative objective measurements. While PSG was the most commonly reported objective measure, with specification of the signals provided for only one third of the studies included in this review, it is unclear how many were in fact overnight, observed type 1 PSG (as specified above) rather than limited channel studies consistent with those described as polygraphy, cardiorespiratory sleep study, cardiorespiratory study, multi positional airway study, and physiological study (Table 1 OS). The lack of information on the specific signals for individual studies or classification according to the AASM impaired our ability to compare or combine the outcomes of intervention studies. This review highlights the wide range in measurement techniques used and emphasizes the importance of clear documentation, if not standardization, of these variables in future studies assessing UAO and OSA in infants with RS. Based on the results of this review, a list of minimal reporting for future treatment studies using PSG in infants with RS is given in Figure 4.

List of minimal reporting for OSA treatment studies using PSG in infants with RS

1. Indication for pre-intervention PSG
2. Age in months at PSG
3. Body position (supine, side, prone, supine/side, supine/prone, supine/side/prone)
4. Time of day and duration of PSG recording
5. Equipment set-up, including specific channels (AASM, other - specify reference or describe protocol)
6. Scoring protocol OSA (AASM, other - specify reference or describe protocol)
7. Thresholds that guide intervention decision (if applicable specify measures and cut-off)
8. Age in months post-intervention PSG to investigate treatment succes

FIGURE 4: List of minimal reporting for OSA treatment studies using PSG in infants with RS
AASM: American Academy of Sleep Medicine, OSA: obstructive sleep apnea, PSG: polysomnography, RS: Robin sequence

There is also considerable variability in the parameters used to define OSA in infants with RS, even within studies using the same objective measurements. We identified 34 different definitions of treatment threshold. This may be attributable to the lack of accepted criteria for the diagnosis of OSA in infants. The limited normative PSG data available from healthy infants support that current pediatric criteria, where OSA is present if AHI is ≥2 events/h or OAHI ≥1 event/h (Kaditis et al. 2017), is not appropriate for neonates and infants. Respiratory event rates are higher in infants with AHI ranging from 1-38 events/h and obstructive apnea index ranging of 0.2-12.5 events/h at <30 days of age (Daftary et al. 2019), with AHI ranging from 1.9-46.4 events/h and mixed-obstructive AHI range of 0.2-7.0 events/h at 3 months (Brockmann, Poets, and Poets 2013); and OAHI range of 0.5-5.5 events/h at 3-4 months (Cielo et al. 2016). This pattern of decreasing number of respiratory events in healthy infants holds true at high altitude where the total number of respiratory events is higher than at lower altitudes (Duenas-Meza et al. 2015), suggesting that thresholds for defining OSA in infancy need to account for changes in respiratory events by age.

While defining OSA by respiratory events above the upper limit for healthy infants alone may be insufficient to identify those at risk for negative outcomes, using pediatric PSG criteria in infants leads to overestimation of OSA compared to a diagnosis based on expert sleep physicians (DeHaan et al. 2015). To avoid inaccurate diagnosis, there is a need to establish criteria to objectively identify OSA in infants with RS that account for age-related changes in respiratory events. Ideally, thresholds will be based on a combination of normative data and the relationship of respiratory event rates to important health outcomes such as growth, feeding, quality of life and neurocognitive function specific to this high-risk population. These longer-term outcomes will ultimately be the evidence to guide early treatment decisions.

The majority (57%) of studies included in this review evaluated only surgical interventions for UAO. This is surprising as surgical interventions are indicated in the minority of infants with severe OSA (Breugem et al. 2016; Evans et al. 2011; Kaditis et al. 2017; Caouette-Laberge, Bayet, and Larocque 1994; Paes et al. 2015). In alignment with the ethical obligation 'primum non nocere' the least invasive, effective interventions must be considered. It is possible that first-line treatment for infants with mild UAO may be side-lying or prone positioning, with minimal objective evaluation if this is successful in supporting breathing during sleep and feeding. Three studies used PSG to estimate the effect of prone positioning and demonstrated that it did not completely resolve OSA in the majority of infants. Therefore, routine PSG evaluation in individual infants undergoing prone positioning as a definitive treatment is recommended (Coutier et al. 2019; Kimple et al. 2014; Hong et al. 2020), although questions remain whether prone positioning can be recommended in all infants (Carpenter et al. 2004). The natural history of early infant OSA has not been well-studied. In a large cohort of 162 infants with RS, 21 infants who were treated conservatively (watchful waiting or

supplemental oxygen) experienced resolution of OSA confirmed by PSG at a median age of 15 months (Ehsan et al. 2019).

Outcome assessments are also limited for other conservative treatments, including the effect of nasopharyngeal airway, non-invasive ventilation and orthodontic appliances (e.g. PEBP) on objective measures of UAO, independently and in comparison to other intervention(s). Future studies focused on objective evaluation of these conservative interventions, to either confirm complete resolution of UAO or to indicate additional interventions, are needed. An important result would be valid comparisons of non-operative to operative interventions. In order to achieve this, at a very minimum, treatment studies must provide standardized reporting on metrics and transparency on the treatment protocols employed. These standards will facilitate improved practice, allowing clinicians to be armed with more accurate information to aid counseling on the risks and benefits on the full spectrum of treatments for UAO in RS. Pediatricians and neonatologists serve an essential role in recognizing UAO in infants with RS and will rely on these improved tools to guide clinical decision making.

There are limitations of this systematic review that must be acknowledged. The included studies were primarily retrospective with only 1 randomized trial and 7 prospective studies. This limits the included studies to those with low methodological quality (MINORS score) and serious risk of bias. The focus of this systematic review was not on treatment outcomes of the included intervention studies. However, missing data on variables such as position (65%), monitoring time (58%), PSG-technique (61%) and time of post-intervention PSG (53%) also contribute to a serious risk of bias. The search focused on 3 objective assessments of UAO used commonly in practice by pediatricians, neonatologists and craniofacial specialists, and did not include all potential measures of UAO. Lastly, the current review did not assess feeding difficulties, however UAO and feeding problems are closely related in infants with RS.

CONCLUSION

This systematic review demonstrates a lack of standardized use, implementation and interpretation of objective measurements in the assessment of UAO and resulting in OSA in infants with RS. A wide variation was observed in the use, interpretation and reporting of these values. Until measures and metrics are systematically assessed and reported, front-line physicians rely on limited evidence and practice variation persists. Future work is needed to establish accepted definitions of the presence and severity of UAO and OSA in infants with RS. Clear reporting of objective measurement techniques to assess airway obstruction, guide decision making and evaluate outcomes is necessary in this high-risk population. To build a valid and useful evidence base, assessments of UAO and treatment in infants with RS should be assessed alongside long term and patient-centered outcomes in this population.

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SUPPLEMENTAL MATERIAL

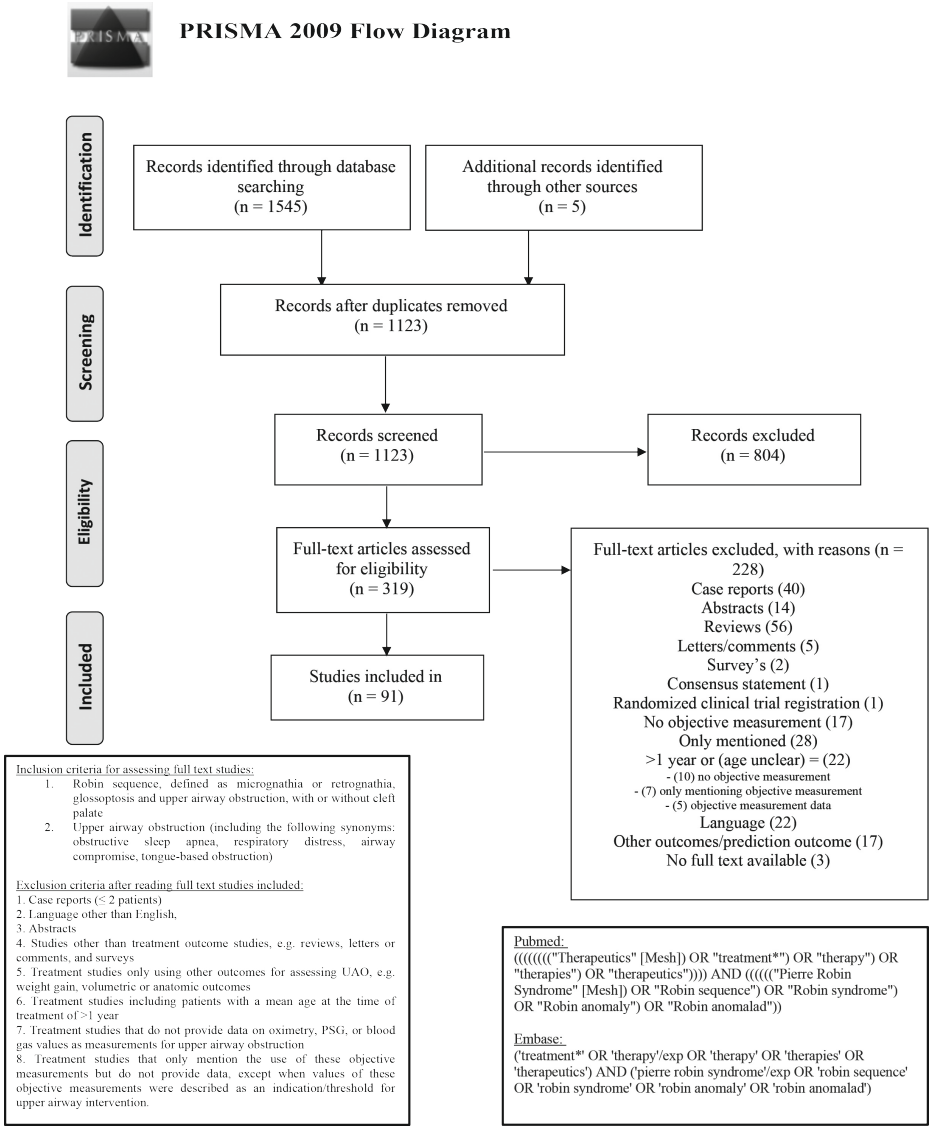

FIGURE 1: PRISMA flowchart, in- and exclusion criteria and search

TABLE 1. Characteristics of all 91 included studies

Name	Year	Type of study	Country	Number RS infants	Mean age (days) at intervention or admission	intervention	type of intervention	Objective measurement reported in study	type of PSG AASM	position	monitoring time	pre and/or post intervention	Indication/ threshold	MINOR score
Evaluation studies														
Hong et al.	2020	prospective	USA	12	55	PP	conservative	PSG	type 1	non-prone (supine, left, right) and prone	overnight	during	no	8
Ehsan et al.	2019	retrospective	USA	21	0.9 m	consv. (= watchful waiting or sup. O2)	conservative	PSG	type 1	supine	overnight	pre & post	no	7
Ho et al.	2019	retrospective	Hongkong	3	13	PEBP	conservative	PSG	PSG NOS	-	overnight	pre & post	no	6
Resnick et al.	2019	retrospective	USA	43	22/69	TLA/MDO	surgical	PSG	PSG NOS	supine	-	pre & post	no	14**
Wiechers	2019	retrospective	Germany	31	median 25 (5.5–48.5)	PEBP	conservative	CRSS	type 3	supine	evening, minimum 8h	pre & post	yes	8
Zhang et al.	2019	retrospective	USA	90	median 35 (4-273)	MDO	surgical	PSG	PSG NOS	-	-	pre & post	no	9
Coutier et al.	2019	retrospective	France	18	median 44 (27-70)	PP	conservative	PSG	type 1/2	supine and prone	overnight	during	no	6
Heffernan et al.	2019	retrospective	USA	13	137	MDO	surgical	PSG	type 1	-	-	pre & post	no	7
Gary et al.	2018	retrospective	USA	20	80	MDO	surgical	PSG	PSG NOS	-	-	pre & post	no	4
Fahradyan et al.	2018	retrospective	USA	71	39 (MDO)	MDO/(Consv.= PP + sup.O2)*	surgical	PSG, blood gas	PSG NOS	-	-	pre & post	no	6
Hammoudeh et al.	2018	retrospective	USA	79	63	MDO	surgical	PSG	PSG NOS	-	-	pre & post	no	8
Broucqsault et al.	2018	retrospective	France	37	45	TLA	surgical	PSG	PSG NOS	-	nap PSG (NS)	pre & post	no	7
Hicks et al.	2018	retrospective	USA	31	newborns (NS)	Consv. (= sup.O2/ PP/NPA)/MDO/ TLA/TRACH	combination	PSG	PSG NOS	-	overnight	pre & post	no	5
Runyan et al.	2018	retrospective	USA	171	68	PP/MDO/TRACH	combination	PSG	PSG NOS	-	-	pre & post	yes	12**

TABLE 1. Continued.

Name	Year	Type of study	Country	Number RS infants	Mean age (days) at intervention or admission	intervention	type of intervention	Objective measurement reported in study	type of PSG AASM	position	monitoring time	pre and/or post intervention	Indication/ threshold	MINOR score
Mermans et al.	2018	retrospective	The Netherlands	41	26.6	TLA	surgical	PSG	type 2	-	overnight	pre & post	no	6
Mullerhagendorn et al.	2017	retrospective	Germany	31	< 3 m	PEBP	conservative	sleep study	type 3	supine	evening, minimum 8h	pre & post	yes	7
Khansa et al.	2017	prospective	USA	28	43	PP or SP/MDO/TLA	combination	PSG	PSG NOS	-	-	pre & post	no	7
Biskup et al.	2017	retrospective	USA	28	<3 m	MDO	surgical	PSG	PSG NOS	-	-	pre & post	no	5
Zellner et al.	2017	retrospective	USA	20	40	MDO	surgical	PSG	PSG NOS	-	overnight	pre & post	no	12**
Poets et al.	2017	prospective	Germany	49	35	PEBP	conservative	CRSS	type 3	supine	evening, minimum 8h	pre & post	yes	10
Buchenau et al.	2017	retrospective	Germany	122	13	PEBP	conservative	CRSS	type 3	supine	evening, minimum 8h	pre & post	no	9
Ramieri et al.	2017	retrospective	Italy	4	17	FEMOD	surgical	PSG	PSG NOS	-	-	post	no	5
Bangiyev et al.	2016	retrospective	USA	26	29	MDO	surgical	PSG	PSG NOS	-	-	pre & post	no	6
Resnick et al.	2016	retrospective	USA	18	28	TLA	surgical	PSG	PSG NOS	supine and prone	-	pre & post	no	6
Albino et al.	2016	retrospective	USA	32	38	Sup.O2 (nasal canula/NPA/intubation)	conservative	PSG	PSG NOS	prone	-	during	yes	7
Adeleye et al.	2016	retrospective	Canada	9	< 12 m	PAP	conservative	PSG	type 1	-	overnight	pre	no	5
Amaddeo et al.	2016	retrospective	France	20	<1 m	PP/CPAP/(TRACH)*	conservative	PG	type 3/4	prone	daytime nap PG (NS)	pre	yes	5
Greathouse et al.	2016	retrospective	USA	89	32/36	MDO/TLA	surgical	PSG	PSG NOS	-	-	pre & post	yes	7

TABLE 1. Continued.

Name	Year	Type of study	Country	Number RS infants	Mean age (days) at intervention or admission	intervention	type of intervention	Objective measurement reported in study	type of PSG AASM	position	moni-toring time	pre and/ or post inter-vention	Indi-cation/ threshold	MINOR score
Ching et al.	2015	retrospective	USA	38	39 + 121 (2 means)	MDO	surgical	MPAS	type 1/2	left lateral, right lateral, supine, and prone position and in a car seat (if available)	-	pre	yes	5
Tahiri et al.	2015	retrospective	USA	81	23	MDO	surgical	PSG	PSG NOS	-	-	pre & post	yes	14**
Lee et al.	2015	retrospective	USA	45	median 12 (0-168 range)	Consv./MDO/ TLA/TRACH/SGP	combination	PSG	type 1	supine or lateral	-	pre &post	no	8
Goldstein et al.	2015	retrospective	USA	28	58	MDO	surgical	PSG	type 1	-	overnight	pre & post	no	6
Tholpady et al.	2015	retrospective	USA	11	< 6 m	MDO	surgical	PSG	PSG NOS	-	-	pre & post	yes	5
Kimple et al.	2014	retrospective	USA	3	3 m	PP	conservative	PSG	type 1	supine and prone	overnight	pre & post	no	5
Cascone et al.	2014	retrospective	Italy	29	11	FEMOD	surgical	PSG	PSG NOS	-	-	pre & post	no	7
Murage et al.	2014	retrospective	USA	50	85	MDO	surgical	PSG	PSG NOS	-	-	pre & post	yes	6
Flores et al.	2014	retrospective	USA	39	32/39	MDO/TLA	surgical	PSG	PSG NOS	-	-	pre & post	yes	14**
Van Lieshout et al.	2014	retrospective	The Nether-lands	59	Median 47 (0-349 range)	PP/resp.support (= NPA,CPAP, and/or O2 sup.)/ TRACH+MDO	combination	PSG	PSG NOS	-	overnight	pre	no	7
Girbal et al.	2014	retrospective	Portugal	5	1 m	NIV: CPAP/BIPAP	conservative	CRS & PSG	PSG NOS	-	-	pre & during	no	7
Dong et al.	2014	retrospective	China	7	14	mandibular traction	surgical	oximetry	-	prone or lateral	24 h	pre & post	yes	6
Daniel et al.	2013	retrospective	Australia	39	5-141	PP/CPAP/MDO	combination	PSG	type 1/2	-	minimum 4h sleep	pre	no	5
Papoff et al.	2013	retrospective	Italy	18	24/35	MDO/TLA	surgical	PSG	PSG NOS	-	-	post	no	10**
Abel et al.	2012	retrospective	UK	104	1d-12 m	PP/NPA/TRACH	combination	PSG	PSG NOS	-	overnight	pre & post	yes	6
Sedaghat et al.	2012	retrospective	USA	8	29	TLA	surgical	PSG	type 1	-	overnight	pre & post	no	9
Caouette-Laberge et al.	2012	retrospective	Canada	31	20 (total cohort of 31)	SPRFM	surgical	PSG, blood gas	PSG NOS	-	-	pre & post	no	7

TABLE 1. Continued.

Name	Year	Type of study	Country	Number RS infants	Mean age (days) at intervention or admission	intervention	type of intervention	Objective measurement reported in study	type of PSG AASM	position	monitoring time	pre and/or post intervention	Indication/ threshold	MINOR score
Han et al.	2012	retrospective	USA	25	19/63 (isolated/ syndromic)	TRACH	surgical	blood gas	-	-	-	pre	no	7
Hammoudeh et al.	2012	retrospective	USA	19	57	MDO	surgical	PSG	type 1	customary sleep position	daytime nap or overnight	pre & post	no	6
Hong et al.	2012	retrospective	Canada	6	65	MDO	surgical	sleep study	PSG NOS	-	-	pre	no	4
Cheng et al.	2011	retrospective	Australia	6	26 d – 11 m	MDO plus TLA	surgical	PSG	PSG NOS	prone	-	pre & post	no	8
Mohamed et al.	2011	retrospective	Saudi Arabia & Egypt	11	2-7 m	MDO	surgical	PSG	PSG NOS	-	-	pre & post	no	6
Bacher et al.	2011	prospective	Germany	15	median 5 (0-60 range)	PEBP	conservative	PG, blood gas	type 3	supine	evening, minimum 8h	pre & post	yes	10
Anderson et al.	2011	retrospective	USA	33	48	prior to surgical intervention (NS)	surgical	PSG	type 1	-	overnight	pre	no	6
Baciliero et al.	2011	retrospective	Italy	246	newborns (mandibular traction: 22 days)	(PP/NPA)*/ mandibular traction	surgical	oximetry	-	-	24 h	pre & post	yes	6
Lebou-langer et al.	2010	retrospective	France	7	4 m	NRS/(TRACH)*	conservative	PS	type 4	-	5 min during noctural sleep, after spontaneous breathing period of 15 min (for treatment evaluation)	pre & during	yes	7

TABLE 1. Continued.

Name	Year	Type of study	Country	Number RS infants	Mean age (days) at intervention or admission	intervention	type of intervention	Objective measurement reported in study	type of PSG AASM	position	moni-toring time	pre and/ or post inter-vention	Indi-cation/ threshold	MINOR score
Miloro et al.	2010	retrospective	USA	19	3.5 m	MDO	surgical	oximetry	-	-	-	pre & post	yes	8
Looby et al.	2009	retrospective	USA	17	105	MDO	surgical	PSG	PSG NOS	-	-	pre & post	no	6
Neto et al.	2009	retrospective	Brazil	14	new borns (NS)	(PP)*/MDO plus TRACH	surgical	PSG	PSG NOS	-	-	pre	no	5
Gifford et al.	2008	retrospective	USA	4	17	MDO	surgical	PSG	PSG NOS	-	-	pre & post	no	9
Mitsukawa et al.	2007	retrospective	Japan	6	5 m	MDO	surgical	PSG	PSG NOS	-	-	pre & post	no	5
Buchenau et al.	2007	prospective, randomized controlled trial	Germany	11	median 3 (0-60 range)	PEBP	conservative	CRSS, blood gas	type 3	supine	evening, minimum 8h	pre & post	yes	n/a
Ludwig et al.	2007	retrospective	Germany	4	newborns (NS)	Orthodontic plate	conservative	oximetry	-	-	-	pre & post	no	3
Burstein et al.	2004	retrospective	USA	15	3 m	MDO	surgical	sleep study	PSG NOS	-	-	pre & post	no	4
Monasterio et al.	2004	retrospective	Mexico	18	120	MDO	surgical	PSG	PSG NOS	supine	8 h	pre & post	no	8
Wittenborn et al.	2004	retrospective	USA	14	29	MDO	surgical	PSG	type 3/4	-	-	pre & post	no	7
Hoffman	2003	retrospective	USA	25	38	TLA	surgical	sleep study	PSG NOS	-	-	pre & post	no	8
Wagener et al.	2002	retrospective	UK	20	13	NPA	conservative	oximetry	-	supine (gently lowered into a supine position while sleeping, if no obstruction occurs this was repeated while bottle feeding).	24-36 h	pre	yes	7
Morovic et al.	2000	prospective	Chile	5	4 m	MDO	surgical	PSG	PSG NOS	-	12 h	pre & post	yes	7

TABLE 1. Continued.

Name	Year	Type of study	Country	Number RS infants	Mean age (days) at intervention or admission	intervention	type of intervention	Objective measurement reported in study	type of PSG AASM	position	monitoring time	pre and/or post intervention	Indication/ threshold	MINOR score
Chang et al.	2000	retrospective	Australia	6	27	NPA	conservative	PSG	type 1	-	overnight	pre & during & post	no	4
Marques et al.	2000	prospective	Brazil	62	<6m	NPA/TLA/ TRACH	combination	oximetry	-	supine	post NPA placement 48h	pre & post	yes	9
Wilson et al.	1999	retrospective	Australia	10	37	O2/CPAP/NPA	conservative	PSG	PSG NOS	-	-	pre & post	no	3
Bull et al.	1990	retrospective	USA	21	14	O2/TLA/TRACH	combination	PSG	type 3	supine, prone and lateral	spontaneous sleep + wakefulness, mean 2h	pre & post	no	10
Studies with only threshold/indication for intervention														
Konofaos et al.	2019	retrospective	USA	24	6 m	MDO	surgical	PSG	PSG NOS	supine	-	-	yes	
Zhang et al.	2019	retrospective	China	73	55	MDO	surgical	oximetry	-	-	-	-	yes	
Li et al.	2017	retrospective	Canada	63	51	PP/TLA/MDO/ FMR/TRACH	combination	oximetry	-	prone	-	-	yes	
Flores et al.	2015	retrospective	USA	81	34	MDO	surgical	PSG	PSG NOS	-	-	-	yes	
Salmen et al.	2015	prospective	Brazil	149	32 (NPA)	PP/NPA/TRACH	combination	oximetry	-	-	-	-	yes	
Paes et al.	2015	retrospective	The Netherlands	75	50 (surgical intervention)	PP/NPA/TLA/ MDO/TRACH	combination	oximetry, TcpCO2 (Tosca®), blood gas	-	prone or lateral	-	-	yes	
Breugem et al.	2012	retrospective	The Netherlands	12	32	MDO	surgical	oximetry	-	-	12 h	-	yes	
Sesenna et al.	2012	retrospective	Italy	9	2.3 m	MDO	surgical	oximetry	-	-	-	-	yes	

TABLE 1. Continued.

Name	Year	Type of study	Country	Number RS infants	Mean age (days) at intervention or admission	intervention	type of intervention	Objective measurement reported in study	type of PSG AASM	position	moni-toring time	pre and/ or post inter-vention	Indi-cation/ threshold	MINOR score
Glynn et al.	2011	retrospective	Ireland	69	NS	PP/NPA/TRACH	combination	oximetry	-	supine (gently lowered into a supine position while sleeping, if no obstruction occurs this was repeated while bottle feeding).	24-36 h	-	yes	
Kolstad et al.	2011	retrospective	USA	22	56	MDO	surgical	CO2 measurement (NOS)	-	-	-	-	yes	
Shen et al.	2009	retrospective	China	6	13	MDO	surgical	oximetry	-	prone	-	-	yes	
Pradel et al.	2009	retrospective	Germany	19	NS	prone or lateral positioning/palatal plate/mandibular traction	combination	oximetry, blood gas	-	-	-	-	yes	
Breugem et al.	2008	retrospective	Canada	14	105	SPRFM	surgical	oximetry	-	-	24 h	-	yes	
de Buys Roessingh et al.	2007	retrospective	Switserland	48	newborns (NS)	PP/NPA	conservative	oximetry, blood gas	-	supine (slowly lowering the child while sleeping into supine position, repeated while bottle feeding)	-	-	yes	
Anderson et al.	2007	retrospective	UK	12	median 6 (1 - 122 days)	NPA	conservative	oximetry	-	supine (gently lowered into a supine position while sleeping, if no obstruction occurs this was repeated while bottle feeding).	24-36 h	-	yes	

TABLE 1. Continued.

Name	Year	Type of study	Country	Number RS infants	Mean age (days) at intervention or admission	intervention	type of intervention	Objective measurement reported in study	type of PSG AASM	position	moni-toring time	pre and/ or post inter-vention	Indi-cation/ threshold	MINOR score
Denny	2004	retrospective	USA	23	<3 m	MDO	surgical	PSG	PSG NOS	-	-	-	yes	
Schaefer et al.	2004	retrospective	USA	21	median 5 (0-32 days)	PP/MDO/TLA/ TRACH	combination	sleep study	PSG NOS	-	12 h	-	yes	
Caouette-Laberge et al.	1994	retrospective	Canada	34	newborns (NS)	PP/NPA/SPRFM	combination	blood gas	-	-	-	-	yes	
Gilhooly et al.	1993	retrospective	USA	15	< 2 months	TLA	surgical	PSG	PSG NOS	prone position except when feeding and other nursing care	-	-	yes	
Augarten et al.	1990	retrospective	Israel	8	newborns (NS)	PP/TLA	combination	respiratory rates, blood gas	-	prone	-	-	yes	

Consv.: conservatively, **SP:** side positioning, **PP:** prone positioning, **PEBP:** pre-epiglottic baton plate/Tubingen plate, **BIPAP:** bilevel positive airway pressure, **CPAP:** continuous positive airway pressure, **PAP:** noninvasive positive airway pressure, **NIV:** noninvasive ventilatory support (both CPAP or BIPAP), **NRS:** noninvasive respiratory support (both CPAP and PAP), **NPA:** nasopharyngeal airway/tube, **MDO:** mandibular distraction osteogenesis, **FEMOD:** fast early mandibular osteogenisis distraction, **TLA:** tongue-lip adhesion, **SPRFM:** subperiosteal release of the floor of the mouth, **SGP:** supraglottoplasty, **TRACH:** tracheostomy, **m:** months, **NS:** not specified

MPAS: multi positional airway study, **CRS:** cardiorespiratory study, **CRSS:** cardiorespiratory sleep study, **PG:** polygraphic study, **PS:** physiologic study, **PSG:** polysomnography, **AASM:** American Academy of Sleep Medicine

* **Between brackets:** if the intervention was mentioned but no actual data pre and/or post intervention was reported.

** comparative study; MINORS score can range from 0-24.

5.

CHAPTER 5.

DISCUSSION ON SLEEP OUTCOMES IN NEONATES WITH PIERRE ROBIN SEQUENCE UNDERGOING EXTERNAL MANDIBULAR DISTRACTION

A Longitudinal Analysis

Robrecht J.H. Logjes, Joanna E. Maclean, Corstiaan C. Breugem

Plastic Reconstructive Surgery 2021

Discussion letter on article:

Ehsan Z, Weaver KN, Pan BS, Huang G, Hossain MM, Simakajornboon N.
Sleep Outcomes in Neonates with Pierre Robin Sequence Undergoing External Mandibular Distraction: A Longitudinal Analysis.
Plastic Reconstructive Surgery. 2020

We read with great interest the recent work of Ehsan et al. 2020 on respiratory and sleep outcomes using polysomnograms (PSG) pre- and post-surgical intervention to objectively measure treatment success of neonatal mandibular distraction in infants with Robin Sequence (RS) (Ehsan et al. 2020).

Objective assessment of obstructive sleep apnea (OSA) by PSG are essential to the baseline evaluation of airway obstruction in infants with RS and to assessing the impact of interventions, especially given the high rate of additional anomalies and high mortality rates of 10-17% (Logjes et al. 2018). The spectrum of OSA in RS is broad and may also change with growth or intervention (MacLean 2019).

Ehsan et al. 2020 assessed treatment success of their surgical intervention in a comprehensive way and is an excellent example how future studies assessing OSA in RS should be designed. The authors report on essential variables including variables derived from full PSG, time of day and duration of PSG recording, age at time of each PSG's, and specific the definition of OSA-based on the PSG results (OSA if OAHI>1). These are all variables necessary to facilitate treatment comparisons across centers and between different interventions. However, for future studies to be able to compare outcome more comprehensively, we would suggest several aspects that are still missing.

First of all, the exact indication to perform mandibular distraction in their cohort of RS infants was unclear. The authors state that the decision to proceed with mandibular distraction was determined by the multidisciplinary team collaboratively after comprehensive evaluation but not state what respiratory and/or sleep parameter thresholds from the baseline PSGs were used to guide intervention decisions.

Secondly, the authors define the presence of OSA based on an OAHI>1 as part of the methodology, but the authors then use OAHI<40 and >40 to categorize the severity of OSA in those infants undergoing MDO based on their institutional practice later in the statistics section and OAHI>10 to define those with persistent OSA after MDO in their results. This suggests that OAHI >1 is not truly used to define OSA in their clinical practice and may not be a useful definition in this age group, since in healthy neonates in the first 30 days of age the median OAHI was recently reported 1.8 (range: 0.2 to 12.5 events/hour) (Daftary et al. 2019).

Thirdly, the authors provide extensive details of their PSG-methodology which is preferable in all future PSG-studies in RS. However, body position during PSG recording was not reported. Whether the recordings were performed in the supine or the prone position can heavily influence the respiratory and sleep parameters assessed by PSG, and assess the impact of prone positioning (Coutier et al. 2019; Hong et al. 2020). Further well-designed studies that include clear documentation of these important variables reported by Ehsan et al. 2020, and these suggested additional variables, will pave the way to a more standardized, evidence-based approach in the assessment and treatment of OSA in infants with RS.

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PART II

SURGICAL TREATMENT OF ROBIN SEQUENCE

6.

CHAPTER 6.

THE INNERVATION OF THE SOFT PALATE MUSCLES INVOLVED IN CLEFT PALATE

A review of the literature

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Clinical Oral Investigations 2016

Presented at

- 31th Annual Meeting of the Dutch Association of Cleft and Craniofacial Anomalies 19th November 2016

ABSTRACT

Objective: Surgical techniques to obtain adequate soft palate repair in cleft palate patients elaborate on the muscle repair, however, there is little available information regarding the innervation of muscles. Improved insights into the innervation of the musculature will likely allow improvements in the repair of the cleft palate and subsequently decrease the incidence of velopharyngeal insufficiency. We performed a literature review focused on recent advances in the understanding of soft palate muscle innervation.

Methods: The Medline and Embase databases were searched for anatomical studies concerning the innervation of the soft palate.

Results: Our literature review highlights the lack of accurate information about the innervation of the levator veli palatini - and palatopharyngeus muscle. It is probable that the lesser palatine nerve and the pharyngeal plexus dually innervate the levator veli palatini - and palatopharyngeus muscle. Nerves of the superior-extravelar part of the levator veli palatini - and palatopharyngeus muscle enter the muscle form the lateral side. Subsequently, the lesser palatine nerve enters from the lateral side of the inferior-velar part of the levator veli palatini muscle. This knowledge could aid surgeons during reconstruction of the cleft musculature. The innervation of the tensor veli palatini muscle by a small branch of the mandibular nerve was confirmed in all studies.

Conclusion: Both the levator veli palatini - and palatopharyngeus muscle receive motor fibres from the accessory nerve (through the vagus nerve and the glossopharyngeal nerve) and also the lesser palatine nerve. A small branch of the mandibular nerve innervates the tensor veli palatini muscle.

Clinical Relevance: Knowledge about these nerves could aid the cleft surgeon to perform a more careful dissection of the lateral side of the musculature.

INTRODUCTION

Achieving adequate velopharyngeal closure for optimal feeding and speech development is a main objective in cleft palate closure. Unfortunately 20-30% of the cleft palate closures result in velopharyngeal insufficiency (Witt et al. 1998; Mahoney et al. 2013). Numerous surgical techniques for palate closure have been described (Sommerlad 2003; Hopper et al. 2014). Most studies focus on the anatomical repair of the musculature of the cleft palate. Surgical techniques do not mention the possible nerve damage that could result from the surgical dissection. Several studies describing the palatal musculature have been described (Huang et al. 1997; 1998). However, for an optimal functional muscular repair of the soft palate, thorough understanding of the motor innervation of these soft palate muscles is crucial. This may prevent nerve damage during surgical dissection and therefore may result in a better functional outcome and less complications in patients with cleft palate or velopharyngeal insufficiency. Two major anatomical textbooks mention that both palatopharyngeus muscle (PP) and the levator veli palatini muscle (LVP) are innervated by the cranial part of the accessory nerve (CN XI) via the pharyngeal plexus and the tensor veli palatini muscle (TVP) is innervated by the mandibular nerve (Hollinshead 1982; Bannister et al. 1995). Nevertheless anatomical uncertainties remain such as the possible involvement of the facial nerve (CN VII) and the exact neural route via the pharyngeal plexus to the soft palate (Hollinshead 1982). This review provides an update of our current understanding of the origin, course and ramification patterns of the nerves that supply the three most important soft palate muscles. The muscles discussed are the palatopharyngeus (PP), the levator veli palatini (LVP) and the tensor veli palatini (TVP) muscles. This information could subsequently aid cleft surgeons during the cleft palate repair.

METHODS

An extensive literature search was conducted using Embase and Medline (April 2015) and performed by RJH Logjes. First the terms “soft palate AND (innervation OR nerve)” and “velum AND (innervation OR nerve)” were used. This resulted in respectively n= 551 and n= 109 results. Secondly the names of the 3 muscles were used as a term resulting in “tensor veli palatini” (n= 226), “levator veli palatini” (n= 283) and “palatopharyngeus” (n= 105). After selecting the relevant articles by reading title and abstracts 12 articles were used in this review. Five articles described the course of the nerves to the soft palate in human cadavers (Broomhead 1951;1957; Doménech-Ratto 1977; Shimokawa et al. 2004; Shimokawa et al. 2005) and 1 article described an electromyography (EMG) study (Sedlácková et al. 1973). An other article did not describe material and methods (Shankland 2001).

TABLE 1. Baseline characteristics of the 7 studies on human material

Authors	Muscle(s) investigated	N =	Method	Results
Broomhead 1951	TVP, LVP, PP	1 adult head, 2 foetal heads, 3 human embryos	Dissecting and serial sections after staining HE and Ranson's silver impregnation	**LVP:** Pharyngeal plexus of the CN X **PP:** CN IX and CN X **TVP:** mandibular nerve (CN V)
Broomhead 1957	TVP, LVP, PP	3 human embryos	Serial sections stained by the De Castro's method	**LVP:** Pharyngeal plexus of the CN X **PP:** CN IX and CN X **TVP:** mandibular nerve (CN V)
Domenech-Ratto 1977	TVP, LVP, PP	51 embryos	Sectioned transversally, frontally or saggitally and stained by HE (n= 35), Azan (n=26) or Bielschowsky method (n=10)	**LVP:** CN IX **PP:** CN IX and CN X **TVP:** mandibular nerve (CN V)
Sedlackova et al. 1973	Soft palate	25 patients with the syndrome of developmental shorting of the soft palate	Electromyography (EMG) of the facial and soft palate muscles	CN VII, CN IX, CN X
Shimokawa et al. 2004	LVP	50 head halves	Dissection by binocular microscope	**LVP:** 3 types of innervation by pharyngeal plexus (CN IX and X)
Shimokawa et al. 2005	LVP, PP	30 head halves	Dissection by stereomicroscope and staining nerve fibres with silver nitrate as described by Kimura and Takahashi	**LVP and PP:** Lesser palatine nerve (CN V) and pharyngeal plexus (CN IX and X)
Shankland 2001	TVP	Undescribed	Undescribed	**TVP:** mandibular nerve (CN V)

TVP = tensor veli palatini muscle, LVP = levator veli palatini muscle, PP = palatopharyngeus muscle,
CN V = trigeminal nerve, CN VII = facial nerve, CN IX = glossopharyngeal nerve, CN X vagus nerve, HE = haematoxylin-eosin.

A total of 5 studies on the innervation of the soft palate muscles in animals were also used in this review (Nishio et al. 1976; Ibuki et al. 1978; van Loveren et al. 1983; Keller et al. 1984; Strutz et al. 1988).

RESULTS

Baseline characteristics of the 7 studies on human material and the 5 studies on animals are presented table 1 and 2.

Levator veli palatini

Most authors agree that the LVP is supplied by the pharyngeal plexus (Broomhead 1951; 1957). However, minor differences in description exist. Broomhead claims that the pharyngeal plexus contains branches of the vagus nerve only, while other authors state that this plexus receives contributions from the glossopharyngeal- and vagus nerves (Broomhead 1951; 1957; Shimokawa et al. 2004; Shimokawa et al. 2005; Sedlácková et al. 1973). Domenech-Ratto (1977) found that the glossopharyngeal nerve reached the LVP without forming a plexus. Sedlackova et al. 1973 concluded from their EMG records in 25 patients that facial muscles disorders combine with a disorder of the LVP and that therefore the LVP is dually innervated: via the facial nerve during speech and via the pharyngeal plexus (the glossopharyngeal - and vagus nerve) during swallowing. A dual innervation of the LVP was also found by Shimokawa et al. 2005 who claims that the lesser palatine nerve and the pharyngeal plexus are innervating the LVP.

Four studies showed more insight into morphological details of the pharyngeal plexus and the course of the supplying nerve towards the LVP. The contributions to the pharyngeal plexus from the glossopharyngeal - and vagus nerve may run as a joint nerve along carotid artery branches or may form a true plexus with multiple communications, together with the branches of the sympathetic trunk in their inferomedial course between the internal and external carotid arteries (Broomhead 1951; 1957; Shimokawa et al. 2004; Shimokawa et al. 2005).

Broomhead states in two articles that one pharyngeal plexus branch, derived from the vagus nerve ascends vertically on the lateral side of the constrictor muscles. This nerve branch passes forwards across the sinus of Morgagni at the level of the upper border of the superior constrictor muscle. It divides into 2 smaller branches before entering the lower lateral border of the extravelar muscle part of the LVP (Broomhead 1951; 1957).

According to Broomhead small branches of the ascending pharyngeal artery accompany this nerve branch on the surface of the constrictor muscles (Broomhead 1951). According to Shimokawa et al. the LVP branch always has a common trunk with the supplying branch to the superior constrictor muscle. It penetrates the superior constrictor first and subsequently enters the LVP at its posterior margin. Tiny branches are distributed throughout the superior-extravelar muscle part of the LVP (Shimokawa et al. 2004; Shimokawa et al. 2005) (Figure 1). This superior-extravelar muscle part of

the LVP, which is supplied by the pharyngeal plexus, is much bigger than the inferior-velar part of the LVP which, according to Shimokawa et al. 2005, is supplied by the lesser palatine nerve. Shimokawa et al. 2004 distinguished three patterns of innervation of the superior part of the LVP, based on their origin in the pharyngeal plexus. Type 1: the supplying nerve branches find their origin in the glossopharyngeal nerve only. Type 2: the supplying nerve branches originate from communicating branches between the glossopharyngeal - and vagus nerve. Type 3: the supplying nerve branches find their origin in the vagus nerve only. Type 2 innervation pattern was found in most specimens in a human cadaver study done by Shimokawa et al 2004.

A contribution from the lesser palatine nerve runs through the lesser palatine foramen and ramifies in multiple small nerve branches. These branches run posteromedially underneath the palatine aponeurosis and the nasal part of the PP. Close to the insertion of the LVP in the midline of the velum almost all branches enter the muscle on its lateral surface. The small nerve branches end up in the inferior-velar part of the LVP and the bigger nerve branches penetrate this muscle to end up in the uvulae muscle or the oral part of the PP. (Figure 2) Most of the time, the anterior most branch of the lesser palatine nerve does not penetrate the LVP but runs underneath the palatine aponeurosis and ends in the glandular tissue of the palate (Shimokawa et al. 2005).

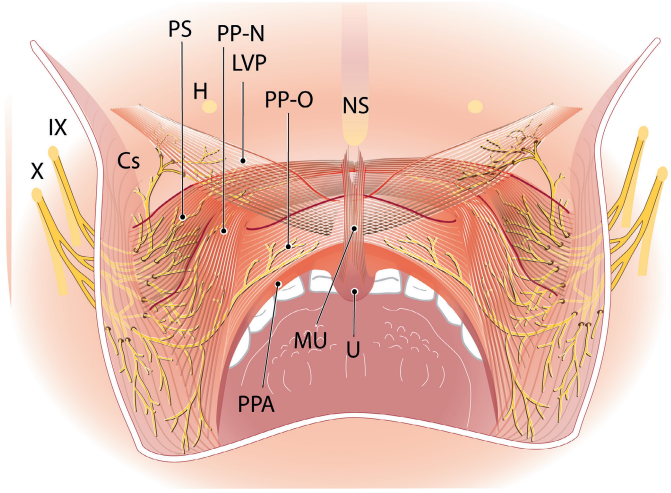

FIGURE 1: Adapted from Shimokawa et al. (2005) by I. Janssen.
Dorsal view. Distribution of the pharyngeal plexus in the superior-extravelar part of the LVP and nasal and oral parts of the PP.
LVP = levator veli palatini muscle, PP-N = palatopharyngeus muscle nasal strand, PP-O = palatopharyngeus muscle oral strand, PS = palatopharyngeal sphincter , MU = uvulae muscle, PPA = palatopharyngeal arch, Cs = constrictor superior muscle, H = hamulus, NS = nasal septum, U = uvula, IX = glossopharyngeal nerve, X = vagus nerve.

In three specimens Shimokawa et al. 2005 found a variation where the posteriormost branch of the lesser palatine nerve enters the PP directly without penetrating the LVP. This entering point on the inferior surface of the medial part of the PP is close to the posterior border of the LVP (Figure 2).

Palatopharyngeus

There is agreement that the palatopharyngeus is supplied by the pharyngeal plexus through contributions from the glossopharyngeal - and vagus nerve (Broomhead 1951; 1957; Doménech-Ratto 1977; Shimokawa et al. 2005). According to Broomhead 1951 the pharyngeal branch of the vagus nerve reaches the lower part of the PP, after running parallel to the posterior border of stylopharyngeus and entering the pharynx between superior and middle constrictors. The glossopharyngeal nerve branch enters the PP, after a course along the anterior border of the stylopharyngeus and coursing between the same constrictors. Once these branches enter the PP they divide into very small nerve branches between the muscle fibres. According to Shimokawa et al. 2005 there is a minor additional supply from the lesser palatine nerve. This branch supplies the anterior part of the oral part of PP. The same authors state that the PP branch from the pharyngeal plexus is from a common branch with the supplying nerves of superior and middle constrictors. After penetrating the constrictors or running between these muscles the nerve enters the PP on its lateral surface. Smaller nerve branches ascend inside the PP and are distributed in the oral and nasal parts of the muscle (Shimokawa et al. 2005) (Figure 1).

Summarizing, all the authors who investigated the human nerve supply towards the soft palate agree that the pharyngeal plexus innervates the levator veli palatini and the palatopharyngeus muscle (Broomhead 1951; 1957; Doménech-Ratto 1977; Shimokawa et al. 2004; Shimokawa et al. 2005; Sedlácková et al. 1973). Although the descriptions of the exact composition of the pharyngeal plexus vary among the authors. According to Broomhead the pharyngeal plexus differs in innervating these two muscles: towards LVP it contains only the vagus nerve; towards the PP it contains both the glossopharyngeal - and vagus nerve (Broomhead 1951; 1957). On the contrary Domenech-Ratto 1977 claims that only the glossopharyngeal nerve innervates the LVP and agrees with Broomhead that the glossopharyngeal - and vagus nerve together innervate the PP.

Sedlackova et al. 1973 thinks the LVP is innervated via the facial nerve during speech and via the pharyngeal plexus, which contains the glossopharyngeal - and vagus nerve, during swallowing.

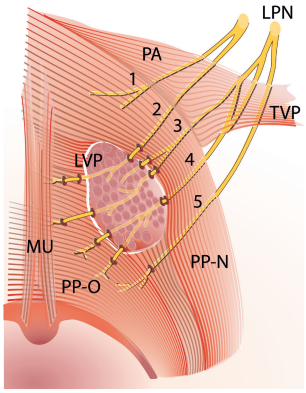

FIGURE 2: Superior view on soft palate with the innervation by the lesser palatine nerve, adapted from Shimokawa et al. (2005) by I. Janssen.
A part of the LVP is removed for better view on the five nerve fibres of the lesser palatine nerve, which were found in the human cadaver study by Shimokawa et al. (2005). These nerves run underneath the palatine aponeurosis and the nasal part of the PP and penetrate the inferior-velar part of the LVP on its lateral surface close to the insertion of the LVP in the midline of the velum.
LPN = lesser palatine nerve, LVP = levator veli palatini muscle, PA = palatine aponeurosis, PP-N = palatopharyngeus muscle nasal strand, PP-O = palatopharyngeus muscle oral strand, TVP = tensor veli palatini muscle, MU = uvulae muscle.

Shimokawa et al. 2005 concluded that both the lesser palatine nerve and the pharyngeal plexus, which contains the glossopharyngeal - and vagus nerve, dually innervate the soft palate muscles LVP and PP. The lesser palatine nerve innervates the small inferior-velar part of the LVP and the anterior part of the oral part of the PP, together referred to as the anteromedial region of the soft palate muscles. The pharyngeal plexus innervates the bigger superior part of the LVP and the nasal and remaining oral part of the PP, also referred as the posterolateral region of the soft palate muscles (Shimokawa et al. 2005). Figure 3 demonstrates the view of the cleft surgeon on the soft palate and the course of both the lesser palatine nerve as the pharyngeal plexus.

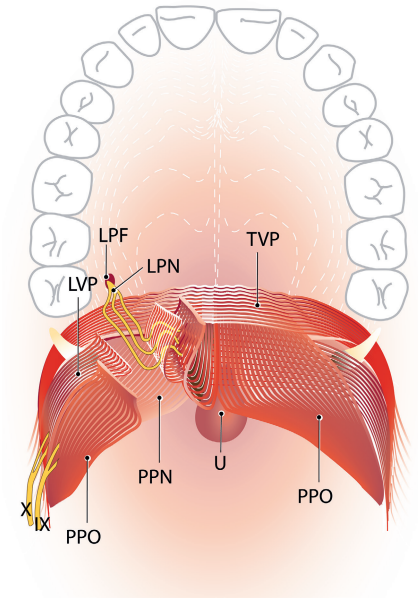

FIGURE 3: The dual innervation of the soft palate by the LPN and the pharyngeal plexus.
(Idea and design by RJH Logjes and CC Breugem after combining the two innervation patterns shown in FIGURE 1 and 2, illustrated by I Janssen).

View of the plastic surgeon on the soft palate, the pharyngeal plexus penetrates the superior-extravelar part of the LVP on the lower lateral border. The lesser palatine nerve runs through the lesser palatine foramen and runs over the palatine aponeurosis of the TVP and the nasal part of the PP to enter the inferior-velar part of the LVP on its lateral surface. Here the LPN innervates the small inferior-velar part of the LVP and the anterior part of the oral part of the PP, together referred to as the anteromedial region of the soft palate muscles.
LPF = lesser palatine foramen, LPN = lesser palatine nerve, IX = glossopharyngeal nerve, X = vagus nerve, TVP = tensor veli palatine muscle, LVP = levator veli palatini muscle, PP-N = palatopharyngeus muscle nasal strand, PP-O = palatopharyngeus muscle oral strand, U = uvula.

Tensor veli palatini

There is agreement that the TVP is supplied by the mandibular nerve, which is the third branch of the trigeminal nerve (Broomhead 1951; 1957; Doménech-Ratto 1977; Shankland 2001). According to Shankland 2001 the mandibular nerve splits into an anterior and a posterior part in the infratemporal fossa just after its passage through the foramen ovale. Just before this division a small branch is given off, the so-called undivided trunk of the mandibular nerve. This undivided trunk ramifies into 4 smaller nerve branches. One of these smaller branches is the nerve to the TVP. This nerve runs through the otic ganglion without having a functional relationship with it and then enters the TVP close to its origin in the scaphoid fossa of the sphenoid bone. The other 3 branches of this undivided trunk include the nerve to medial pterygoid, nerve to tensor tympani and the meningeal branch also known as nervus spinosus (Shankland 2001). Broomhead (1951 & 1957) found the supplying branch to the TVP splitting from the nerve to medial pterygoid, passing forwards and medially to enter the posterior border of TVP as one branch or the lateral and posterior borders via two branches.

Nerve supply in animals

Van Loveren et al. (1983), Keller et al. (1984), and Strutz et al. (1988) localized motorneurons of the soft palate muscles in the brainstem of cats, guinea pigs and monkeys by using a retrograde neuroanatomical tracing technique. Nishio et al. (1976) and Ibuki et al. (1978) studied the motor innervation of respectively the soft palate muscles and the LVP by evoked electromyography (EMG) responses in rhesus monkeys. Except for the TVP there is controversy about the location of the motorneurons for the soft palate muscles. The TVP in humans receives its motor fibres from the trigeminal nerve (Broomhead 1951; Doménech-Ratto 1977; Shankland 2001). Keller et al. (1984) confirmed this by retrograde tracing.

Nishio et al. (1976) claims that the soft palate receives motor fibres from both the facial nerve and pharyngeal plexus of the glossopharyngeal - and vagus nerve. Ibuki et al. (1978) found that the LVP was only supplied by the facial nerve. Both Nishio et al. (1976) and Ibuki et al. (1978) agreed that motor fibres of the facial nerve ran through the pterygopalatine ganglion and mixed with sensory fibres of the lesser palatine nerve to reach the soft palate and the LVP respectively. On the other hand Van Loveren et al. (1983) and Keller et al. (1984) excluded the role of the facial nerve in the motor innervation of the LVP and found the LVP dually motor innervated by the glossopharyngeal - and vagus nerve. Strutz et al. (1988) claimed that the glossopharyngeal, vagus and accessory nerve are all responsible for the motor supply of the soft palate muscles.

TABLE 2: Baseline characteristics of the 5 studies on animals

Authors	Muscle(s) investigated	N =	Method	Results
Nishio et al. 1976	LVP, MU, SCP, OO	20 rhesus monkeys	Evoked electromyography (EMG) responses	**LVP:** CN VII and pharyngeal plexus (CN IX,X)
Ibuki et al. 1978	LVP, OO	10 rhesus monkeys	Evoked electromyography (EMG) responses	**LVP:** course of the facial nerve for the LVP through the greater petrosal nerve
Van Loveren et al. 1983	LVP	18 cats	HRP injection in LVP and after 24-48 hours microscopically examination of the brainstem sections	NA, RFN (CN IX, X) No labelled cells in the FN
Keller et al. 1984	TVP, LVP	19 cats	HRP injection in TVP and LVP and after 24-48 hours microscopically examination of the brainstem sections	**TVP:** TMN **LVP:** NA, RFN No labelled cells in the FN
Strutz et al. 1988	Soft palate	9 guinea pigs 4 monkeys	HRP injection of the velum and after 48 hours microscopically examination of the brainstem sections	NA, RFN (CN IX, X, XI) TMN

HRP = horseradish peroxidase, NA = nucleus ambiguus, RFN = retrofacial nucleus, TMN = trigeminal motor nucleus, FN = facial nucleus, OO = orbicularis oris muscle, SCP = superior constrictor pharyngeus muscle, MU = uvulae muscle. TVP = tensor veli palatini muscle, LVP = levator veli palatini muscle, CN VII = facial nerve, CN IX = glossopharyngeal nerve, CN X vagus nerve, CN XI = accessory nerve.

DISCUSSION

Only few studies investigated the innervation of the soft palate muscles in humans. The innervation of the TVP by the mandibular nerve is universally accepted (Broomhead 1951; 1957; Doménech-Ratto 1977; Shankland 2001). However, knowledge about the innervation of the LVP and PP remains controversial. All authors mentioned the contribution of the pharyngeal plexus but details of their descriptions vary. According to two major anatomical textbooks the pharyngeal plexus receives its motor fibres from the cranial part of the accessory nerve (Hollinshead 1982; Bannister et al. 1995).
The studies by Broomhead (1951 & 1957) were on small series of human heads. The same applies to the study by Domenech-Ratto (1977) who only investigated 10 embryos. Studies by Shimokawa et al. (2004 & 2005) were far more extensive and resulted in more robust conclusions about the course of the nerves and ramification patterns towards the soft palate muscles. Shimokawa et al. in 2004, who mainly focussed on the LVP and the superior constrictor, did not report any contribution of the lesser palatine nerve to the supply of LVP. In another manuscript Shimokawa et al. concluded in 2005 that the LVP and PP are innervated by the lesser palatine nerve and the pharyngeal plexus. Subsequently in this second manuscript nerve staining was performed by Shimokawa et al., which could explain the finding of the small lesser palatine nerve innervating part of the soft palate.

Furthermore Shimokawa et al. (2005) assumes that the hypothesis of Nishio et al. (1976) and Ibuki et al. (1978) that motor fibres of the facial nerve run inside the lesser palatine nerve in animals is also applicable to humans. Shimokawa et al. (2005) dissected the lesser palatine nerve but did not perform a functional characterization of the nerve fibres. Gray's Anatomy states that every branch of the trigeminal nerve contains afferent fibres, including the maxillary nerve from which the lesser palatine nerve is derived (Bannister et al. 1995). There is a possibility that lesser palatine nerve fibres which run to the LVP and PP contain sensory fibres only, namely for propriocepsis, pain and temperature information. There are examples in human anatomy where motor and sensory supplies of muscles go via different nerves. For instance, the trapezius muscle receives its motor supply from the spinal root of the accessory nerve and plexus cervicalis, whereas only the second, third and fourth cervical spinal nerves carry proprioceptive fibers from it (Tubbs et al. 2011). Another example are the facial muscles, which are efferently innervated by the facial nerve while their afferent fibers are part of the trigeminal nerve and end up in the mesencephalic nucleus (Bannister et al. 1995).

It would be useful to investigate the presence of motor fibres in the lesser palatine nerve by specific staining techniques. Sedlackova et al. did the only human study that assumes the involvement of the facial nerve innervating the LVP together with the pharyngeal plexus (Sedlácková et al. 1973).

Studies on the motor nerves to the soft palate muscles in animals had very conflicting results and seem to be less useful as a model for the human situation.

This review demonstrates crucial information for the cleft surgeon that innervation of the superior-extravelar part of the LVP and the PP enters the muscle form the lateral side. Subsequently the lesser palatine nerve enters from the lateral side of the inferior-velar nasal part of the LVP. Although this anatomy is applicable to the normal soft palate, it will likely be applicable to the cleft palate. During cleft surgery intravelar velar reposition is performed when the LVP is released from PP and retropostioned ventrally (Sommerlad 2003). This analysis suggests that during surgical dissection caution should be taken to dissect the dorsal/lateral aspect of the LVP from the PP because that is the area where the lesser palatine nerve enters the LVP. This theory is applicable to the von Langenbeck, two flap palatoplasty and also to the Furlow plasty. During the von Langenbeck procedure the LVP should be adequately released from the nasal mucosa (and a thin layer of PP) and care should be taken not to perform a rigorous dissection on the lateral side of the LVP.

CONCLUSION

This review of the literature demonstrates the lack of accurate information about the innervation of the levator veli palatini - and palatopharyngeus muscle. Most likely the lesser palatine nerve and the pharyngeal plexus dually innervate these two muscles. However, since the type of nerve fibres of the lesser palatine nerve is unclear, the role of the facial nerve in motor-innervating the soft palate is uncertain. The pharyngeal plexus plays a major role in innervating the levator veli palatini - and palatopharyngeus muscle and receive its motor-fibres from the accessory nerve. The tensor veli palatini is innervated by the mandibular nerve. This information should aid the surgeon during repair of the cleft palate.

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CHAPTER 7.

VELOPHARYNGEAL INSUFFICIENCY TREATED WITH LEVATOR MUSCLE REPOSITIONING AND UNILATERAL MYOMUCOSAL BUCCINATOR FLAP

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ABSTRACT

Introduction: Velopharyngeal insufficiency (VPI) is common (20-30%) after cleft palate closure. The myomucosal buccinator flap has become an important treatment option for velopharyngeal insufficiency, however published studies all use bilateral buccinator flaps. This study assesses the outcome of a unilateral myomucosal buccinator flap which might result in less operating time and might prevent the need of a bite block and an extra procedure for division of the flap pedicle at a later stage.

Methods: Forty-two consecutive patients who underwent a unilateral myomucosal buccinator flap procedure were retrospectively reviewed. Overall clinical judgment of speech, speech-analysis and velopharyngeal closure were evaluated by a multidisciplinary cleft-palate-team.

Results: Median follow-up was 1,2 years and in 83% optimal overall clinical judgment of speech was obtained and thus no further velopharyngeal surgery was necessary. In 7 patients further surgery was necessary of whom 57 percent (4/7) had bilateral cleft-lip-palate. Mean level of intelligibility improved significantly as evaluated by speech pathologists (2.5±0.9 vs 3.5±0.9;P< 0.0001) and by parents (2.1±0.9 vs 3.2±0.7;P< 0.0001). Mean level of resonance improved significantly (0.7±0.9 vs 2.0±1.0; P<0.0001) and velopharyngeal closure improved in 83% postoperatively.

Conclusion: The unilateral myomucosal buccinator flap seems to be an effective and safe procedure and should become part of the armamentarium of cleft surgeons.

INTRODUCTION

In patients with velopharyngeal insufficiency (VPI) effectively separating airflow between the nasal and oral cavities during speech fails due to insufficient palate length and/or mobility. This insufficiency of the soft palate and the lateral/posterior pharyngeal walls leads to hypernasality, nasal air emission and compensatory misarticulation, which decreases speech intelligibility (Sloan 2000; Johns et al., 2003; Lam et al., 2007).

Unfortunately, 20-30% of the primary cleft palate closures still have velopharyngeal insufficiency and often secondary surgery is imperative (Witt et al., 1998; Bicknell et al., 2002; Mahoney et al., 2013). Numerous treatments for VPI, both prosthetic appliances and surgical treatments, have been described. Treatment by using prosthetic appliances like palatopharyngeal obturators, palatal lifts, or pharyngeal bulbs are non-operative options (Tachimura et al., 2004; Pinto et al., 2007). However, most frequently either a posterior pharyngeal flap or a sphincter pharyngoplasty are used (Hynes 1950; Trier 1985; Rudnick and Sie 2008). Snoring, mouth breathing, obstructive sleep apnea (OSA), hyponasal speech, nasal mucous flow disruption, disrupted maxillary outgrowth and even death are complications reported in the literature (Sphrintzen 1998; Orr et al., 1987; Hill et al., 2004; Abyholm et al., 2005). A recent study from Madrid et al. 2015, demonstrated with polysomnography sleep studies that > 80% of cleft patients with VPI treated with a dynamic pharyngoplasty presented with obstructive sleep apnea > 1 year after pharyngeal surgery. Both the cranial based flap and the dynamic pharyngoplasty alter the anatomy of the lateral pharyneal walls and posterior pharynx, while other more recent described surgical techniques for VPI, like the double opposing Z-palatoplasty (DOZ) or the use of the bilateral buccinators myomucosal flap, pay more respect to the original anatomy of the velum during reconstruction (Hill et al., 2004; Chim et al., 2015). Hill et al., 2004 published the first experience of using a bilateral myomucosal buccinator flap in 16 VPI-patients after primary cleft repair, resulting in normal resonance in 87% of the patients postoperatively.

Two recent studies demonstrated that use of the buccinator myomucosal flap is an important surgical treatment option for VPI (Hill et al., 2004; Mann et al., 2011; Hens et al., 2013). However, these published studies all use bilateral myomucosal buccinator flaps to lengthen the velum. A unilateral myomucosal buccinator flap procedure hypothetically results in less operating time for patients. The incorporation of an oral mucosa Z-plasty, could impede the need for a bite block postoperatively to protect the buccal flap pedicle. More importantly, by using this new technique an extra procedure to divide the flap pedicle at a later date could be prevented. Additionally, by reconstructing the velum with a unilateral myomucosal buccinator flap the other contralateral flap is still available as a possible salvage option. Robertson et al. 2008, described the use of a unilateral myomucosal buccinator flap for the first time in secondary repairs of 20 cleft-patients suffering from velopharygeal insufficiency, oronasal fistulas or both. The small patient group, mixed indication for surgical treatment (only 7 patients suffered from VPI) and the fact that 50% of the patients were treated with additional palatoplasties

before the postoperative analysis for their study, question the effectiveness of this procedure (Robertson et al., 2008).

In this study, the effect of levator muscle repositioning and an oral Z-plasty in combination with a unilateral myomucosal buccinator flap for treatment of secondary velopharyngeal insufficiency was investigated in a group of consecutive cleft patients.

Patients and Methods:

We retrospectively reviewed 42 consecutive patients that presented with symptoms of secondary velopharyngeal insufficiency in the Wilhelmina Children's Hospital (2012-2014) who underwent a palatal Z-plasty with unilateral myomucosal buccinator flap procedure performed by the senior author. All patients that presented with velopharyngeal insufficiency after cleft palate surgery were included and no specific exclusion criteria were applied, specifically no exclusion of syndromic patients. In all patients the primary palatoplasty was performed by the modified Von Langenbeck technique.

The multidisciplinary cleft palate team in the Wilhelmina Children's hospital who participated in this study consists of three certified speech pathologists, an ENT-surgeon and a plastic surgeon. Optimal overall clinical judgment of speech was achieved when postoperatively speech improved such that no secondary surgery was needed. Speech analysis was performed by evaluating the level of of intelligibility and the resonance to assess hypernasality, which is the result of air escaping through the nasopharynx mainly when patients use vowels. The nasality was graded on a scale ranging from 0 (normal nasality) to 3 (severe hypernasality) by the speech pathologists. With the use of nasometry, a computer-based method to measure the ratio between the oral air escape and the nasal air escape during speech, the objective level of hypernasality was assessed. The Nasometer, Kay Pentax Model 6450, converts these measures to a percentage value for the nasalance score. The sentences produced by the child are displayed in table 1 and 2. These sentences contain both oral and nasal sounds, representing normal speech. In children < 8 years normal nasalance score was assessed in a range of 17-34% (2SD) and in 21-44%(2SD) in children ≥ 8 years (Van der Heijden et al., 2011).

TABLE 1: Oronasal sentences for children < 8 years of age to asses nasality by nasometry used in the Wilhelmina Children's Hospital (comparable to Zoo passage, excludes nasal consonants)

Miep is op school. [mip Is ɔp sɣol] (Miep is at school)
Nu gaat zij kleuren. [nu ɣat zɛi klørən] (Now she will colour)
Zij tekent de juf. [zɛi ˈtɛkənt də jɎf] (She is drawing the teacher)
Dat wordt heel mooi. [dɑt wɔrt hel moj] (This is becoming very beautiful)
Juf geeft Miep stickers. [jɎf ɣeft mip stIkərs] (The teacher gives Miep stickers)

TABLE 2: Oronasal sentences for children ≥8 years of age to assess nasality by nasometry used in the Wilhelmina Children's Hospital (11,67% of nasal consonants, corresponding to the English Rainbow passage (11,5%))

Papa en Marloes staan op het station. [ˈpapa ɛn Mɑrlus stan ɔp hət stɑʃɔn] (Daddy and Marloes are at the trainstation)
Ze wachten op de trein. [Zə wɑXtən ɔp də trɛin] (They are waiting for the train)
Eerst hebben ze een kaartje gekocht. [erst hɛbən zə en kartjə ɣəkɔɣt] (First they bought a ticket)
Er stond een hele lange rij, dus dat duurde wel even. [ər stɔnt ən helə lɑŋə rɛi] (there was a long queue, so it took a while)
Nu wachten ze tot de trein eraan komt. [ny ˈwɑXtən zə tɔt də trɛin ˈəran kɔmt] (Now they are waiting for the train to come)
Het is al vijf over drie, dus het duurt nog vier minuten. [Hət Is ɑl vɛif ˈovər dri, dɣs hət dyrt nɔɣ vir minytən] (It is five past three, so it will take 4 more minutes)
Er staan nog veel meer mensen te wachten. [ər stan nɔg vel mɛnsən tə wɑXtən] (there are more people waiting)
Marloes kijkt naar links, in de verte ziet ze de trein al aankomen. [ˈMɑrlus kɛikt nar lIŋks, In də ˈvɛrtə zit zə də trɛin ɑl ˈankomən] (Marloes looks to the left, she sees the train coming in the distance)

TABLE 3: Intelligibility score used by parents

1	Speech is understandable and normal
2	Speech differs from other children. This does not lead to comments and speech is understandable
3	Speech differs from other children. This leads to comments, but speech is understandable
4	Speech is poorly understandable
5	Speech is not understandable

TABLE 4: Intelligibility score used by speech-language pathologist in the Wilhelmina Children's Hospital

1	Always understandable for everybody without difficulty
2	Speech-disorder hearable, although understandable
3	Speech-disorder hearable, understandable with some difficulty
4	Speech-disorder hearable, understandable for family with some difficulty, however poorly understandable for strangers despite effort
5	Barely or not understandable for anyone despite effort

A description of the of intelligibility scores used by the parents and speech pathologists is presented in table 3 and 4.

Additionally, the ENT-surgeon carried out a nasopharyngoscopy before and one year after surgery to assess velopharyngeal closure. These results were scored in 3 different levels by the ENT-surgeon (inadequate, subadequate or adequate velopharyngeal closure, see table 5). All postoperative complications 1 year after follow up were noted.

The Wilcoxon signed rank test was used for data-analysis of the intelligibility scores and resonance. Data-analysis considering the relationship between the need of secondary surgery and multiple variables was conducted using the Fisher's Exact Test since the small amount of patients who needed secondary surgery (IBM SPSS statistics 21). A p-value of <0.05 was considered to be significant.

TABLE 5: Three different levels of velopharyngeal closure as assessed by the ENT-surgeon using nasopharyngoscopy.

Inadequate velopharyngeal closure	Velopharyngeal gap with no velopharyngeal closure and no closure movement to the posterior pharyngeal wall.
Subadequate velopharyngeal closure	Partial velopharyngeal closure, but still no complete closure against the pharyngeal wall or multiple small gaps where air is escaping.
Adequate velopharyngeal closure	Complete velopharyngeal closure, closure against the posterior pharyngeal wall.

SURGICAL TECHNIQUE

The palatal Z-plasty with unilateral myomucosal buccinator flap procedure differs from the bilateral procedure of Hill et al. (2004) and is presented in figure 1. First a Z-plasty (60 degree angles) of the oral mucosa is performed. This leads to adequate exposure to subsequently reposition the levator veli palatini muscle under the operating microscope in a more dorsal position in the soft palate. If there is tension in the nasal mucosa, another Z-plasty is made in the nasal mucosa. The two limbs of the oral mucosa are subsequently sutured, leading to lengthening of the oral mucosa. Next the buccal buccinator mucosa flap is performed from the patient's left side and subsequently placed between the two combining limbs of the oral mucosa Z-plasty. This flap is sutured to the nasal mucosa to prevent the levator muscle from moving ventrally during the healing phase. The flap is taken from the mid-part of the cheek just below the opening of the parotid duct. The base of the buccal flap and its pedicle are located in the retromolar trigone to prevent potential trauma of the pedicle by biting.

RESULTS

Patient characteristics

The median time of follow-up of 40 (of the total of 42) patients after surgery was 1,2 years (range 0,5 -2,1 years) and median age at time of surgery was 4,9 years (range 2,6- 17,6 years). One patient developed a psychiatric illness and was unable to be evaluated, but his caretakers described his speech as good and well understandable one year after surgery. Another patient experienced distal flap necrosis followed by a partial dehiscention of the flap. This resulted in a cranial based pharyngeal flap procedure 3 months postoperatively. Two patients had such a bad speech analysis after six months follow-up that the multidisciplinary decision was made to directly perform secondary surgery, explaining the lower limit range of 0.5 years. As presented in table 6, twenty-seven of the 42 patients in this study were male and fifteen female. All patients were diagnosed with velopharyngeal insufficiency after primary cleft surgery.

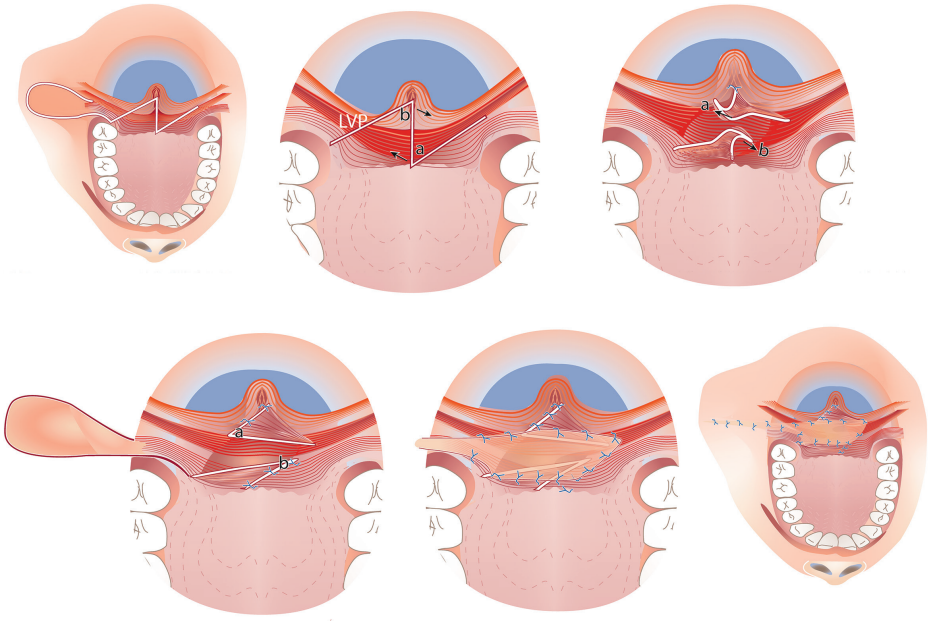

FIGURE 1: Surgical technique
The palatal Z-plasty and myomucosal buccinator flap procedure. First a Z-plasty of the oral mucosa is performed, followed by a Z-plasty of the nasal mucosa if necessary. Secondly, dorsal repositioning of the levator veli palatini muscle by using the operating microscope is performed. Next the two limbs of the oral mucosa are sutured which results in lengthening of the oral mucosa. Finally, the myomucosal buccinator flap is performed from the left side of the patient and subsequently placed between the two combining limbs of the oral mucosa Z-plasty, followed by closing of the donor site. The flap is sutured to the nasal mucosa to prevent the levator muscle from moving ventrally during the healing phase.

Eight patients suffered from a bilateral cleft-lip-palate, seventeen patients from a unilateral cleft-lip-palate and another seventeen from cleft palate alone (3 submucous clefts, 8 palatal clefts, 5 submucous clefts + bifid uvula and 1 bifid uvula). A total of eleven children were adopted and eight patients were diagnosed with a syndrome.

The speech pathologists evaluated of intelligibility in 40 patients (1 inadequate follow up and 1 patient had a complication as described before) pre- and postoperatively and the parents of 33 patients evaluated the intelligibility of their child. Resonance was scored in 38 patients and the nasalance-score measured by nasometry in eleven patients pre- and postoperatively. Speech pathologists did not assess hypernasality when the patient had underdeveloped speech or intellect, compensatory speech, the occurrence of a cold or bad cooperation.

TABLE 6: Patients characteristics

Patient #	Age at surgery (years)	Gender	Cleft type	Adoption	Syndrome
1	4.5	M	CLP-Bi	+	-
2	3.6	M	CLP-R	-	-
3	3.9	F	P	-	Robin
4	4.0	M	CLP-L	-	-
5	5.6	F	SC, BU	-	-
6	4.3	F	SC, BU	-	-
7	5.1	M	BU	-	-
8	6.7	F	SC	-	-
9	4.9	M	P	-	Robin
10	4.2	M	SC, BU	-	Auriculo Condylar Syndrome
11	6.3	F	P	-	Robin
12	3.6	M	CLP-R, BU	-	-
13	9.9	M	CLP-L	+	-
14	5.5	F	P	-	-
15	15.2	M	CLP-L	-	-
16	6.3	M	P	-	Robin
17	6.4	M	SC	-	-
18	17.6	M	SC	-	Robin
19	6.1	M	CLP-R	+	-
20	4.2	M	CLP-L	-	-
21	5.4	M	CLP-Bi	-	-
22	4.5	M	P	-	Van der Woude Syndrome
23	3.0	F	SC,BU	-	-
24	3.8	F	CLP-R	-	-
25	9.7	F	SC,BU	-	-
26	4.7	M	CLP-Bi	-	-
27	4.3	M	CLP-L	+	-
28	4.1	M	CLP-Bi	-	-
29	4.3	F	CLP-Bi	-	-
30	3.9	M	CLP-R	-	-
31	2.6	F	CLP-L	+	-
32	5.2	F	P	-	Beckwith Wiedemann Syndrome
33	3.2	M	CLP-Bi	-	-
34	4.3	M	CLP-L	+	-
35	4.1	F	CLP-R	+	-
36	9.4	F	CLP-Bi	+	-
37	4.9	M	CLP-R	-	-
38	8.6	M	CLP-Bi	+	-
39	6.3	M	CLP-L	+	-
40	6.3	M	CLP-L	-	-
41	5.0	M	P	-	-
42	4.9	F	CLP-L	+	-

M= male**, F=** female**, CLP-Le =** Left cleft lip palate, **CLP-Re =** Right cleft lip palate, **CLP-Bi =**Bilateral cleft lip palate, **P=** Palatocleft, **SC:** Submucous cleft, **BU:** Bifid uvula.

In 29 patients velopharyngeal closure was assessed with nasopharyngoscopy pre- and postoperatively by the ENT-surgeon. Nasopharyngoscopic evaluation was not possible in 13 patients either before or after surgery (only in 4 patients preoperatively, since this nasopharyngoscopic evaluation was an important part of decision to perform surgery) due to various reasons like too much mucus, insufficient cooperation of the patient or technical problems of the nasopharyngoscope. In 2 patients the clinical speech outcome was so good that nasopharyngoscopy was not performed postoperatively.

Results

In 83% (35/42 patients) sufficient speech outcome was achieved postoperatively. In 6 patients the combination of poor clinical speech outcome, poor improvement in level of intelligibility and resonance and/or inadequate improvement in velopharyngeal closure postoperatively made a secondary cranially based pharyngeal flap necessary. The one other patient that needed secondary surgery had the complication of the flap as described before. Four of the 7 patients in need of secondary surgery had bilateral cleft-lip-palate, the other 3 patients had unilateral cleft-lip-palate and none had a palatal cleft only. None of the patients in need of secondary surgery had a syndrome and there was no significant relationship considering gender (p=0,399) and adoption (p=0,319). The median age at time of unilateral myomucosal buccinator flap surgery of the patients who needed a secondary procedure was 4,3 years (range 3,2 - 4,9 years).

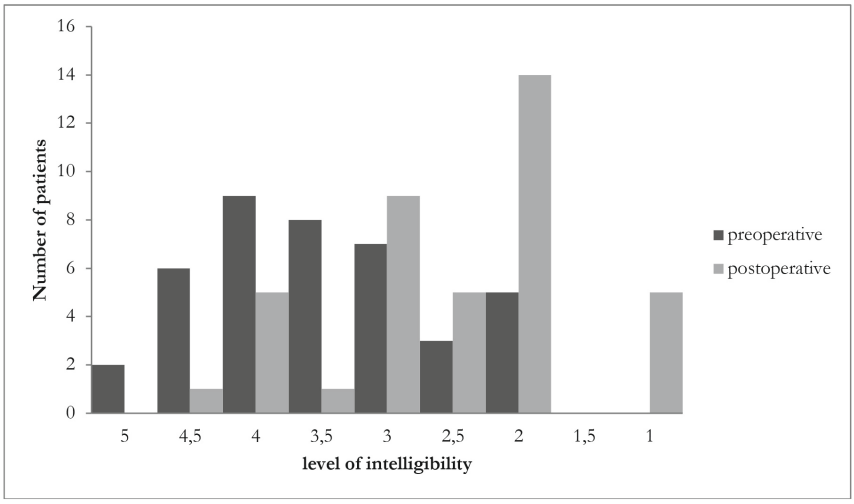

FIGURE 2: Intelligibility scores (n= 40) evaluated by the speech pathologists pre- and postoperatively

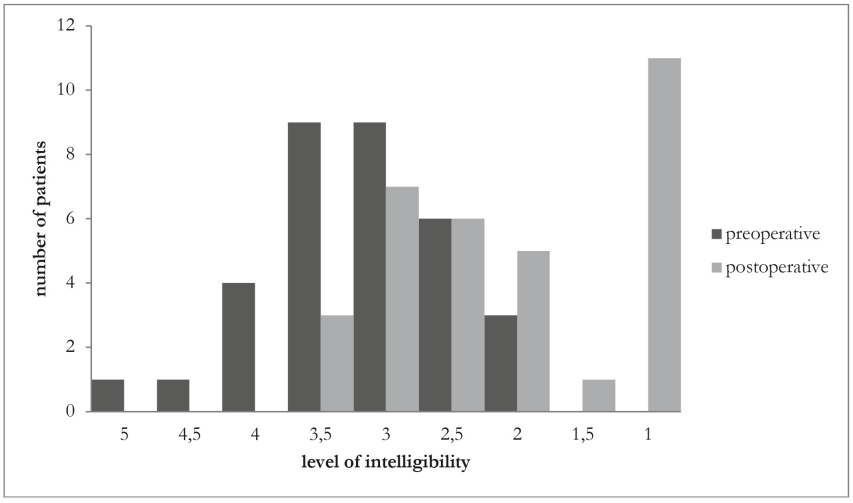

FIGURE 3: Intelligibility scores (n= 33) evaluated by the parents pre- and postoperatively

The intelligibility scores evaluated by the speech pathologist and the parents pre– and postoperatively are presented in figure 2 and 3. The level of intelligibility improved in 79% (26/33) and 80% (32/40) as evaluated by the parents and speech pathologists respectively. Mean level of intelligibility improved postoperatively significantly as evaluated by speech pathologists 2.5±0.9 vs 3.5±0.9 (P< 0.0001) and by parents 2.1±0.9 vs 3.2±0.7 (P< 0.0001) as presented in figure 4.

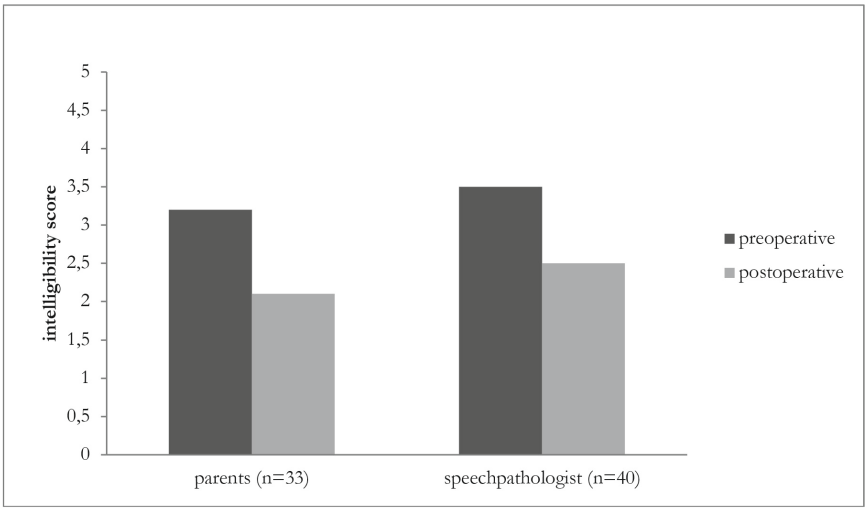

FIGURE 4: Mean level of intelligibility scores pre- and postoperatively.
Mean level of intelligibility improved postoperatively significantly as evaluated by speech pathologists 2.5±0.9 vs 3.5±0.9 (P< 0.0001) and by parents 2.1±0.9 vs 3.2±0.7 (P< 0.0001).

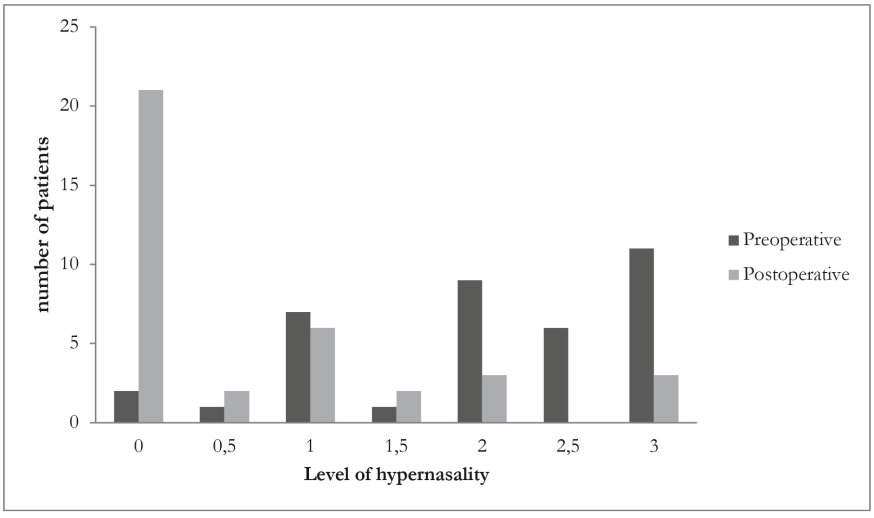

FIGURE 5: Resonance-scores (n=38) evaluated by speech pathologists pre- and postoperatively.
Resonance was graded on a scale ranging from 0 (normal nasality) to 3 (severe hypernasality).
The mean level of resonance improved significantly 0.7±0.9 vs 2.0±1.0 (P<0.0001)

TABLE 7: Results of the syndromic versus the non-syndromic patients

	Syndromic patients		p-value	Non-syndromic patients		p-value
	Preoperative (n)	Postoperative (n)		Preoperative (n)	Postoperative (n)	
Mean level of intelligibility - Speech pathologists	3.2±0.8 (7)	1.9±0.9 (7)	= 0.017	3.5±0.9 (33)	2.6±0.9 (33)	<0.0001
Mean level of intelligibility – Parents	2.9±0.7 (6)	1.5±0.8 (6)	= 0.027	3.2±0.7 (27)	2.2±0.9 (27)	<0.0001
Mean level of resonance	2.1 ± 0.5 (7)	0.4±0.5 (7)	= 0.015	2.0±1.0 (31)	0.8±1.0 (31)	<0.0001
Improvement in velopharyngeal closure	100% (5)			79% (24)		

Comparison of the syndromic versus the non-syndromic patients showed better results in all outcome measurements for the syndromic patients postoperatively. None of the syndromic patients needed secondary velopharyngeal surgery.

The mean level of resonance also improved significantly 0.7±0.9 vs 2.0±1.0 (P<0.0001) which is shown in figure 5. The median level of hypernasality in 8 patients improved from 43.5% to 25.5% (age <8 years 17-34% 2SD) and in 3 patients from 48.0% to 30.0% (age ≥ 8 years 21-44% 2SD) postoperatively.

Improvement of velopharyngeal closure was seen by nasopharyngoscopy in 83% (24/29); 41% (12/29) of these patients improved from inadequate to subadequate velopharyngeal closure and another twelve patients improved from subadequate to adequate velopharyngeal closure postoperatively. Comparison of the syndromic versus the non-syndromic patients showed better results in all outcome measurements for the syndromic patients postoperatively (See table 7).

DISCUSSION

This retrospective study demonstrates that the unilateral buccinator myomucosal flap is a valuable adjunct to the armamentarium of the cleft surgeon when confronted with velopharyngeal insufficiency in cleft patients. Optimal speech outcome was obtained in nearly 85%, with significant improvements in resonance and level of intelligibility respectively evaluated by the parents and the speech pathologists postoperatively. However, some strengths and potential limitations should be discussed.

This study included 42 consecutive patients with VPI, irrespective of the gap size found during nasopharyngoscopy. Further specification of the group of patients that are more likely to benefit from this technique is necessary, since in this present study

no specific exclusion criteria considering the extent of the velar gap before surgery was indicated. Most likely applying exclusion criteria would have resulted in better speech results and thus less revision pharyngeal surgery. Mann et al. (2011), described the effective bilateral opposing myomucosal buccinator flap procedure in a group in which wide velar gap patients were excluded. Only velopharyngeal dysfunction patients with good velar movement, <5 mm posterior velar gap and competent neurologic function of the velar musculature were included in his study. The fact that 57% (4/7) of the patients who underwent secondary cranially based pharyngeal flap surgery had bilateral cleft-lip-palate and that eventually 4 of the total 8 patients presenting with bilateral cleft-lip-palate needed secondary surgery, suggests that this technique is less suitable for patients with bilateral cleft-lip-palate and thus a wide velar gap assessed with nasopharyngoscopy. However, the relationship between bilateral versus unilateral cleft-lip-palate and the need of secondary surgery was not significant (p=0,156). All these 7 patients had preoperatively inadequate velopharyngeal closure and only 2 of these them improved to subadequate velopharyngeal closure postoperatively. Currently, the senior author tends to perform a bilateral myomucosal buccinator flap in patients with a bilateral cleft-lip-palate and wide velar gap.

In this study subjective outcome measurements (clinical speech outcome, resonance, intelligibility and velopharyngeal closure) were used by the members of the multidisciplinary cleft palate team to evaluate the extent of VPI. The evaluation of the resonance and intelligibility was scored by 3 different speech pathologists which could potentially lead to outcome bias. In the future research on the effectiveness of this unilateral myomucosal buccinator flap procedure by objective outcome measurements, such as palate length and size of velopharyngeal gap assessed by videofluoroscopy, and blind analysis of pre- and postoperative speech audio–video recordings, is mandatory. Additional research is also needed to determine the kappa value of inter-rater reliability for the resonance and intelligibility scores.

This new procedure has few wound complications; only one patient experienced partial flap necrosis requiring a cranial based pharyngeal flap procedure 3 months postoperatively. In all other 41 patients no complications of the donor site or flap necrosis were observed.

Although VPI is not uncommon following primary cleft palatoplasty, it is often believed that surgical procedures to treat VPI rarely result in obstructive sleep apnea (Hynes 1950; Trier 1985; Orr et al., 1987; Sphrintzen 1998; Sloan 2000; Johns et al., 2003; Hill et al., 2004; Abyholm et al., 2005 ; Lam et al., 2007, Rudnick and Sie 2008). However objective criteria analyzing possible sleep apnea after these surgical procedures are scarce. A recent study indicated that >80% of cleft patients with VPI treated with the widely used dynamic pharyngoplasty presented with obstructive sleep apnea > 1 year after surgery (Madrid et al., 2015). The presented unilateral buccal flap tries to create a more physiological anatomical reconstruction of the velum. Although not the scope of this study, prospective studies analyzing possible obstructive sleep apnea for this method are mandatory for comparison to other surgical methods treating VPI.

Compared to Hens et al. (2013), who described a success rate in 81% of his patients, this unilateral myomucosal buccinator flap procedure gives similar results, whereas it takes less operation time and avoids the need of a bite block to protect the pedicle after surgery (Mann et al., 2011; Hens et al., 2013). Moreover, this procedure is even more cost effective and less stressful for patients since it also avoids an extra procedure to divide the flap pedicle at a later stage. Additionally, by reconstructing the velum with a levator muscular sling a more physiological result is achieved. Another advantage of the unilateral flap is that the contralateral side is still available as a salvage procedure. The incorporation of the oral mucosa Z-plasty has several advantages. It will increase the exposure to the levator muscle to optimize the muscular reconstruction and it will also increase the length of the velum with the performed Z-plasty. Another advantage is that the buccal flap will fit nicely in between the two limbs of the Z-plasty subsequently avoiding the need of the bite-block since the flap will be at the retromolar trigone.

In the treatment of cleft palate patients with secondary velopharyngeal insufficiency, cleft surgeons should keep these benefits in mind and consider the use of the unilateral myomucosal buccinator flap procedure.

CONCLUSION

The levator muscle reconstruction with an oral Z-plasty and a unilateral myomucosal buccinator flap is a valuable adjunct to the armamentarium of the cleft surgeon in the secondary management of VPI following primary palatoplasty. This is an effective and safe procedure and has become a routinely practiced intervention for velopharyngeal insufficiency at our institution.

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8.

CHAPTER 8.

LONG-TERM SPEECH OUTCOMES OF CLEFT PALATE REPAIR IN PATIENTS WITH ROBIN SEQUENCE VERSUS ISOLATED CLEFT PALATE

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- The Annual Meeting of the Dutch Association of Plastic and Reconstructive Surgery in Ede, The Netherlands, 3th November, 2018.
- The American Cleft Palate-Craniofacial Association's 75th Annual Meeting in Pittsburgh, USA, 13th April, 2018.

ABSTRACT

Background: Whether treatment of cleft palate (CP) associated with Robin sequence (RS) should attain similar outcomes to 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. Fistula occurred in 5% of RS vs. 0% of ICP patients ($p = 0.049$). Velopharyngeal insufficiency (VPI) occurred in 41% of RS vs. 17% of ICP patients ($p = 0.012$) and in 60% of patients with syndromic RS vs. 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 to isolated RS, isolated RS compared to 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. We also demonstrate that patients with isolated RS should ultimately attain similar VPI outcomes compared to ICP patients. Obstructive speech operations in RS patients can be avoided without compromising speech outcome by reserving the Furlow procedure for secondary cases.

INTRODUCTION

Robin sequence (RS) refers to micrognathia, glossoptosis and upper airway obstruction with cleft palate present in 90% of cases (Robin 1923; Breugem and Mink van der Molen 2009; Breugem et al. 2016; Evans et al. 2011). In RS, there are unique challenges and considerations in the treatment of cleft palate, and questions remain about speech outcomes as compared to isolated cleft palate (ICP) (Witt et al. 1997; Goudy et al. 2011; Stransky et al. 2013; Hardwicke et al. 2016). In particular, it is 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 cleft palate characteristic of RS (Logjes et al. 2018; Latham 1966; Hanson and Smith 1975). 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 (Hanson and Smith 1975; Burg et al. 2016). Airway obstruction and congenital anomalies associated with RS make cleft palate treatment more challenging compared to ICP and often prompt modified approaches, such as delaying surgery. For some surgeons (including the authors) choice of primary repair technique depends on cleft anatomy and presence of airway obstruction, whereas for others, technique is independent of these factors (Witt et al. 1997; Khosla et al. 2008; Goudy, Ingraham, and Canady 2011; Patel et al. 2012; Stransky et al. 2013; Black and Gampper 2014; Morice et al. 2018; Basta et al. 2014).

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 (Logjes et al. 2018). 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") (Logjes et al. 2018).

Several studies have examined the treatment of cleft palate in patients with RS, with some investigating total RS cohorts and others comparing isolated RS versus ICP, or syndromic RS versus isolated RS (Witt et al. 1997; Khosla et al. 2008; Goudy et al. 2011; Patel et al. 2012; Stransky et al. 2013; Black and Gampper 2014; Morice et al. 2018; Basta et al. 2014; Filip et al. 2015; Lehman et al. 1995; de Buys Roessingh et al. 2008; Hardwicke et al. 2016). These previous studies describe the challenges associated with treatment of cleft palate in RS and variables possibly affecting outcomes, such as craniofacial anatomy, comorbidities, and associated airway treatments. Since 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 cleft palate repair at UCSF (1990-2016). Patients diagnosed with RCP or ICP (excluding submucous cleft palate) 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 (Vargervik et al. 2009). 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 to 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 cleft palate 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), cleft palate 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) (Jensen et al. 1988) 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.

TABLE 1: Patient characteristics

	RS patients (%)	**ICP patients (%)**	**p-value**
No. of patients			
Mean age at cleft repair in months	13.7 (SD 5.3)	11.3 (SD 5.1)	p = 0.004
Female-male ratio	39 : 36 (52:48)	56 : 27 (67:33)	p = 0.047
Furlow-SLIV repair ratio	13 : 62 (17:83)	56 : 27 (67:33)	p = 0.001
Surgeon 1 - Surgeon 2 ratio	67 : 8 (89:11)	61 : 22 (73:27)	p = 0.014
Jensen cleft classification*			p = 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**			p = 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)	-	

RS: Robin sequence, **ICP:** Isolated cleft palate, **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, **Width of the cleft palate:** 1 = narrow < 5 mm, 2 = medium ≥ 5 mm and < 10 mm, 3 = wide ≥ 10 mm and ≤ 14 mm, 4 = extremely wide ≥ 15 mm, **UAO** = upper airway obstruction, **TLA:** tongue-lip adhesion, **MDO:** mandibular distraction osteogenesis

* 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, 1 TLA + tracheostomy.

TABLE 2: Patient characteristics and outcomes between the two cleft surgeons

	Surgeon 1 (%)	Surgeon 2 (%)	p-value
No. of patients	128 (81)	30 (19)	
RS - ICP ratio	67:61 (52:48)	8:22 (27:73)	p = 0.014
Female - male ratio	77:51 (60:40)	18:12 (60:40)	p = 1.000
Furlow-SLIV repair ratio	54:74 (42:58)	15:15 (50:50)	p = 0.540
Jensen cleft classification*			p = 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**			p = 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)	p = 0.573
VPI	25 (31)	1 (10)	p = 0.271
Secondary Furlow	19 (24)	1 (10)	p = 0.450

* Jensen cleft classification was not reported in 12 patients.
** The cleft width was not reported in 4 patients.
RS: Robin sequence, **ICP:** isolated cleft palate, **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, **Width of the cleft palate:** 1 = narrow < 5 mm, 2 = medium ≥ 5 mm and < 10 mm, 3 = wide ≥ 10 mm and ≤ 14 mm, 4 = extremely wide ≥ 15 mm, **VPI:** Velopharyngeal insufficiency, **Secondary Furlow:** Secondary double opposing Z-plasty to resolve velopharyngeal insufficiency.

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 (Henningsson et al. 2008; Peterson-Falzone et al. 2017). 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 ± standard deviation (SD), median and range, or percentages. Categorical variables were compared using the Chi-square test or Fisher's exact test, 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, 128 of whom 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. Syndromic RS-patients were older at repair than isolated RS-patients (14.9 ± 6.4 months vs 12.2 ± 3.1 months; $p = 0.027$).

Of the 75 RS-patients, 26 were cleared for repair by pulmonology based on polysomnogram, 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.

TABLE 3: Reasons for cleft palate 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

RS: Robin sequence

TABLE 4: Characteristics of RS patients

	No. of 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 Congenita	1
Femoral Facial Syndrome	1
Fetal Alcohol Syndrome	1
Other associated anomalies or chromosomal abnormalities	25 (33)

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

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 was 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 Table 1 of the supplemental digital content. A wider and more severe cleft palate anatomy, and the diagnosis of RS (compared to ICP), respectively, demonstrated increased odds ratios for SLIV of 48.5 (95%CI: 13.1-180.3, p < 0.0001) and 8.0 (95%CI: 2.8-23.1, p = 0.0001).

TABLE 5: Characteristics of patients lost to follow up for speech evaluation

	patients lost FU no appropriate age (%)	patients included (%)	p-value
RS : ICP	7:13 (14:22)	44:47 (86:78)	p = 0.278
	Lost FU before the age of 4 years (%)	**included (%)**	**p-value**
RS : ICP	22:23 (33:33)	44:47 (67:67)	p = 0.953
s-RS : i-RS	9:13 (27:41)	25:19 (73:59)	p = 0.223
i-RS: ICP	13:23 (41:33)	19:47 (59:67)	p = 0.506

RS: Robin sequence, **ICP:** isolated cleft palate, **s-RS:** Syndromic Robin sequence, **i-RS:** Isolated Robin sequence, **FU**: follow up.

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 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. This data was available for 91 patients: 44 RS-patients (19 isolated, 25 syndromic) and 47 ICP-patients, with 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 one 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 was observed (Table 5). Two syndromic RS-patients were non-verbal due to cognitive language disorders and therefore excluded.

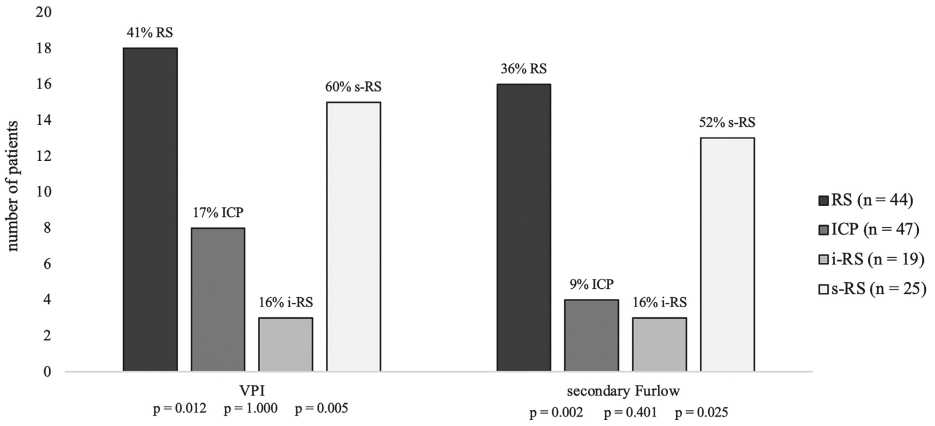

FIGURE 1: Rate of velopharyngeal insufficiency and secondary Furlow to resolve velopharyngeal insufficiency in the RS group (n = 44) versus the ICP group (n = 47), and subgroups isolated RS (n = 19) and syndromic RS (n = 25).

RS: Robin sequence, i-RS: Isolated RS, s-RS: syndromic RS, ICP: isolated cleft palate.

Velopharyngeal insufficiency 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 velopharyngeal insufficiency was performed in 36% of the RS group (n = 16) versus in 9% of the ICP group (n = 4), p = 0.002. Velopharyngeal insufficiency 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 velopharyngeal insufficiency 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, velopharyngeal insufficiency 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 velopharyngeal insufficiency was performed in 52% of the syndromic RS group (n = 13) versus 16% of the isolated RS group (n = 3, p = 0.025).

Velopharyngeal insufficiency

No difference in VPI rates between the two cleft surgeons were observed (Table 2). VPI was diagnosed in significantly more RS-patients than ICP-patients (41% vs 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% vs 17%; p = 1.000). In the RS-group, VPI was diagnosed significantly more often in syndromic RS than in isolated RS (60% vs 16%; p = 0.005) (Figure 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) cleft palate anatomy was associated eight-fold greater odds for VPI (OR: 8.2, 95%CI: 1.3-54.0, p = 0.028). Syndromic RS, compared to 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 to ICP) and initial tongue-lip adhesion in RS-patients (compared to RS-patients without tongue-lip adhesion) were also not associated with VPI.

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 vs ICP (15% vs 9%, p =.401). Thirteen syndromic RS-patients (52%) versus three isolated RS-patients (16%) underwent secondary Furlow (p = 0.025) (Figure 1).

TABLE 6: Multivariable logistic regression analysis for variables associated with RS to predict velopharyngeal insufficiency (n = 91 patients)

Variables	OR	95% CI	p-value
Age in months	1.01	0.92 - 1.10	0.895
Surgical airway intervention			
Robin sequence without TLA	Ref		
Robin sequence with TLA	1.30	0.28 - 6.05	0.741
Diagnosis			
Isolated cleft palate	Ref		
Isolated Robin sequence	0.58	0.11 - 2.96	0.511
Isolated Robin Sequence	Ref		
Syndromic Robin sequence	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

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 cleft palate:** 1 = narrow < 5 mm, 2 = medium ≥ 5 mm and < 10 mm, 3 = wide ≥ 10 mm and ≤ 14 mm, 4 = extremely wide ≥ 15 mm. 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
Please note: The use of SLIV or Furlow repair was determined by our surgical protocol of using SLIV in wider and more severe cleft palates. Therefore, this variable was the consequence of the variable "composite cleft palate anatomy", in statistics called "a mediator", and not included in this analysis.

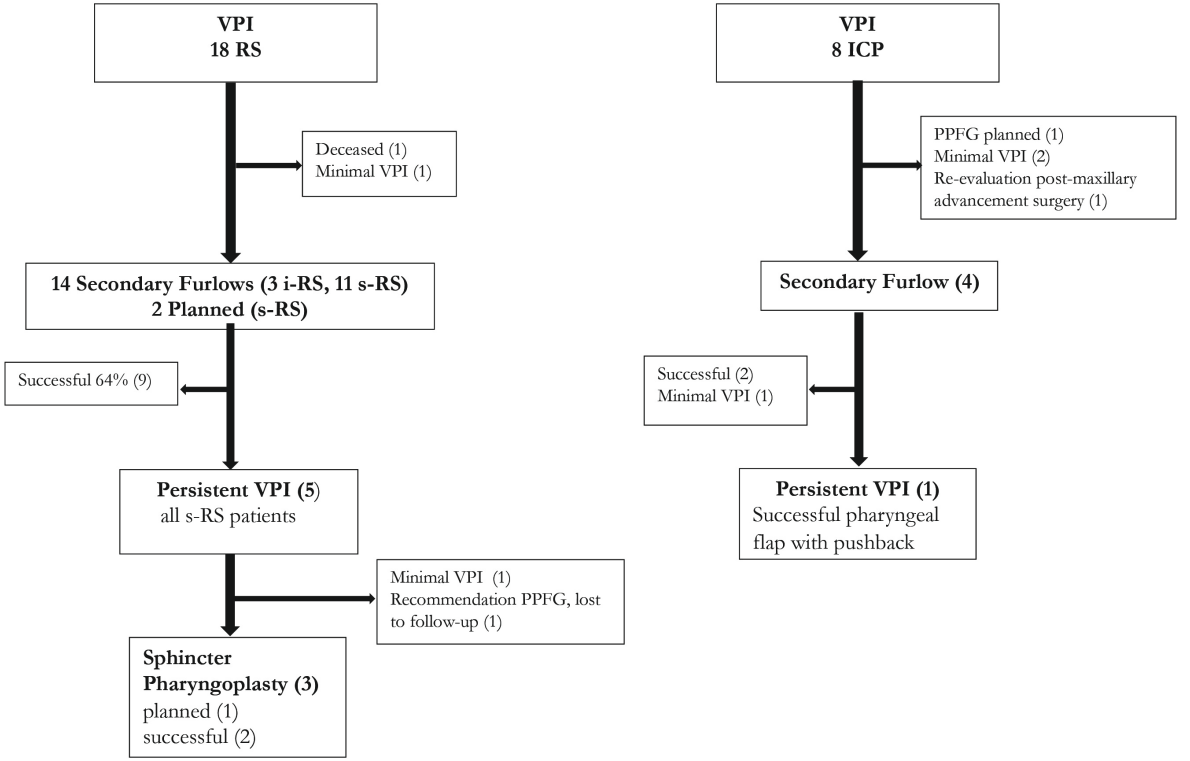

FIGURE 2: Speech operations to resolve velopharyngeal insufficiency.
RS: Robin sequence, ICP: isolated cleft palate, i-RS: Isolated RS, s-RS: syndromic RS, VPI: velopharyngeal insufficiency, PPFG: posterior pharyngeal fat grafting, Minimal VPI: velopharyngeal insufficiency without personal or social consequences, Successful: complete resolution of velopharyngeal insufficiency.

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).

TABLE 7: Rates of velopharyngeal insufficiency, secondary Furlow to resolve velopharyngeal insufficiency, and cleft speech characteristics in the aggregate of all speech evaluations and at the latest speech evaluation.

Patients	RS (%)	ICP (%)	p-value	s-RS (%)	i-RS (%)	p-value	i-RS (%)	ICP (%)	p-value
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 time of the latest evaluation, two had a planned secondary Furlow, one had a planned sphincter pharyngoplasty, and one had a planned secondary Furlow, but died during the follow-up period. **RS:** Robin sequence, **ICP:** isolated cleft palate, **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, **MCA:** Maladaptive compensatory articulation errors.

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 one 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.

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 (Landheer et al. 2010). Evaluation of anterior-to-posterior and side-to-side dimension demonstrated a wider and more severe cleft palate in RS, supporting previous descriptions (Filip et al. 2015; Godbout et al. 2014). 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 cleft palate patients and demonstrated cleft width to be an independent predictor (Lam et al. 2012; Mahoney et al. 2013; Leclerc et al. 2014; Lee et al. 2015; Yuan et al. 2016; Wu et al. 2017; Botticelli et al. 2020). 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.

Reported VPI rates in RS range from 0% to 58% (Witt et al. 1997; Khosla et al. 2008; Goudy et al. 2011; Patel et al. 2012; Stransky et al. 2013; Black and Gampper 2014; Morice et al. 2018; Basta et al. 2014; Filip et al. 2015; Lehman et al. 1995; de Buys Roessingh et al. 2008; Hardwicke et al. 2016). 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%)(Stransky et al. 2013; Morice et al. 2018; Hardwicke et al. 2016). 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 (Hardwicke et al. 2016). But cleft width was not included and may be

independently responsible for VPI in RS, as in non-RS cleft patients (Lam et al. 2012; Mahoney et al. 2013; Leclerc et al. 2014; Lee et al. 2015; Yuan et al. 2016; Wu et al. 2017; Botticelli et al. 2020). This latter conclusion is supported by our multivariable logistic regression analysis which identified a wider and a more severe cleft palate 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 to ICP suggests that inherent differences in cleft etiology or anatomy are similarly treatable with existing surgical techniques. Whereas several studies that compared isolated RS versus ICP would support this conclusion (Khosla, Mabry, and Castiglione 2008; Goudy, Ingraham, and Canady 2011; Black and Gampper 2014), two studies made contrary observations of higher VPI rates in isolated RS versus ICP (Witt et al. 1997; Stransky et al. 2013). 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 to ICP in our multivariable logistic regression analysis, lead us to conclude that similar VPI outcomes should be expected in isolated RS compared to 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 (Logjes et al. 2018; Basart et al. 2015; Gomez-Ospina and Bernstein 2016). As in our study, two prior studies found significantly higher VPI rates in syndromic RS compared to isolated RS (Patel et al. 2012; Morice et al. 2018). 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 (Morice et al. 2018). In our multivariable analysis, the odds of VPI for syndromic RS were increased (4.2) compared 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 (Logjes et al. 2018). 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. 2013. 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 (Hardwicke et al. 2016). 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 cleft palate repair in RS (Lehman et al. 1995; Hoffman et al. 1965; Costa et al. 2014; van Lieshout et al. 2016). The safety of our protocol may relate to later surgical timing in RS, choice of surgical technique, and to adequate interdisciplinary airway assessment prior to 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 (Abdel-Aziz et al. 2018). Another study found that of 7 isolated RS-patients that underwent a superiorly based pharyngeal flap for VPI, 6 developed OSA and subsequently required flap take-down (Abramson et al. 1997). Apart from the effect of secondary speech operations on the RS airway, our follow-up data on obstructive sleep apnea, together those from another study (van Lieshout et al. 2017), 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 which 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.

CONCLUSION

Patients with RS have features that necessitate individualized treatment protocols and that could possibly affect surgical and speech outcomes compared to ICP-patients. Patients with RS have wider and more severe cleft palate anatomy and airway compromise that resulted in delayed repair and greater use of straight line repair

with intravelar veloplasty. Despite different cleft palate etiology and the presence of several other RS- associated variables, our findings demonstrate that cleft palate anatomy is the only independent variable predictive of VPI in RS-patients compared to ICP-patients. Age at repair, syndromic RS compared to isolated RS, isolated RS compared to ICP and initial tongue-lip adhesion in RS are not predictive. Patients with isolated RS attain similar VPI outcomes compared to 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 cleft palate repair for patients with RS and their families.

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TABLE 1: Multivariate logistic regression analysis for SLIV technique compared to Furlow according to the authors' CP protocol

Variables	OR	95% CI	p-value
Diagnosis			
ICP	Ref		
RS	8.00	2.77 - 23.14	0.0001
Composite CP anatomy			
Width 1,2 & Jensen 1,2	Ref		
Width 1,2 & Jensen 3,4	2.86	0.75 - 10.97	0.125
Width 3,4 & Jensen 1,2	7.81	1.51 - 40.35	0.014
Width 3,4 & Jensen 3,4	48.52	13.06 - 180.33	< 0.0001

OR: Odds ratio, **CI:** Confidence interval, **RS:** Robin sequence, **ICP:** isolated cleft palate**, CP:** cleft palate, **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, **Width of the cleft palate:** 1 = narrow < 5 mm, 2 = medium ≥ 5 mm and < 10 mm, 3 = wide ≥ 10 mm and ≤ 14 mm, 4 = extremely wide ≥ 15 mm.

9.

CHAPTER 9.

LONG-TERM SPEECH OUTCOME IN PATIENTS WITH ROBIN SEQUENCE AFTER CLEFT PALATE REPAIR AND TONGUE-LIP ADHESION

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ABSTRACT

Introduction: Tongue-lip adhesion (TLA) is commonly used as a surgical treatment for upper airway obstruction (UAO) in patients with Robin sequence (RS). The effect on speech and articulation outcomes after TLA and subsequently cleft palate (CP) repair is insufficiently investigated.

Methods: All consecutive patients with RS (with or without TLA) versus isolated cleft palate (ICP) that underwent cleft palate repair were retrospectively reviewed. Speech and articulation included all assessments between the age of 3-6 years. Secondary speech operations, velopharyngeal insufficiency (VPI), hypernasality, and articulation errors by cleft type characteristics (CTC), including 4 categories: 1.Passive 2.Non-oral 3.Anterior-oral 4.Posterior-oral.

Results: 41 RS-patients (56% syndromic, 44% isolated) and 61 ICP-patients underwent repair with sufficient follow-up. Of them, 56% underwent a TLA at median age of 12 days. Rates of hypernasality ($p = 0.004$), secondary speech operations ($p = 0.004$) and posterior oral CTC ($p = 0.042$) were higher in RS compared to ICP. Isolated RS had similar speech outcomes compared to ICP, however syndromic RS-patients needed more secondary speech operations compared to isolated RS ($p = 0.043$). TLA-RS-patients did not demonstrate differences in speech outcomes or any CTC's (all $p > 0.05$) compared to non-TLA-RS-patients, except for the anterior oral CTC (74% TLA-RS vs. 28% non-TLA-RS, $p = 0.005$).

Conclusion: RS-patients have higher rates of hypernasality and needed more secondary speech operations compared to ICP-patients. In RS-patients, our findings demonstrated that TLA does not affect long-term velopharyngeal function. However, TLA-RS-patients demonstrated higher rates of anterior-oral CTC, that might be related to a different positioning of the tongue after TLA.

INTRODUCTION

Robin sequence (RS) is a congenital anomaly in newborns that was clinically defined in 1923 by the triad of micrognathia, glossoptosis, and upper airway obstruction (UAO) (Robin, 1923). RS may occur in isolation, as part of a syndrome (e.g. Stickler syndrome or Treacher-Collins-syndrome), or with additional anomalies or chromosomal defects but without a (yet) identified associated syndrome, classified as "RS-plus"(Tan et al., 2013; Basart et al., 2015; Breugem et al., 2016; Xu et al., 2016; Logjes et al., 2018). Cleft palate was added as an associated malformation, but is not considered a prerequisite for the diagnosis (Robin, 1923; Breugem et al., 2016).

Diagnostic criteria and treatments for RS vary widely among centers (Breugem et al., 2016; Logjes et al., 2021). If there is evidence of UAO that is not successfully managed by positioning alone, numerous operations e.g. mandibular distraction (MDO) or tongue-lip-adhesion (TLA) could be performed. In our center if there is evidence of UAO that is not successfully managed by positioning alone or by positioning and nasogastric feeding, a TLA is performed (Bijnen et al., 2009; Mermans et al., 2018).

TLA, first advocated by Shukowsky in 1911, is usually performed in the first few weeks of life and involves surgically tethering the tongue forward to the lower lip, relieving UAO caused by micrognathia and glossoptosis (Viezel-Mathieu et al., 2016). The procedure is usually reversed between 9 to 12 months of age at the time of palate repair (Bijnen et al., 2009).

The period from birth to 30 months of age includes critical phases in the acquisition of speech and language (Hasenstab, 1982). Patients with a cleft palate might develop difficulty with speech and language development due to velopharyngeal insufficiency (VPI) that can result in hypernasality in speech and multiple articulation disorders (Hasenstab, 1982; John et al., 2006; Spruijt et al., 2018). In addition, patients with RS and severe UAO who undergo TLA might develop extra difficulties in speech and/or articulation development. The tongue and lip are affected by TLA and these articulators are vital in the production of early developing speech sounds (LeBlanc and Golding-Kushner, 1992).

TLA is commonly used with current practice in Europe and United States ranging from 20-27% if surgical intervention is indicated (Scott and Mader, 2014; van Lieshout et al., 2015; Resnick et al., 2018). The long-term effect on speech and articulation outcomes after TLA and subsequently cleft palate repair is unknown. In order to improve care, this information would be of great value in counseling families of patients with RS, and for physicians and cleft speech pathologist involved in the care of patients with RS. The purpose of this study was to assess the effect of TLA on the long-term speech and articulation outcomes of patients with RS after cleft palate repair. These outcomes were compared to patients with RS who required positioning alone and to isolated cleft palate (ICP) patients. We hypothesized that TLA should not affect velopharyngeal function, but might interfere with long-term articulation outcomes.

MATERIALS AND METHODS

For this study approval by our institutional review board was obtained (number: FWA00017598). A retrospective chart review was performed of all consecutive patients with RS that underwent a Von Langenbeck repair with intravelar veloplasty between 1993 and 2014 at our centre and compared to patients with ICP. RS was defined as micrognathia, glossoptosis and UAO (Bijnen et al., 2009; Mermans et al., 2018).

In patients with "isolated", either in isolated RS or ICP, there was clear documentation of no associated syndrome or any other congenital anomalies after genetic evaluation. At our institution all patients received treatment by the multidisciplinary cleft team. This includes evaluation by a pediatrician and early genetic screening by a clinical geneticist to investigate for a possible underlying syndrome or for additional anomalies or chromosomal defects but without a (yet) identified associated syndrome (RS-plus), referred to as "syndromic RS". If no syndrome was found, we refer to these patients as "isolated RS".

A more detailed description of the performed TLA procedure for UAO is reported separately by one of the senior surgeons (J.P.D.G.) (Bijnen et al., 2009).

Cleft palate repair was performed between 9 to 12 months of age and in patients with RS plus TLA the takedown was usually performed at the same time. If preoperatively, cleft palate anatomy didn't allow one stage closure of the hard and soft palate, delayed repair of the hard palate was performed at a later stage, referred to as "remaining anterior cleft" in this article. Fistula was defined in patients that underwent a primary total cleft palate repair and later developed an oronasal fistula.

Data retrieved included date of birth, gender, cleft palate type (soft palate only or soft and hard palate), associated syndromes with RS, age at TLA (in days), age at cleft palate repair (in months), fistula, the need for a secondary speech operation to resolve VPI, if applicable the age at time of secondary speech operation (in years), and perceptual speech outcomes. This included binary speech outcomes (present or absent), without grading by a quantitative scale, for VPI, hypernasality, and articulation errors.

Perceptual speech assessment

The senior craniofacial speech pathologist of our multidisciplinary cleft team assesses speech outcomes at different ages using the Dutch cleft speech evaluation test (DCSET) (Spruijt et al., 2018; Meijer, 2003). During these perceptual speech assessments hypernasality and articulation errors are assessed live based on a short sample of connected speech or separate words and classified. In our retrospective analysis, all perceptual speech assessments between the ages of 3 and 6 years were included. Medical charts were reviewed by the third author (M.J.C) who has more than 20 years experience with assessment of speech of children with cleft lip and palate. The diagnosis of VPI as binary outcome was made if hypernasality and/or one of the passive cleft articulation errors were present during one of these assessments.

Patients with cleft palate can demonstrate consonant errors in articulation, the so called "cleft type characteristics" (John et al., 2006). These consonant errors can be categorized based on the nature of the error, primary in relation to the place of articulation in the oral cavity or pharynx. Therefore, these cleft type characteristics (CTC) were classified in four categories: anterior oral (retraction, palatalization, lateralisation, inter/addentality, fronting), posterior oral (backing) nonoral (glottal realization, glottal endorsement, pharyngeal fricative, active nasal fricative) and passive (nasal emission, nasal turbulence, nasal realization). All these 4 different CTC categories were assessed as binary outcome: present or absent.

Besides hypernasality, passive and nonoral articulation errors are indicators directly related to VPI, while the anterior-oral and posterior oral CTC in speech can also have other causes than VPI related to different oral morphology. These causes can include a fistula, dental issues and/or tongue problems like a misplaced tongue placement or a hypotonic or reduced mobile tongue muscle due to a short frenulum.

In patients with a fistula or a remaining cleft of the anterior hard palate at time of speech evaluation, nasal air loss due to VPI was distinguished from nasal air loss due to a fistula by temporary fistula closure of the fistula during the perceptual speech assessment of the senior cleft speech pathologist. In patients with significant nasal air loss due to inadequate velopharyngeal function, another speech operation in the form of a pharyngeal flap was performed to resolve VPI.

Exclusion criteria were as follows: (1) patients with severe mental retardation as this could influence speech development and outcome (2) patients who were not assessed by our multidisciplinary cleft team pre- and postoperatively (3) patients who did not have speech assessments available between the age of 3 and 6 years (4) patients in which phonology was not completely developed by the time of speech assessment; and (5) patients with a submucous cleft palate.

Statistical analysis

Data was collected in Excel and analyzed using IBM SPSS version 25.0.
To compare the main outcomes between groups, contingency tables (with corresponding chi-square test or Fisher exact test) were used for the categorical variables. For normally distributed variables the independent samples t-test and for non-normally distributed variables data the Mann-Whitney U test was used. All data are given as frequency (percentage), mean ± standard deviation (SD) or median (interquartile ranges (IQR)) in case of categorical data, normal data and non-normal continuous data respectively.

If the type of cleft or the presence of a remaining anterior cleft differed significantly between comparing groups, we tested their association with the speech and articulation outcomes. In case of a significant association, we performed additional multivariable logistic regression analysis to correct for this difference when comparing groups. A p-value of <0.05 was considered statistically significant.

TABLE 1: Patient characteristics RS and ICP patients.

	RS (%)	ICP (%)	P-value
No. Patients	41	61	
Male: female ratio	17:24 (41:59)	24:37 (39:61)	0.831
Type cleft palate			0.001
Soft palate	10 (24)	36 (59)	
Soft + hard palate	31 (76)	25 (41)	
Median age at CP-repair in months (range)	9.3 (8.3 - 42.5)	9.4 (8.3 – 31.7)	0.79

Type of RS	**Syndromic RS(%)**	**Isolated (%)**	**P-value**
	23 (56) 6 Stickler syndrome (26) 1 Fragile X- syndrome (4) 1 Carbohydrate deficient glycoprotein syndrome (4) 1 Van den Ende-Gupta syndrome (4) 1 Trichorhinophalangeal syndrome (4) 1 22q11.2 deletion syndrome (4) 12 Other associated anomalies or chromosomal abnormalities (RS-plus) (52)	18 (44)	
Age at CP repair in months (range)	9.4 (8.5 – 24.5)	9.2 (8.3 – 10.6)	0.207
Total RS group	**TLA (%)**	**Prone positioning (%)**	
Treatment for UAO	23 (56)	18 (44)	
Time TLA in days (range)	12 (2-100)		

RS: Robin sequence, **ICP:** isolated cleft palate
Syndromic RS: underlying syndrome or additional anomalies or chromosomal defects but without a (yet) identified associated syndrome (RS-plus)
Isolated RS: there was clear documentation of no associated syndrome or any other congenital anomalies after genetic evaluation. **CP:** cleft palate. **TLA:** tongue-lip adhesion. **UAO:** upper airway obstruction.

RESULTS

Patient characteristics

After exclusion, a total of 41 consecutive patients with RS and 61 patients with ICP who required cleft palate repair, at median ages of 9.3 and 9.4 months (p = 0.79), respectively, were selected. Patient characteristics are presented in Table 1. The senior author (J.P.D.G.) performed the majority of the cleft palate repairs (n = 63, 21 RS vs. 42 ICP), followed by two other cleft surgeons (n = 22, 13 RS vs 9 ICP) and (n = 17, 7 RS vs.10 ICP) (p = 0.11). Cleft palate characteristics included: soft palate only in 24% of patients with RS vs. 59% of patients with ICP, and soft plus hard palate in 76% of patients with RS vs. 41% patients with ICP (p = 0.001).

Of the 41 patients with RS, 23 (56%) underwent a TLA vs. 18 (44%) who underwent prone positioning (Table 1). The median age for TLA was 12 days and the majority of 91% (21/23) patients had TLA-release during cleft palate repair (Table 1).

Twenty-three patients with RS had a syndromic diagnosis (56%) versus 18 (44%) isolated patients with RS. There was no difference in age at time of repair (9.4 vs 9.2 months, respectively, p = 0.207) (Table 1). Fifty-six percent (10/18) of the isolated patients with RS underwent TLA vs. 57% (13/23) of the syndromic patients with RS, p = 0.951.

Surgical outcomes

Surgical outcomes are demonstrated in Table 2 and Figure 1. Patients with RS required significant more delayed closures of the remaining anterior cleft of the hard palate (24%) compared to the patients with ICP (8%), p = 0.024. Fistula after primary closure of the total cleft palate that needed surgical repair occurred in 3 with RS and 3 patients with ICP, p = 0.61. Patients with RS needed more secondary speech operations to resolve VPI (51%) compared to patients with ICP (23%), p = 0.004. In the RS-group, patients with syndromic RS underwent significant more secondary speech operations to resolve VPI (61%) compared to patients with isolated RS (33%), p = 0.043. No difference was observed in secondary speech operations between isolated RS vs ICP (23% vs. 33%, p = 0.37) and between TLA-RS vs. non-TLA-RS (57% vs. 44% p = 0.54).

TABLE 2: Surgical outcomes RS and ICP patients

	RS (%)		**ICP (%)**	**P-value**
Delayed closure hard palate required	10 (24)		5 (8)	0.024
Delayed closure hard palate performed	8		2	
Timing closure (median years (IQR))	8.2 (3.6-10.0)		7.8 & 8.5 (N/A)	
Fistula	3 (7)		3 (5)	0.614
Fistula repair	3		2	
Timing repair (median years (IQR))	6.2 (3.2 – 9.7)		6.0 & 6.3	
Secondary speech surgery	21 (51)		14 (23)	0.004
	I-RS (%)	S-RS (%)		
	6 (33)	15 (61)		0.043
	TLA	No TLA		
	13 (57)	8 (44)		0.54
Pharyngeal flap	20		14	
Age (median years (IQR))	3.9 (3.2 – 7.4)		4.3 (2.9 – 10.2)	
Redo palate	1			
Age (year)	18.5			

RS: Robin sequence, **ICP:** isolated cleft palate, **S-RS:** Syndromic RS**, I-RS:** Isolated RS, **TLA:** tongue-lip adhesion, **IQR**: interquartile range

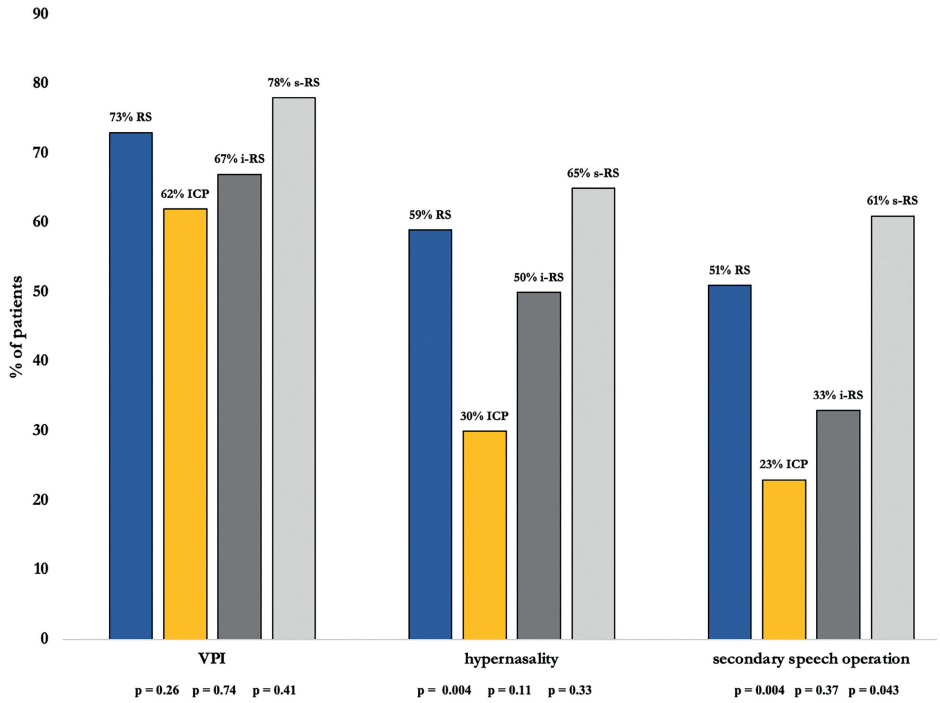

FIGURE 1: speech outcomes RS vs ICP, isolated RS and syndromic RS
RS: Robin sequence, ICP: isolated cleft palate, S-RS: Syndromic RS, I-RS: Isolated RS, VPI: velopharyngeal insufficiency

Speech outcomes

Median age at time of all speech evaluations was 4.5 years (range: 3.0-6.3) in the RS-group vs. 4.6 years (range: 3.3-6.3) in the ICP-group, p = 0.58. Mean number of included speech evaluations was 2.51 (SD ± 0.90) in patients with RS versus 2.15 (SD ± 0.77) in patients with ICP, p = 0.031.

Patients with RS (n=41) vs. patients with ICP (n=61)

Patients with RS demonstrated higher rates of hypernasality (p = 0.004) than patients with ICP, 59% (24/41) vs 30% (18/61) respectively (Table 3, Figure 1). When comparing the CTC-rates between the two groups, the RS group had more posterior oral speech CTC than the ICP group, 34% (14/41) vs 16% (10/61) (p = 0.042). There were no differences in VPI, passive, anterior-oral or non-oral CTC rates (Table 3, Figure 1).

There was a lower rate of hypernasality in the soft palate only cleft group, with 17% (8/ 46), compared to the soft and hard palate cleft group with 61% (34/56) (p < 0.001), and in the non-anterior cleft group with 35% (30/87) compared to the remaining anterior cleft group with 80% (12/15) (p = 0.001). After correction for type of cleft and the presence of a remaining anterior cleft using multivariable logistic regression, there was no significant difference in hypernasality (p = 0.16). For the articulation

outcomes only correction for the presence of a remaining anterior cleft was necessary and resulted in a non-significant difference in posterior oral CTC rates between RS and ICP (p = 0.21) (Table 3).

Syndromic patients with RS (n=23) vs. isolated patients with RS (n=18)
No difference was found for VPI or hypernasality rates between the isolated and syndromic patients with RS (p = 0.41, p = 0.33, respectively) (Figure 1). However, syndromic patients with RS underwent more secondary speech operations to resolve VPI (61%) compared to isolated patients with RS (33%) (p = 0.043).

Isolated patients with RS (n=18) vs. patients with ICP (n=61)
There was no difference in VPI rates, between isolated RS and ICP (p= 0.74), with 67% (12/18) compared to 62% (38/61), nor in hypernasality (p = 0.11) or required secondary speech surgery (p = 0.37) (Figure 1).

TABLE 3: Speech and articulation outcomes RS vs. ICP and TLA-RS vs non-TLA-RS

Patients	**RS (%)**	**ICP (%)**	**p-value**	**corrected p-values**	**TLA-RS (%)**	**non-TLA-RS (%)**	**p-value**
VPI	73	62	0.26	0.74 (0.021* & 1.0**)	78	67	0.49
secondary speech operations	51	23	0.004	0.035 (0.23* & 0.210**)	57	44	0.54
hypernasality	59	30	0.004	0.16 (0.002* & 0.070**)	65	50	0.36
CTC							
passive	51	57	0.54	0.15 (0.006**)	52	50	1.0
non-oral	24	25	0.98	0.71 (0.13**)	26	22	1.0
anterior oral	54	41	0.21	0.43 (0.046**)	74	28	0.005
posterior oral	34	16	0.042	0.21 (0.001**)	30	39	0.74

RS: Robin sequence, **ICP:** isolated cleft palate, **TLA:** tongue-lip adhesion, **VPI:** velopharyngeal insufficiency, **CTC:** cleft type characteristics

When comparing the RS-group vs. the ICP group the variables type of cleft palate & anterior cleft palate were both significantly different and demonstrated an association with the outcomes VPI, hypernasality and secondary speech operations, and therefore the corrected p-value was calculated to correct for these 2 possible confounders.
* p-value for type of cleft palate in corrected model
**p-value for the presence of an anterior cleft in corrected model

When comparing the RS group vs. ICP group the variable anterior cleft palate was significantly different and demonstrated an association with the outcomes passive, non-oral, anterior oral and posterior oral articulation groups, and therefore the correct p-value only included correction for the presence of an anterior cleft, to correct for this possible confounder.
For the comparison TLA-RS vs. non-TLA-RS, none of the variables was significantly different between these two groups.

Non-TLA-RS (n=18) vs. TLA-RS (n=23)
The TLA-RS-group had more anterior oral CTC with 74% (17/23) compared to 28% (5/18) in the non-TLA-RS-group (p = 0.005). There were no differences in rates of VPI (p = 0.49), hypernasality (p = 0.36), secondary speech operations (p = 0.54) and passive, non-oral or posterior oral CTC's (Table 3, Figure 2).

When zooming in on the different errors of the anterior-oral CTC-group, lateralization, inter or addentality and fronting demonstrated higher rates in the TLA-group, however, only retraction neared statistical significance (35% TLA-RS vs 6% Non-TLA-RS, p = 0.054) (Figure 3).

Isolated non-TLA-RS-patients (n= 8) compared to isolated TLA-RS-patients (n= 10).
No difference was found for VPI (p = 1.00), hypernasality scores (p = 0.64), secondary speech surgery (p = 0.64), or any of the 4 different CTC-categories. Nevertheless, a higher rate of anterior-oral CTC was seen in the isolated TLA-RS-patients, with 70% (7/10), compared to 25% (2/8) in the isolated non-TLA-RS-patients (p = 0.15) (Figure 3). Since a total of 18 patients could be included in this analysis, it should be stated that this analysis is underpowered.

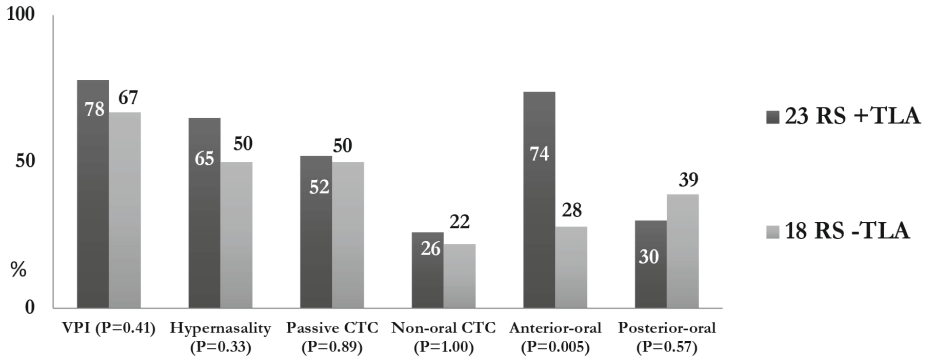

FIGURE 2: Speech and articulation outcomes TLA-RS vs non-TLA-RS
RS: Robin sequence, ICP: isolated cleft palate, VPI: velopharyngeal insufficiency, CTC: cleft type characteristics, TLA: tongue-lip adhesion.
These groups were not statistical significant different in type of cleft, therefore correction for type of cleft was not required.

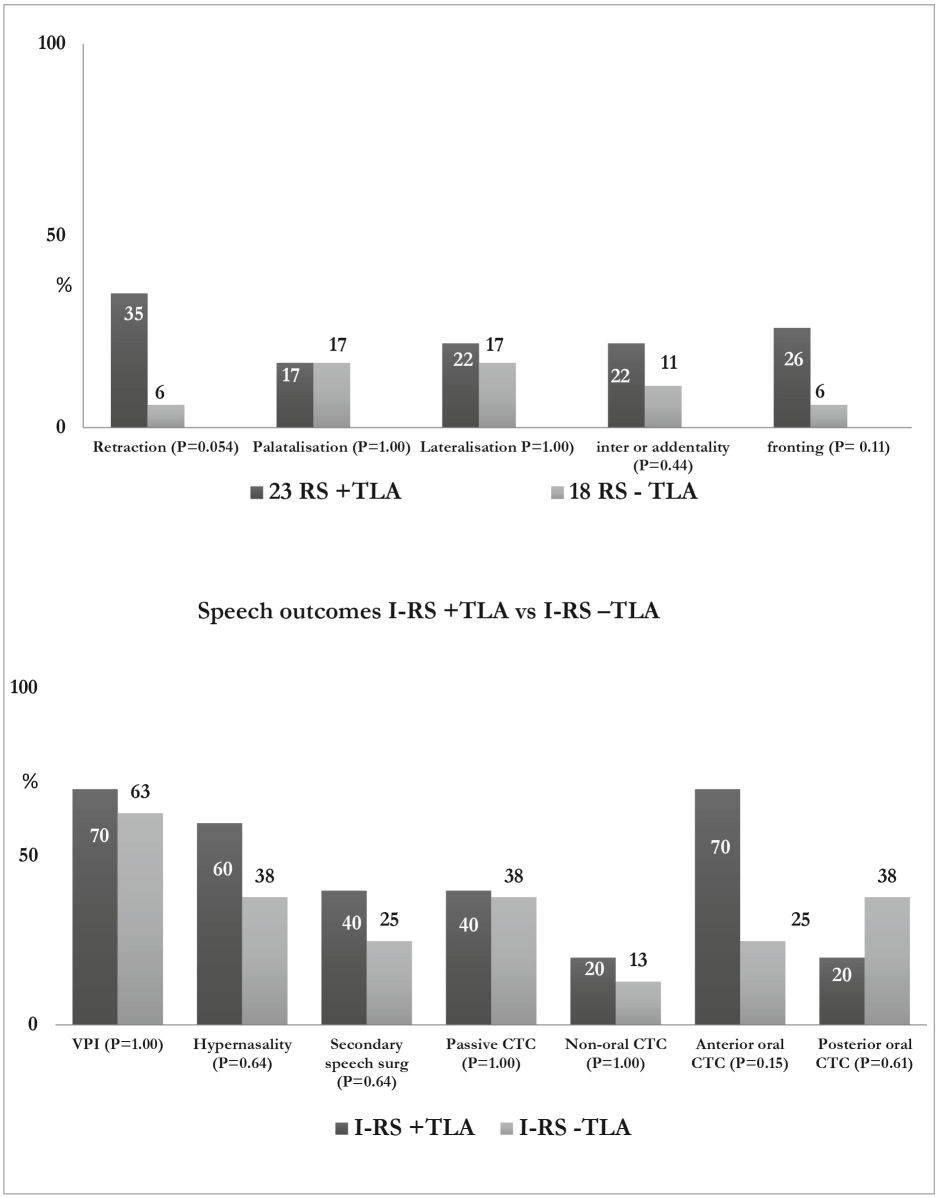

FIGURE 3: Anterior oral CTC TLA-RS vs non-TLA-RS and TLA-isolated-RS vs non-TLA-isolated RS
RS: Robin sequence, CTC: cleft type characteristics, TLA: tongue-lip adhesion, I-RS: Isolated RS, VPI: velopharyngeal insufficiency.
These groups were not statistical significant different in type of cleft, therefore correction for type of cleft was not required.

DISCUSSION

This study was initiated to assess the long-term effect of TLA on the long-term speech and articulation outcomes of patients with RS after cleft palate repair. To achieve this, we retrospectively compared these outcomes with a non-TLA-RS-group and with an ICP-group. We were able to study comprehensively the effects of TLA on long-term speech outcomes that included assessments of hypernasality and articulation by different groups of CTC (John et al., 2006).

Our results showed that TLA-RS-patients have more anterior-oral CTC (74%), compared to non-TLA-RS-patients (28%), p = 0.005 (figure 2). LeBlanc et al. suggested that TLA seemed to disrupt early speech development by delaying sound production, but after detachment this development accelerated and TLA-RS-patients seemed to "catch-up" (LeBlanc and Golding-Kushner, 1992). However, they observed compensatory adaptations in lingual posturing that maintained after TLA-release which affected the production of lingua-alveolar phonemes in more than half of the patients with RS up to 18 months post-TLA-release. Although visual distortion in speech was observed by the use of the tongue blade instead of the tongue tip, the production of these lingua-alveolar sounds was judged to be accurate perceptually (LeBlanc and Golding-Kushner, 1992). The results of our study provide longer follow up when compared to Le Blanc et al., and could be explained by the effect of the TLA since the anterior oral CTC are associated with the placement of the tongue. Possible causes of this altered tongue placement post TLA could be scarring, neural injury caused by the pullout suture (dysphagia), long-term positioning of the tongue in a lower anterior position, or altered motoric brain innervation.

If we look more specific in the different errors of the anterior-oral group, lateralization, inter or addentality and fronting demonstrated higher rates in the TLA-RS-group, however, only retraction neared statistical significance, p = 0.054 (Figure 3). Cleft speech pathologists who work with this population should be aware of the potential lingual articulation errors with patients who present with a history of TLA.

We did not find any difference between TLA-RS-patients and non-TLA-RS-patients on long term speech outcomes. This is in line with previous research that investigated VPI outcomes in patients with RS and a TLA for airway compromise (Stransky et al., 2013; Logjes et al., 2021). This can be interpreted in two ways: the severity of UAO on itself does not correlate with long-term speech outcomes or the effect of the surgical procedure TLA does not affect long-term velopharyngeal function. However, the indication to perform a TLA was not purely based on objective PSG data in all patients but on clinical assessment as well (Mermans et al., 2018). Sometimes in severe clinical cases, a TLA was performed after the patient needed to be intubated because of severe UAO. Therefore, we believe that our data suggests, as expected, that the surgical procedure TLA does not affect long-term velopharyngeal function.

The passive (nasal emission, nasal turbulence, nasal realization) and nonoral (glottal realization, glottal endorsement, pharyngeal fricative and active nasal fricative) CTC

are errors that are indicators directly related to VPI. Our previous finding that TLA does not affect long-term velopharyngeal function is confirmed by our demonstrated rates: passive CTC 52% TLA-RS vs. 50% non-TLA-RS (p = 1.00) and nonoral CTC 26% TLA-RS vs. 22% non-TLA-RS (p = 1.00).

Furthermore, the overall findings in our study suggest that surgical and speech outcomes are significantly worse for patients with RS compared to patients with ICP. Patients with RS require more delayed closure of the hard palate (24% RS vs 8% ICP, p = 0.024) and secondary speech surgery for VPI (51% RS vs 23% ICP, p = 0.004). Also, patients with RS had worse hypernasality scores (59% RS vs 30% ICP, p = 0.004) and worse posterior-oral CTC, in specific backing (34% RS vs 16 % ICP, p = 0.042), compared to the ICP-group.

Comparison of our findings with other published studies is challenging because of the variability of the comparison groups and outcome measures used. To date, several studies have investigated speech outcomes in patients with RS (Lehman et al., 1995; Witt et al., 1997; Khosla et al., 2008; de Buys Roessingh et al., 2008; Goudy et al., 2011; Patel et al., 2012; Stransky et al., 2013; Black and Gampper, 2014; Basta et al., 2014; Filip et al., 2015; Hardwicke et al., 2016; Morice et al., 2018; Kocaaslan et al., 2020; Gustafsson et al., 2020; Logjes et al., 2021; Schwaiger et al., 2021). However, these studies have reported both similar and contrasting results on speech outcomes. Two prior speech outcomes studies investigated speech outcomes and different articulations errors in patients with RS vs. patients with ICP (Hardwicke et al., 2016; Logjes et al., 2021). Hardwicke et al. found worse speech outcomes in patients with RS, with significantly more VPI, hypernasality, higher rates of posterior-oral and non-oral CTC and no differences in anterior-oral or passive CTC (Hardwicke et al., 2016). Logjes et al. investigated the passive and non-oral CTC and found besides higher VPI rates significant higher rates of non-oral CTC in patients with RS, which as previously stated, is an indicator directly related to VPI (Logjes et al., 2021). We found significant higher rates of the posterior-oral CTC in patients with RS, which is in line with Hardwicke et al. (Hardwicke et al., 2016), but does not directly correlate with VPI.

In this study, after statistical correction for cleft-type and/or presence of anterior cleft, no statistical significant difference was found between RS and ICP for hypernasality (p = 0.16) or posterior oral CTC (p = 0.21) (Table 3). This could suggest that the severity of the cleft plays a major role (p = 0.002) and the presence of an anterior cleft a minor part (p = 0.070) in defining the difference in hypernasality and not the RS sequence. Logjes et al. investigated predictors for VPI in patients with RS by multivariable logistic regression analysis, and found despite the different cleft palate etiology no increased odds for VPI in isolated patients with RS compared to patients with ICP. The only independent predictor for VPI was a more severe and wider cleft palate anatomy when controlling for different variables (Logjes et al. 2021). Other studies demonstrated cleft palate width to be an independent predictor for VPI in cleft lip and/or palate patients (Lam et al. 2012; Mahoney et al., 2013; Leclerc et al., 2014; Lee et al., 2015; Yuan et al., 2016; Wu et al., 2017; Botticelli et al., 2020). Patients with RS often have an U-shaped

cleft palate caused by the superiorly and posteriorly displaced tongue. A wider and more severe cleft palate might result in an impaired embryological development of the soft palate muscles compared to patients with a smaller and less severe cleft palate. After cleft palate repair, these factors may all contribute to a shorter and less mobile velum (Logjes et al. 2018; 2021).

In our previous cited studies the VPI rates found ranged from 0-58% in patients with RS (Lehman et al. 1995; Witt et al. 1997; Khosla et al. 2008; de Buys Roessingh et al. 2008; Goudy, Ingraham, and Canady 2011; Patel et al. 2012; Stransky et al. 2013; Black and Gampper 2014; Basta et al. 2014; Filip et al. 2015; Hardwicke et al. 2016; Morice et al. 2018; Kocaaslan et al. 2020; Gustafsson et al. 2020; Logjes et al. 2021; Schwaiger et al., 2021). We observed higher rates of VPI in our RS-group (73%) and in our ICP-group (63%) compared to the literature. This can be explained by our outcome diagnosis of VPI as binary outcome was made if hypernasality and/or one of the cleft articulation errors was present during one of the multiple assessments per individual patient. We did not assess VPI on a quantitative scale, ranging from mild to severe, and therefore for example patients who demonstrated no hypernasality but one single articulation error in the non-oral or passive groups, were diagnosed with the presence of VPI. When looking at the presence of hypernasality (59% RS vs. 30% ICP, $p = 0.004$) and the need for secondary speech operation (51% RS vs 23% ICP, $p = 0.004$), these rates are in line with the current literature.

Lastly, non-surgical treatment for airway compromise in patients with RS like the pre epiglottal baton plate approach with velar extension might replace most other forms of surgical treatment like a TLA if applied by a comprehensive cleft team in the future (Bacher et al. 2011). This pre epiglottal baton plate treatment has demonstrated excellent long-term results in many treatment aspects in patients with RS (breathing, sleep apnea, speech) and could help to avoid articulations errors in patients with RS in the future (Poets et al. 2019).

The present study is limited by its retrospective design and the completeness of the data that is determined by the level of accuracy of the previously reported medical files.

Therefore, we could only retrieve the severity of the cleft palate and not the exact length and width of the cleft. A recent study demonstrated that a wider cleft palate significantly correlates with a higher Veau classification (Wu et al., 2017). We assume this is also applicable for our RS and ICP cohort.

Regarding the surgical outcome of occurrence of fistula, we only included patients who had sufficient speech follow-up from the age of 3 years or older. Therefore, our present study might be subjected to selection bias. The speech outcomes were assessed by a two-level scale: present or absent. In statistics as applied to perceptual judgments, we learn that the fewer the rankings on a rating scale, the more valid and reliable the outcomes will be. The present study reported used perceptual speech analysis that was recently converted to a universal score for international comparison (Spruijt et al., 2018; Meijer, 2003).

Perceptual speech evaluation by speech pathologists is subjected to inter- and intrarater variability (Spruijt et al., 2018). In our study a total of 6 craniofacial speech pathologists assessed perceptual speech evaluations in our cohort of patients. However, this was not evaluated by audio and/or video recordings, making a calculation of the inter- and intrarater reliability not possible. In addition, speech outcomes can differ with age, however, age at speech assessment was not controlled for in our included speech assessments from 3 to 6 years.

Despite these limitations, we believe the present study demonstrates new insights in the long-term speech and articulation outcomes in patients with RS that undergo a TLA.

CONCLUSION

The present study demonstrated that patients with RS have higher rates of hypernasality and needed more secondary speech operations to resolve VPI compared to patients with ICP.

In patients with RS, our findings demonstrated that the surgical procedure TLA does not affect long-term velopharyngeal function. However, patients with RS and a TLA demonstrated higher rates of anterior-oral articulation errors, which might be related to a different positioning of the tongue after TLA. In patients with RS and a history of TLA, cleft speech pathologists who treat such patients should be more aware of this phenomenon in order to improve long-term articulation outcomes. This information is of great value in counseling families of patients with RS, and physicians and cleft speech pathologist involved in the care of patients with RS.

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CHAPTER 10.

ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE IN ROBIN SEQUENCE

A Comparison of Mandibular Distraction Osteogenesis and Tongue-Lip Adhesion

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ABSTRACT

Background: Numerous studies have proven the efficacy of mandibular distraction osteogenesis or tongue-lip adhesion in Robin sequence infants with upper airway obstruction. However, none have compared health-related quality of life outcomes.

Methods: In the present retrospective study, Robin sequence infants younger than 1 year, who underwent mandibular distraction osteogenesis or tongue-lip adhesion, were included (2006 to 2016). The infants' caregivers were asked to complete a questionnaire based on the Glasgow Children's Benefit Inventory.

Results: The response rate was 71 percent (22 of the 31 questionnaires; mandibular distraction osteogenesis, 12 of 15; and tongue-lip adhesion, 10 of 16) and median age at surgery was 24 days (range, 5 to 131 days). Median total Glasgow Children's Benefit Inventory scores after mandibular distraction osteogenesis and after tongue-lip adhesion were 21.9 (interquartile range, 9.4) and 26.0 (interquartile range, 37.5), respectively ($p = 0.716$), indicating an overall benefit from both procedures. Positive changes were observed in all subgroups emotion, physical health, learning, and vitality. In syndromic Robin sequence, both procedures demonstrated a lower positive change in health-related quality of life compared with isolated Robin sequence ($p = 0.303$).

Conclusions: Both surgical procedures demonstrated an overall benefit in health-related quality-of-life outcomes with no significant differences. The authors' findings contribute to the debate regarding the use of mandibular distraction osteogenesis versus tongue-lip adhesion in the surgical treatment of Robin sequence; however, studies evaluating health-related quality of life in larger Robin sequence cohorts are necessary to identify which procedure is likely to be best in each individual Robin sequence infant.

INTRODUCTION

Robin sequence (RS) is a congenital anomaly defined by the triad of micrognathia, glossoptosis, and varying degrees of upper airway obstruction, with or without a cleft palate (Robin 1923; Breugem et al. 2016). There are numerous continuing controversies related to the management of this condition (Evans et al. 2011; Breugem et al. 2016). In RS, the failure in mandibular outgrowth with the associated glossoptosis pushes the base of the tongue back into the oropharyngeal space. Subsequently, the elevated tongue can prevent the fusion of the vertical palatal shelves, leading to a cleft palate. Airway management due to glossoptosis is one of the greatest challenges for clinicians confronted with RS infants directly after birth; and treatment options vary according to the severity of the airway obstruction. Non-surgical interventions include prone or side positioning of the infant, a palatal baton plate or the use of a nasopharyngeal airway (Mondini et al. 2009; Evans et al. 2011; Bacher et al. 2011). When facing severe respiratory distress, surgical management, such as subperiosteal release of the floor of the mouth, tongue-lip adhesion (TLA), and mandibular distraction osteogenesis (MDO), are applicable, if used with the right indications, and could prevent the need for a tracheostomy (Breugem et al. 2008; Bijnen et al. 2009; Flores 2014).

Many authors have reported on the efficacy of both MDO and TLA. Recent studies indicate that MDO outperforms TLA. It should be noted, however, that MDO is a more complex surgical procedure with the possibility of more severe complications(Greathouse et al. 2016; Flores et al. 2014; Almajed et al. 2017). Based on objective polysomnography data and systematic review of the literature, MDO seems to have a better outcome regarding airway obstruction than TLA (MDO 4% vs. TLA 50%) (Almajed et al. 2017).

In addition to the traditional clinical evaluations, proxy and patient-reported outcome itself is being increasingly acknowledged as useful in assessing the result of surgical interventions. Health-related quality of life (HRQoL) is described as a multidimensional concept, which assesses physical, psychological, and social parameters(Guyatt, Feeny, and Patrick 1993). Clinicians should be aware that surgical interventions might affect many aspects of the daily life of patients, and that proxy and patient-reported outcome can be evaluated by assessing HRQoL.

Two recent studies assessed overall HRQoL in RS (Basart et al. 2017; Dulfer et al. 2016). To the best of our knowledge, there is only one study available in the literature that reported on HRQoL outcomes in both isolated and syndromic RS infants post-MDO (Hong et al. 2012). To this date, no study has reported on the comparison between HRQoL outcomes of MDO and TLA, although these patient and parents' perspective judgments could have a significant impact on deciding for either MDO or TLA as surgical treatment in RS infants. To address this, the present study compares HRQoL outcomes post-MDO and post-TLA in RS.

METHODS

All 31 consecutive RS infants, with severe respiratory distress after birth, that were primarily treated at an age younger than 1 year, using either MDO or TLA, in two tertiary medical centers (Wilhelmina Children's Hospital and VU Medical Center) between 2006 and 2016 were included in the present study. RS was defined as micrognathia, glossoptosis, and upper airway obstruction, with or without a cleft palate.

MDO was performed using a Lactosorb internal distractor from W. Lorenz Surgical; TLA was done by two opposite-based mucosal flaps with a supporting mandibular suture. A more detailed description of the two techniques is described separately by the two senior surgeons (C.C.B. and J.P.D.G.) (Bijnen et al. 2009; Breugem et al. 2012).

This study was approved by the medical ethical board (16/647). Informed consent was obtained from each caregiver of the RS infants.

To assess HRQoL, caregivers were asked to complete the Glasgow Children's Benefit Inventory (GCBI) questionnaire. The GCBI is a validated questionnaire that is suitable for the retrospective assessment of HRQoL in pediatric surgical interventions (Kubba, Swan, and Gatehouse 2004). The GCBI consists of 24 questions by means of which changes in HRQoL (as given by parents or caregivers) can be individually measured. The questionnaire is suited for measuring patient-related outcome after otorhinolaryngologic interventions. Answers are selected on a five-point Likert scale that ranges from "much worse (-2)" through "no change (0)" to "much better (+2)". We calculated the total GCBI-score after summing up all points, dividing by 24 and multiplying by 50. In addition to the total GCBI-score (ranging from -100 through 0 to +100), the subgroup scores "emotion", "physical health", "learning" were also calculated (Kubba, Swan, and Gatehouse 2004). One additional question was also introduced: All caregivers were asked if they would recommend MDO/TLA to other caregivers of RS infants with the same surgical indication. These 25 questions are given in Table 1.

After obtaining informed consent, the questionnaires were sent with a pre-paid return envelope to all of the caregivers of the RS infants that enrolled in the study. Medical files were reviewed to extract patient characteristics and postoperative complications related to MDO or TLA.

Statistical analysis was performed with IBM SPSS Statistics 24.0 (IBM Inc., NY, USA). Mean and median values of all GCBI-scores of the MDO- and TLA-group were calculated to conduct descriptive statistics. The distribution of quantitative data was tested by the Shapiro-Wilk test and depending on the normality this data was analyzed by the Independent T-test or the Mann-Whitney U-test. When comparing the MDO and TLA groups, the Mann-Whitney U-test and Kruskal-Wallis test were used to test for significant differences in the total GCBI-scores and subgroup scores.

TABLE 1: The Glasgow Children's Benefit Inventory to assess health-related quality of life as reported by Kubba et al.

	THE GLASGOW CHILDREN'S BENEFIT INVENTORY
1	Has your child's operation made his/her overall life better or worse?
2	Has your child's operation affected the things he/she does?
3	Has your child's operation made his/her behavior better or worse?
4	Has your child's operation affected his/her progress and development?
5	Has your child's operation affected how lively he/she is during the day?
6	Has your child's operation affected how well he/she sleeps at night?
7	Has your child's operation affected his/her enjoyment of food?
8	Has your child's operation affected how self-conscious he/she is with other people?
9	Has your child's operation affected how well he/she gets on with the rest of the family?
10	Has your child's operation affected his/her ability to spend time and have fun with friends?
11	Has your child's operation affected how embarrassed he/she is with other people?
12	Has your child's operation affected how easily distracted he/she has been?
13	Has your child's operation affected his/her learning?
14	Has your child's operation affected the amount of time he/she has had to be off nursery, playgroup, or school?
15	Has your child's operation affected his/her ability to concentrate on a task?
16	Has your child's operation affected how frustrated and irritable he/she is?
17	Has your child's operation affected how he/she feels about himself/herself?
18	Has your child's operation affected how happy and content he/she is?
19	Has your child's operation affected his/her confidence?
20	Has your child's operation affected his/her ability to care for himself/herself as well as you think they should, such as washing, dressing and using the toilet?
21	Has your child's operation affected his/her ability to enjoy leisure activities such as swimming and sports, and general play?
22	Has your child's operation affected how prone he/she is to catch colds or infections?
23	Has your child's operation affected how often he/she needs to visit a doctor?
24	Has your child's operation affected how much medication he/she has needed to take?
25*	Would you recommend your child's operation for the same surgical indication to other caregivers?

* An additional question was introduced: caregivers were asked if they would recommend MDO or TLA to other caregivers of RS-infants with the same surgical indication (yes or no).

RESULTS

Patients

In the overall study period, 60 RS infants were treated and followed at the Wilhelmina Children's Hospital, of which 21 RS infants underwent MDO (35%). Of these, 15 RS infants met the inclusion criteria and were eligible for the present study. In the VU Medical Center, 16 RS infants (70%) of the total 23 RS infants had TLA as surgical treatment for their respiratory distress, of which 15 RS infants could be included.

The response rate was 71% (22 of the 31 questionnaires, MDO 12/15 and TLA 10/16). All 12 MDO procedures were performed at the Wilhelmina Children's Hospital, and nine out of ten TLA procedures were performed at the VU Medical Center. Table 2 provides the characteristics of all 22 RS infants; 12 were girls, and ten were boys. A total of 13 infants had syndromic RS, and in five infants RS was found associated with anomalies or chromosomal defects. The median time of follow-up was 5.9 years (range 1.3–10.5 years). The median age at the time of surgery was 35 days for MDO (IQR 69) and 16 days for TLA (IQR 79) ($p = 0.176$). Mean age at administration of the GCBI was 7.4 years (SD 2.1) in the MDO-group versus 4.1 years (SD 2.6) in the TLA group ($p = 0.003$). The median lengths of hospital stay related to MDO and TLA were 28 (IQR 15) and 16 (IQR 33) days ($p = 0.262$), respectively. One infant in the MDO-group experienced a complication of device failure (unilateral dislocation of the distraction wire), and one RS infant that underwent TLA experienced partial dehiscence of the adhesion. Two infants needed additional surgical airway interventions: One infant was diagnosed with RS and Stickler syndrome needed a re-TLA 6 days after primary TLA, and was successfully extubated 2 days postoperatively. In follow-up, no respiratory problems occurred in this RS-infant after this re-TLA. Another infant that was diagnosed with RS and osteopathia striata with cranial sclerosis, continued to have respiratory difficulties after MDO that resulted in a delayed cleft palate repair at 3.1 years post-MDO. This cleft palate repair was preoperatively complicated by an intubation trauma with subsequent edema, requiring a tracheostomy for 24 days. Seven days after the tracheostomy, the cleft palate repair was performed successfully in this infant.

TABLE 2: Patient characteristics and individual total GCBI-scores

Patient	Age at surgery (days)	Gender	Syndromic/ Isolated	Syndrome	Surgery	Age at GCBI administration (years)	Total GCBI-score
1	83	F	isolated		MDO	10.2	22.9
2	15	F	syndromic	Stickler syndrome	MDO	9.6	20.8
3	19	F	isolated		MDO	9.2	8.3
4	17	M	syndromic*		MDO	9.0	25.0
5	48	M	syndromic**	Osteopathia striata with cranial sclerosis	MDO	8.4	12.5
6	94	F	isolated		MDO	8.6	41.7
7	45	F	isolated		MDO	6.8	34.4
8	24	F	syndromic*		MDO	6.6	18.8
9	24	F	isolated		MDO	5.0	25.0
10	93	M	syndromic	Hemifacial microsomia	MDO	5.9	18.8
11	17	F	syndromic	Stickler syndrome	MDO	5.1	29.2
12	87	F	isolated		MDO	4.0	20.8
13	109	M	syndromic	Peters Plus syndrome	TLA	9.0	- 4.2
14	15	M	syndromic	Cornelia de Lange syndrome	TLA	1.0	27.1
15	6	M	isolated		TLA	0.9	35.4
16	78	M	syndromic*		TLA	7.1	72.9
17	11	M	isolated		TLA	2.0	64.6
18	5	F	syndromic***	Stickler syndrome	TLA	3.4	- 87.5
19	16	F	syndromic*		TLA	4.0	35.4
20	36	M	syndromic*		TLA	2.7	16.7
21	7	M	syndromic	Fragile X-syndrome	TLA	5.2	8.3
22	131	F	isolated		TLA	5.3	25.0

M = Male, F = Female, MDO = Mandibular distraction osteogenesis, TLA = Tongue-lip adhesion, Syndromic = Robin sequence as part of a syndrome, Syndromic * = Robin sequence with associated anomalies or chromosomal defects, GCBI = Glasgow Children's Benefit Inventory.
** = This infant had a delayed cleft palate repair at 3.1 years post-MDO that was preoperatively complicated by an intubation trauma with subsequent edema, requiring a tracheostomy for 24 days. Seven days after the tracheostomy, the cleft palate repair was performed successfully in this infant.
*** = This infant needed a re-TLA 6 days after primary TLA and was successfully extubated 2 days postoperatively.

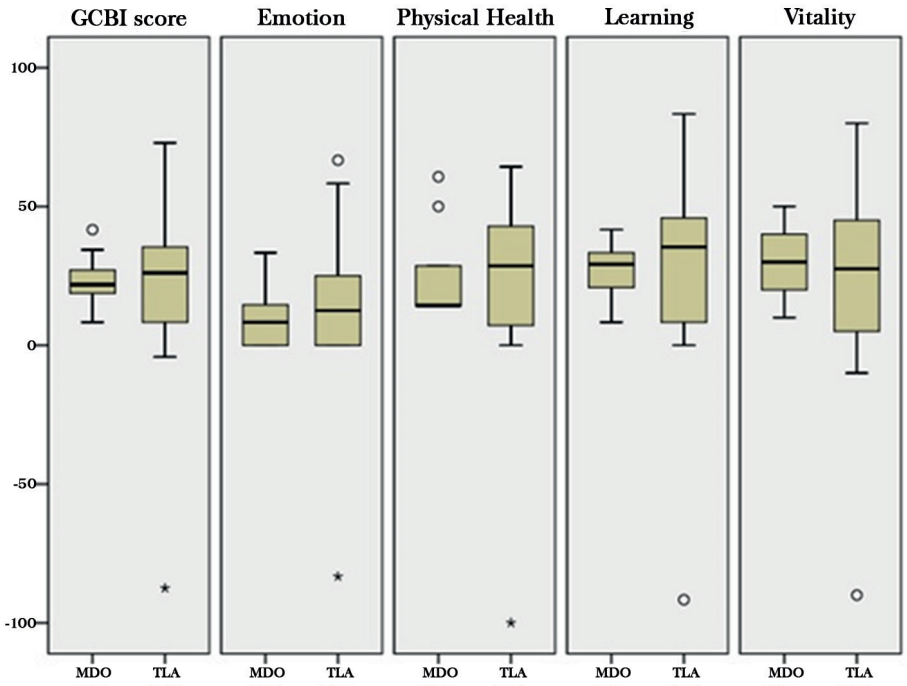

FIGURE 1: Box plot analysis of the total GCBI-scores and the subgroup scores post-MDO (n = 12) and post-TLA (n = 10).
MDO = Mandibular distraction osteogenesis, TLA = Tongue-lip adhesion, GCBI = Glasgow Children's Benefit Inventory.
Black lines in the boxes represent the median GCBI-scores. The bottom and top part of the boxes indicate the 1st Quartile (lower quartile) and 3st Quartile (upper quartile) of the data, respectively. T- and inverted T-lines stand for the maximum and minimum GCBI-scores, respectively. Outliers are marked with circles (o) representing mild outliers (GCBI-score > 1.5 IQR and < 3.0 IQR) and with asterisks (*) representing extreme outliers (GCBI-score > 3.0 IOR). All identified outliers appeared to be legitimate since the GCBI-score is ranging from -100 through 0 to +100.

Health-related quality of life

The median total GCBI-scores post-MDO vs. post-TLA were 21.9 (9.4 IQR) vs. 26.0 (37.5 IQR), and the mean total GCBI-scores were 23.2 (17.4–28.9 95%CI) vs. 19.4 (-12.3–51.0 95%CI) respectively, indicating an overall benefit from both surgical procedures. Table 3 and Figure 1 demonstrate all GCBI-score results of the MDO and TLA groups. Due to the wide range of 160 in the TLA group (Table 3 and the mild and extreme outliners demonstrated in the box plot in Figure 1), the distribution of the data was tested. Median scores seem more suited for comparing the GCBI-scores between the MDO and TLA groups since a non-parametric distribution of total GCBI-scores and all subgroup-scores was observed. The TLA-group had a slightly higher median total GCBI-score than the MDO-group (26.0 vs. 21.9, p = 0.716).

TABLE 3: GCBI-scores post-MDO (n = 12) and post-TLA (n = 10)

	Total GCBI-score	Emotion	Physical Health	Learning	Vitality
MDO (n = 12)					
Mean	23.2	8.7	24.7	27.8	30.0
95%CI	17.4-28.9	2.2-15.1	14.7-34.7	21.3-34.3	22.2-37.8
Median	21.9	8.3	14.3	29.2	30.0
IQR	9.4	15.6	25.0	14.6	20.0
SD	9.0	10.1	20.0	10.3	12.2
minimum	8.3	0	14.3	8.3	10.0
maximum	41.7	33.3	60.7	41.7	50.0
Range	33.3	33.3	46.4	33.3	40.0
TLA (n = 10)					
Mean	19.4	11.7	18.6	26.7	21.5
95%CI	-12.3-51.0	-17.3-40.6	-14.3-51.4	-8.8-62.1	-13.1-56.1
Median	26.0	12.5	28.6	35.4	27.5
IQR	37.5	33.3	39.3	49.0	51.3
SD	44.2	40.5	45.9	49.6	48.3
Minimum	-87.5	-83.3	-100	-91.7	-90
Maximum	72.9	66.7	64.3	83.3	80
Range	160.4	150.0	164.3	175.0	170
Normality*	0.759	0.763	0.733	0.768	0.817
p-value**	0.716	0.380	0.661	0.485	0.790

Legend: MDO = Mandibular distraction osteogenesis, TLA = Tongue-lip adhesion, GCBI = Glasgow Children's Benefit Inventory, CI = confidence interval, SD =Sstandard deviation, IQR: Interquartile range.
*Distribution of the total GCBI-scores and all subgroup scores in the 22 RS infants were tested using the Shapiro Wilk-test. This demonstrated a non parametric distribution of total GCBI-scores and all subgroup scores.
** Significant differences between the post-MDO group and the post-TLA group in GCBI-scores were analyzed by the Mann Whitney U-test. A p-value of < 0.05 was considered to be significant.

All median GCBI-scores of the subgroups (emotion, physical health, learning, and vitality) also indicated a positive change for both MDO and TLA (8.3 vs. 12.5, 14.3 vs. 28.6, 29.2 vs. 35.4, and 30.0 vs. 27.5 respectively, Table 3). Higher median GCBI-scores in the subgroups of emotion, physical health, learning, and vitality were observed in the TLA-group; although similar to the total GCBI-scores, none of the four subgroup scores were significantly different between the TLA and MDO groups (Table 3).

When comparing the infants with syndromic RS and those with isolated RS, no significant differences were observed in total GCBI-scores (Table 4). However, in both the MDO and TLA group, the syndromic RS infants demonstrated a lower positive change in HRQoL compared to the isolated RS infants (19.8 and 16.7 versus 24.0 and 35.4, p = 0.303).

TABLE 4: Total GCBI-scores in syndromic and isolated RS infants

	MDO Syndromic RS (n = 6)	MDO Isolated RS (n = 6)	TLA Syndromic RS (n = 7)	TLA Isolated RS (n = 3)	p-value*
Median Total GCBI-score	19.8	24.0	16.7	35.4	p = 0.303
IQR	8.9	18.5	39.6	-	
95% CI	14.8-26.9	13.4-37.6	-35.9-55.5	-9.3-92.6	

GCBI = Glasgow Children's Benefit Inventory, RS = Robin sequence, Syndromic RS = Robin sequence as part of a syndrome or with associated anomalies/chromosomal defects, MDO = Mandibular distraction osteogenesis, TLA = Tongue-lip adhesion, CI = confidence interval, IQR = Interquartile range.
* Significant differences between the 4 different groups in GCBI-scores were analyzed by the Kruskal Wallis-test. A p-value of < 0.05 was considered to be significant.

All caregivers of the 12 infants in the MDO-group indicated a positive change in HRQoL. In the TLA group, however, negative total GCBI-scores were found in two RS infants. The outcome of the additional question demonstrated that caregivers of one RS infant would not recommend MDO to other caregivers with the same surgical indication, whereas in the TLA-group, caregivers of two RS infants would not give this recommendation.

DISCUSSION

Numerous studies have reported on the clinical outcomes after MDO or TLA surgery to prove their efficacy (Almajed et al. 2017). In the latest studies that objectively compare these two surgical interventions, it seemed that MDO surgery achieves superior clinical outcome measurements, resulting in significantly less postoperative airway obstruction (Flores et al. 2014; Greathouse et al. 2016; Almajed et al. 2017). The present study found that the HRQoL outcomes after MDO and TLA are similar, with median total GCBI-scores of 21.9 (9.4 IQR) and 26.0 (37.5 IQR) respectively. Additionally, positive changes in GCBI-scores for the emotion, physical health, learning, and vitality subgroups were observed for both surgical interventions. No significant differences were found between the MDO and TLA groups.

Because a non-parametric distribution of total GCBI-scores and all subgroup-scores was observed, we decided to use the median scores to compare the GCBI-scores between the MDO and TLA groups. However, the cohorts were small and, if the mean scores were used, the total GCBI-scores remained comparable (23.2 for MDO and 19.4 for TLA), compared to the median total GCBI-scores of 21.9 and 26.0 for MDO and TLA respectively.

The GCBI is a well-designed and validated questionnaire that has been proven to be effective in assessing HRQoL for various surgical procedures in children of any age (mandibular distraction osteogenesis, bone-anchored hearing aid, otoplasty, cochlear

implantation and adenotonsillectomy) (Kubba, Swan, and Gatehouse 2004; Braun et al. 2010; Wood et al. 2011; de Wolf et al. 2011; Sparreboom, Snik, and Mylanus 2012; Hong et al. 2012; Kanmaz et al. 2013; Hao et al. 2013; Fan et al. 2014; Songu and Kutlu 2014). Our mean total GCBI-scores (23.2 and 19.4) are comparable to the mean total GCBI-scores after otoplasty reported by Braun et al. (24.1), Hao et al. (24.4) and Songu et al. (23.9), and after bone-anchored hearing aid fitting reported by De Wolf et al. (24.7). The results of the present study are less comparable to mean total GCBI-scores after placement of bone-anchored hearing devices reported by Fan et al. (45.6) and after adenotonsillectomy reported by Kanmaz et al. and Wood et al. (58.0 and 41.5). Unlike general questionnaires that assess HRQoL, the GCBI-questionnaire is advantageous because the items are directly related to the intervention, making it well-suited for otorhinolaryngologic interventions(Kubba, Swan, and Gatehouse 2004). The GCBI-questionnaire allows investigators to report on changes in HRQoL outcomes as reported by caregivers, after surgical intervention, without having to evaluate these HRQoL outcomes pre- and postoperatively. On the other hand, the GCBI-questionnaire could potentially confuse caregivers: some of the questions are not well-suited to the specific age group that was used in the present study (e.g., '*Has your child's operation affected his or her confidence?'*) (Table 1). This is a limitation of the GCBI-questionnaire, and we asked the caregivers to answer these non-applicable questions with 'no change'.

Hong et al. conducted the first study to assess HLQoL post-MDO, reporting a mean total GCBI-score of 54. This is higher compared to the present findings with median total GCBI-scores of 21.9 and 26.0 for MDO and TLA respectively and mean total GCBI-scores of 23.2 for MDO and 19.4 for TLA (Hong et al. 2012). This discrepancy might be because Hong et al. asked the parents to answer these non-applicable questions by thinking about their children in 'social settings' and how they would interact and play with other children (for example at play dates and daycare) at a later stage (personal communication with P. Hong November 3, 2016). The above limitations implicate the call for a new validated modified questionnaire for the specific age group as used in the present study. In addition, Hong et al. minimized the risk of recall bias by applying a maximum interval of 4 years between MDO and administration of the GCBI, that might also explain their higher total GCBI-scores.

Two other recent studies evaluated the overall HRQoL in RS infants but did not focus on a treatment intervention (Dulfer et al. 2016; Basart et al. 2017). In a sub-analysis of one of these two studies, parental distress seemed to be slightly higher in the MDO-group when compared to the TLA-group; this was similar to RS infants treated with a nasopharyngeal airway (Basart et al. 2017). Parental distress was not the focus of the present study. The other study focused on the impact of obstructive sleep apnea on HRQoL outcomes, and did not specify the surgical treatment that was performed to resolve the airway obstruction in each RS infant (Dulfer et al. 2016).

The strength of the present study is that the indication to perform either MDO or TLA was based on the center where the infant was treated, which was dictated by the surgeon's preference. In the study period, all infants admitted to the VU Medical Center

underwent TLA as surgical treatment of RS, once positional treatment resulted in unsatisfactory improvement. All RS infants with the same indication in the Wilhelmina Children's Hospital underwent MDO, except for one infant (this infant had clear glossoptosis but with a relatively normal mandible, and the surgeon opted for TLA instead of MDO). However, it remains questionable if the patient populations of the two centers in the present study are 100% comparable, especially because the overall number of RS infants seen in each center and the number of RS infants that underwent surgical treatment during the study period, were different. The indications to perform surgery were made by a multidisciplinary team in both centers, however, the exact reason could have differed per center. In addition, it is well-known that RS is a heterogeneous condition making a 100% comparison difficult and it is possible that the average degree of micrognathia could have been different between the two centers.

Since the wide variability of the results it is important to discuss the infants with the lowest and highest GCBI scores in both groups. In the TLA group the infant with the lowest GCBI-score (-87,5) had Stickler syndrome with congenital lobular emphysema of the left long and thyroid hemiagenesis. In addition, this infant underwent a re-TLA 6 days after the primary TLA that had a negative impact on the HRQoL outcomes reported by its caregivers. The other infant in the TLA group that reported a negative total GCBI-score (-4.2) had RS with the Peter Plus Syndrome and tracheomalacia that did not require surgical intervention. Both of these 2 infants had other respiratory problems rather than the upper airway obstruction caused by micrognathia and glossoptosis, that could potentially have influenced the HRQoL outcomes in these infants reported by their caregivers. The infant with the highest GCBI score (72.9) in the TLA group had no major anomalies except for myopia with proptosis and genetic analysis ruled out the diagnosis of Stickler syndrome. The infant with the second highest GCBI-score (64.6) had RS as an isolated condition. Interestingly, in the MDO group both the infant with the lowest GCBI-score (8.3) and the infant with the highest GCBI-score (41.7) had isolated RS.

Complications related to MDO-surgery include infection, hypertrophic scarring, ankylosis of the temporomandibular joint, mandibular growth disturbance, tooth and nerve injuries (inferior alveolar and facial), and device failure (Ow and Cheung 2008; Genecov et al. 2009; Master, Hanson, and Gosain 2010; Flores et al. 2014). Of all the 13 RS infants who underwent MDO in the present series, only one RS infant had a complication (device failure). The long-term effects of MDO within the present group remain unknown. A recent study evaluating children of 6 years and older after MDO demonstrated more root malformations of molars, shape anomalies, and positional changes after MDO compared to a control group (Paes et al. 2016). In the present TLA-group, one RS infant experienced dehiscence of the adhesion requiring a repeated intervention.

Although MDO is considered a more complex surgical intervention than TLA, this seemed to have less of an impact on HRQoL in RS infants, as demonstrated by the small differences between the total median GCBI-scores of 21.9 for MDO and 26.0 for TLA ($p = 0.716$).

However, we should be cautious when making assumptions/conclusions based on the present study, due to the small sample size, the response rate of 71%, and the wide range of GCBI-scores in the TLA-group. The results of the present study might be hampered by recall bias, because RS infants were included between 2006–2016 and a significant difference in median ages at administration of the GCBI was observed. This means there might be differences in accuracy or completeness of the caregivers' memory of the surgical intervention that could bias the HRQoL outcomes. Although, the numbers were too small to observe any potential association between age at administration of the questionnaire and the total GCBI-score, this should be taken in consideration when analyzing these HRQoL outcomes.

Nevertheless, the present study is the first to compare the HRQoL outcomes of MDO and TLA. These results are useful in the debate about the best surgical treatment in severe RS.

CONCLUSION

Both MDO and TLA demonstrated an overall benefit in HRQoL in RS. No significant differences were observed between MDO and TLA. The present findings contribute to the debate regarding the use of MDO versus TLA as surgical treatment in RS; however, long-term outcome studies evaluating HRQoL in larger RS cohorts are necessary to identify which procedure is best for the individual RS infant.

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11.

CHAPTER 11.
DISCUSSION

Robin sequence (RS) is a rare craniofacial anomaly with existing controversies in both diagnosis and its multidisciplinary approach. This thesis was initiated to provide better insight in different treatment strategies (analysis, assessment and approach) for patients with RS, with a special focus on long-term outcomes.

Understanding of the etiology/pathogenesis and optimizing treatment modalities should lead to better counseling by the involved physicians and should result in better educating and managing expectations of patients with RS and their families. This could also lead to a more shared decision making approach in the treatment of RS.

To date, there still remains controversy on the three characteristics that result in this craniofacial sequence. For example, on the website of the Genetic and Rare Diseases Information Center, which is a program of the National Center for Advancing Translational Sciences and is funded by National Institutes of Health in the United States, the triad is described as Pierre Robin sequence that includes the triad of micrognathia, glossoptosis and a cleft palate (National Center for Advancing Translational Sciences and Genetic and Rare Diseases Information Center 2021). However, the medical condition should preferably be called Robin sequence, and should include upper airway obstruction (UAO) while a cleft palate is not a perquisite for the diagnosis (Breugem et al. 2016; van Nunen, van den Boogaard, and Breugem 2018).

GENETICS

The goal of genetic evaluation is to identify the underlying etiology for the triad that patients with RS. Important information regarding associated health risks, guiding treatment choices and prognosis can be provided to family members and physicians involved (Hing, Mefford, and Cunningham 2012). Awareness of the associated health risks could affect the choice for (surgical) intervention. Its outcome is naturally of great importance, especially since a subgroup of patients with RS may need multiple (surgical) interventions throughout their lives.

Besides extensive family history and a full physical examination, medical geneticists have multiple confirmatory genetical tests available including karyotyping, fluorescence in situ hybridization (FISH), array comparative genomic hybridization (CGH), gene sequencing and metabolic studies (Hing, Mefford, and Cunningham 2012; Sanchez-Lara 2015).

In 2005 a new technique of massively parallel sequencing was introduced, referred to as "next generation" exome and genome sequencing. As reported in **chapter 2** the use of these new techniques, which became quickly cost effective and rapidly continued to develop, resulted in the first discovery of the underlying gene that was responsible for the phenotype of Miller syndrome (micrognathia, cleft lip and/or palate, hypoplasia or aplasia of the postaxial elements of the limbs, coloboma of the eyelids and supernumerary nipples). By only decoding the protein-coding exons of the genome, also called the 'exome', the genetic mystery of this rare craniofacial syndrome was solved.

Protein-coding genes account for only 1% of the human genome, however these genes bear the bulk of the mutations that could be causative to craniofacial diseases (Ng et al. 2010). Specific gene panels for craniofacial anomalies are emerging and will change genetic evaluation significantly in the future for patients with craniofacial anomalies (Sanchez-Lara 2015).

In **chapter 2** better understanding of the pathophysiology in RS was discussed and should be used as a starting point to a more personalized care in every individual patient with RS. Multiple mechanisms (extrinsic, instrinsic en neurological) were discussed that are involved in the development of the RS-phenotype. The increasing use of next-generation exome sequencing provides clinicians access to a more etiological diagnosis. Categorization of patients with RS based on etiological diagnosis was achieved by linking the RS-phenotype to the different embryologic, developmental and genetic mechanisms that include: *1. Collagen or bone development group* including the Stickler syndrome, Catel-Manzke syndrome, Kniest dysplasia, Osteopathia striata with cranial sclerosis, and the isolated form of RS. 2. *Neural crest group,* including the Treacher Collins syndrome, Miller syndrome and 22q11.2 deletion syndrome. 3. *Neuromuscular group* including congenital myotonic dystrophy, Carey-Fineman-Ziter syndrome and the Moebius syndrome 4. *Metabolic group*, including two types of congenital disorder of glycosylation 5. *Pharyngeal arch group,* including three types of Auriculocondylar syndrome 6. *Transcriptional defects group*, including the Glass syndrome 7. *RNA related group* including Mandibulofacial dysostosis, Acrofacial dysostosis, TARP syndrome, Cerebro-costo-mandibular syndrome and the Richieri-Costa-Pereira syndrome.

A newborn with RS can have other craniofacial features besides the triad of micrognathia, glossoptosis and UAO (or obstructive sleep apnea (OSA)) that could suggest the presence of an underlying syndromic diagnosis. Consultation by a medical geneticist is essential in the first multidisciplinary evaluation of each newborn with RS (Suri 2005; Breugem et al. 2016).

However, the clinical diagnosis of a newborn with a craniofacial syndrome can be challenging since only a limited number of syndromes present themselves with its craniofacial characteristics in the neonatal period. Characteristic craniofacial features of some syndromes are age dependent and may not be evident directly after birth. Therefore, it is important to schedule follow-ups in these patients to be informed on the development, growth and other clinical features that might emerge later on (Suri 2005). Re-evaluation of genetic diagnosis in patients with RS should be standardized, emphasized by re-assessment in a large cohort that changed initial genetic diagnosis in a quarter of all patients (Basart et al. 2015).

Future perspectives

All this genetic craniofacial knowledge on developmental malformations that is made available by next generation whole exome and genome sequencing should preferable be shared in international databases. Up on till today, there is no widely used instrument that collects data on clinical and genetic diagnosis (and their follow-up) that ensures

comparisons between different populations with RS and that has the potential to investigate genotype-phenotype correlations. A web-based application named *CranFlow-Craniofacial Anomalies: Registration, Flow, and Management* has recently been developed and could facilitate prospectively data collection on patients with craniofacial anomalies (Volpe-Aquino et al. 2018). This type of international database might result in a consistent genetic approach that is linked with clinical data that results in valuable information to develop and improve personalized treatment in patients with RS.

With the fast development of genetic diagnostic tools, an increasing number of patients and families with RS will have access to a confirmed underlying genetic diagnosis. In the future it would be desirable to provide personalized care for each individual patient with RS regarding different treatment options and prognosis based on the etiology of the sequence that originates from a genetic diagnosis, rather than purely navigate on clinical symptoms. As of today, the optimal treatment choice of neonatal UAO/OSA in patients with RS has been determined by clinical severity, ranging from conservative interventions for mild cases to surgical interventions for severe cases (Caouette-Laberge, Bayet, and Larocque 1994; Paes et al. 2015). The new classification (discussed in **chapter 2)** based on an etiological diagnosis rather than a clinical diagnosis has the potential to adjust treatment protocols because treatment and prognosis for each individual patient with RS may differ based on their underlying etiology. It would be desirable to include this etiological diagnosis more in clinical practice, in order to guide treatment decisions together with the clinical diagnosis that has been established by all involved clinicians. This more personalized treatment regime based on the etiological diagnosis of every individual patient with RS could also shed new light on the controversial "catch-up growth" of the mandible in patients with RS. Recent review of the literature demonstrated that a minority of objective studies suggest increased mandibular growth rates in isolated RS. Even fewer studies suggest that the maxillomandibular discrepancy in RS completely resolves (Purnell et al. 2019). The association between the underlying etiological diagnosis and mandibular morphology and eventual mandibular growth, could influence neonatal airway management in the future.

Future studies comparing craniofacial, pharyngeal and airway morphology and growth in patients with RS with different underlying etiological diagnosis are necessary to provide evidence for more optimal treatment choices and possible surgical planning (Glander and Cisneros 1992; Rogers et al. 2009; Chung et al. 2012).

MORTALITY AND ASSOCIATED GENETIC DIAGNOSIS IN RS

The importance of genetic evaluation as part of a multidisciplinary cleft team consultation and re-evaluations beyond infancy were also emphasized in **chapter 3.** In this chapter greater insight was gained into the mortality rate and the characteristics of deceased patients in a large cohort of 103 consecutive patients with RS. Ten percent died at a median age of 0.8 years (with a range of 0.1 – 5.9 years) and nine of these ten patients (90%) were diagnosed with an associated syndrome. Of these, seven patients died of respiratory insufficiency due to various causes (with only two related to the tongue based UAO). This stresses that clinicians should be more aware of respiratory problems in syndromic patients with RS, also after the first year of life (van Lieshout et al. 2017). These patients represented a heterogeneous patient population and were associated with a high level of underlying syndromes. Cardiac anomalies were observed in 41% and neurological anomalies in 36%. The mortality rate of 10% that was significantly associated with syndromic RS and the presence of neurological anomalies advocates that all patients with RS should be investigated for the presence of anomalies. By adopting a more universally accepted minimum "norm" of gene-analysis performed by the clinical geneticist, especially with the introduction of the next-generation sequencing, more patients with RS can be identified with an additional genetic condition in the future. **Chapter 3** demonstrated that a multidisciplinary approach in all patients born with RS, including genetic testing and examination of neurological anomalies in a standardized way, is crucial to identify patients with underlying syndromes potentially associated with an increased mortality risk.

OBJECTIVE MEASUREMENTS IN UPPER AIRWAY MANAGEMENT

In **chapter 4**, a systematic review of the literature was conducted to investigate the use of objective measurements in UAO/OSA management as indications for treatment and evaluation of outcomes for patients with RS. While families are counseled that a primary indication for treating early airway obstruction in RS is to protect long term brain development, we do not yet have the evidence to support this. Until we systematically assess UAO, including the proposed mechanisms (oxygenation, CO2 retention, OSA) driving the outcomes important to patients and families, the different interventions will not be based in evidence.

Objective assessments of UAO/OSA, both before and after interventions, are essential in evaluating patients with RS and to assess the impact of interventions, especially given the high rate of additional anomalies in RS and an associated mortality of 10–17% (Costa, Tu, et al. 2014) (**Chapter 3**). In addition, measurement of UAO/OSA is necessary because the absence of clinical respiratory distress or snoring does

not indicate the absence of UAO/OSA. The latter cannot be well characterized by clinical assessment alone, and the spectrum of UAO/OSA in patients with RS is broad (Anderson et al. 2011; MacLean et al. 2012; Cielo et al. 2016; Manica et al. 2018). The nature and severity of UAO/OSA may also change with growth or intervention (Wilson et al. 2000; Lee et al. 2015). A further complicating factor is the heterogeneous nature of this condition making 100% comparisons between centers challenging. Therefore, an objective assessment is essential to the evaluation of infants with RS and in assessing the impact of interventions. Quantifying UAO/OSA also allows for an objective comparison of treatment modalities and different centers, and builds an evidence-base to assist physicians treating UAO/OSA in patients with RS (Almajed et al. 2017).

Chapter 4 demonstrated a lack of standardized use, implementation and interpretation of objective measurements in the assessment of UAO and resulting in OSA in patients with RS. Polysomnography (PSG) was the most commonly used measurement, but PSG type and other essential variables (like indication, age, body position, duration, technique, and OSA scoring protocol), and interpretation of results varied or were lacking. Although oximetry was less commonly used as an evaluation measure, parameters from oximetry were frequently used to define treatment thresholds for UAO/OSA interventions. In total, 34 different definitions for treatment threshold were identified. Based on the results, a list of minimal reporting for future studies using PSG in patients with RS was suggested (listed below). The overall quality of the evidence to support treatment decision making for patients with RS and UAO remains low and practice variation persists.

List of minimal reporting for OSA treatment studies using PSG in infants with RS
1. Indication for preintervention PSG
2. Age in months at PSG
3. Body position (supine, side, prone, supine/side, supine/prone, supine/side/prone)
4. Time of day and duration of PSG recording
5. Equipment setup, including specific channels (AASM, other—specify reference or describe protocol)
6. Scoring protocol OSA (AASM, other—specify reference or describe protocol)
7. Thresholds that guide intervention decision (if applicable, specify measures and cut-off)
8. Age in months postintervention PSG to investigate treatment success

AASM = American Academy of Sleep Medicine, **OSA** = obstructive sleep apnea, **PSG** = polysomnography, **RS** = Robin sequence.

Future perspectives

Future work is needed to establish accepted definitions of the presence and severity of UAO and OSA in patients with RS. Clear reporting of objective measurement techniques to assess airway obstruction, guide decision making and evaluate outcomes is necessary in this high-risk population, as discussed in **chapter 4 & 5**. This thesis may serve as a starting point for future consensus recommendations to build a valid and useful evidence base approach in the assessments of UAO/OSA and its treatment in patients with RS.

CLEFT PALATE REPAIR

Velopharyngeal insufficiency (VPI) is present in up to 40% of patients following cleft palate repair (Sell et al. 2001; Britton et al. 2014). Most studies focus on the anatomical repair of the musculature of the cleft palate and do not mention the possible nerve damage that could result from the surgical dissection. However, for an optimal functional muscular repair of the soft palate, thorough understanding of the motor innervation of the muscles involved is essential. In **chapter 6** a literature review was performed that focused on recent advances in the understanding of the innervation of the soft palate. **Chapter 6** highlights the lack of accurate information about the innervation of the levator veli palatini - and palatopharyngeus muscles.

Only few studies have investigated the innervation of the soft palate muscles in humans. The innervation of the tensor veli palatini muscle by the mandibular nerve is universally accepted (Broomhead 1951; 1957; Doménech-Ratto 1977; Shankland 2001). However, knowledge about the exact innervation of the levator veli palatini - and palatopharyngeus muscles remains unclear. All authors mentioned the contribution of the pharyngeal plexus but details of their descriptions vary.

It is probable that the lesser palatine nerve and the pharyngeal plexus dually innervate the levator veli palatini - and palatopharyngeus muscles (Broomhead 1951; 1957; Sedlácková, Lastovka, and Sram 1973; Doménech-Ratto 1977; Shimokawa et al. 2004; Takashi Shimokawa, Yi, and Tanaka 2005). The exact course and distribution of these small nerve branches are discussed in this **chapter 6.**

The lesser palatine nerve innervates the small inferior-velar part of the levator veli palatini muscle and the anterior part of the oral part of the palatopharyngeus muscle, together referred to as the anteromedial region of the soft palate muscles (Takashi Shimokawa, Yi, and Tanaka 2005) The lesser palatine nerve runs through the lesser palatine foramen and ramifies in multiple small nerve branches. These branches run posteromedially underneath the palatine aponeurosis and the nasal part of the palatopharyngeus muscle. Close to the insertion of the levator veli palatini muscle in the midline of the velum almost all branches enter the muscle on its lateral surface (Takashi Shimokawa, Yi, and Tanaka 2005). However, since the type of nerve fibres of the lesser palatine nerve is still unclear, the role of the facial nerve in motor-innervating

the small inferior-velar part of the levator veli palatini muscle and the anterior part of the oral part of the palatopharyngeus muscle is uncertain (Takashi Shimokawa, Yi, and Tanaka 2005). There is a possibility that the lesser palatine nerve fibres which run through to the lesser palatine foramen to these muscles contain sensory fibres only, namely for propriocepsis, pain and temperature information.

Both the levator veli palatini - and palatopharyngeus muscle receive motor fibres from the accessory nerve (through the vagus nerve and the glossopharyngeal nerve, also referred to as the pharyngeal plexus). The pharyngeal plexus innervates the bigger superior part of the levator veli palatini muscle and the nasal and remaining oral part of the palatopharyngeus muscle, also referred as the posterolateral region of the soft palate muscles. The pharyngeal plexus nerves enter these muscles from the lateral side (Broomhead 1951; 1957; Doménech-Ratto 1977; Shimokawa et al. 2004; Takashi Shimokawa, Yi, and Tanaka 2005).

It has been agreed upon that cleft surgeons should perform a more careful dissection of the lateral side of the musculature. This knowledge may prevent nerve damage during surgical dissection and therefore may result in a better functional outcome and less complications in patients with cleft palate or VPI.

CLEFT PALATE REPAIR IN PATIENTS WITH RS

There exists a need for more evidence-based approaches in the surgical treatment of cleft palate in RS. Outcomes of cleft palate repair in RS were incompletely described because of limited patient cohorts and complexity of additional variables that include different etiology and anatomy, underlying syndromic diagnosis, a possible delayed repair, and neonatal airway interventions.

The significant and novel aspects of **chapter 8 and 9** advance understanding of cleft palate in RS and provide information that should be used in counseling families and predicting long-term speech outcome. These chapters demonstrated that patients with isolated RS should attain similar VPI outcomes compared to patients with isolated cleft palate (ICP) and suggested that inherent differences in cleft etiology or anatomy are similarly treatable with existing surgical techniques.

In **chapter 8** accurate anatomic description of the cleft palate (a combination of anterior-to-posterior and side-to-side dimension) was provided that permitted evaluation of its association with VPI. A wider and more severe cleft palate anatomy was the only factor independently associated with VPI, in contrast to age at repair, syndromic RS compared to isolated RS, isolated RS compared to ICP, and initial tongue-lip adhesion (TLA). These findings are statistically more robust compared to all the previous research, because we analyzed our variables in a multivariable logistic regression model. Therefore, we were able to answer the question: *Which associated variables can predict VPI in patients with RS?* This is a result of a higher level of statistical analysis and resulted in

more evidence-based conclusions compared to prior studies on speech in RS that were all unable to answer this question.

To date, several studies have investigated speech outcomes in patients with RS (Lehman, Fishman, and Neiman 1995; Witt et al. 1997; Khosla, Mabry, and Castiglione 2008; de Buys Roessingh et al. 2008; Goudy, Ingraham, and Canady 2011; Patel et al. 2012; Stransky et al. 2013; Black and Gampper 2014; Basta et al. 2014; Filip et al. 2015; Hardwicke et al. 2016; Morice et al. 2018; Kocaaslan et al. 2020; Gustafsson et al. 2020;). These 14 speech outcomes studies demonstrated the inconsistent reporting of essential variables that could potentially influence outcomes. Of these, 86% did not report cleft width and 36% did not report cleft palate type. Of the 64% of studies that did assess cleft palate type, the majority used the Veau classification (75%) and the remaining 25% used the Jensen cleft classification (Jensen et al. 1988). In addition, other variables including cleft palate repair technique, age at repair, age at speech evaluation and number of cleft surgeons were not reported in 14% each.

Future perspectives

A more evidence-based approach and standard way reporting these variables is essential in future cleft research in order to compare outcomes between different centers and patient populations. The accurate anatomic description of the cleft palate investigated in **chapter 8** could predict long term speech outcome in RS and can be used in counseling of patients with RS and their families.

Traditional measurements tools include a ruler, caliper (**chapter 8**) or transparent disk with millimeter marks, however recent work demonstrated a valid and reproducible 3-D assessment of cleft size and morphology by a high-resolution laser scanner or 3D stereophotogrammetry system of plaster casts of unilateral cleft lip and palate patients (De Menezes et al. 2016; Botticelli et al. 2019). Posterior hard palate cleft dimensions were found to be an indicator for the development of VPI (Botticelli et al. 2020). More work is needed to eventually use these type of 3D assessments directly in patients instead of plasters so that this might become a standard measurement in the cleft palate clinic.

The fact that all speech studies on RS analyzed their results in a univariate analysis fashion is notable. Future studies in cleft research in general (and specific in RS) should include multivariable analysis in order to attain high evidence scientific quality studies that can draw conclusions. In this thesis, in **chapter 9** multivariable analysis was applied to investigate the association of possible confounding variables with speech outcomes in order to compare treatment groups in a correct way. In **chapter 8**, multivariable analysis was used for a prediction model to identify risk factors for VPI, by controlling for all other variables.

In order to improve research in the field of cleft palate repair, we can hope that standard templates that are easily accessible in electronic medical record software, will be broadly incorporated in the daily practice of cleft surgeons. For example, a template for operative reports, that includes filling in mandatory fields for all variables (of interest) is easily build.

Applying deep learning to the development of high-performing and fast learning natural language processing models for medical text analysis is emerging (Senders et al. 2020). The steep learning curve demonstrated by these models based on machine/deep learning can be valuable especially for rare diseases or for institutions with lower patient volumes (Senders et al. 2020). These models could accelerate retrospective chart review and assemble clinical registries. This will pave the way for innovation in medical research and has the potential to put the extensive work to retrospectively recover patient data from medical records behind us.

CLEFT PALATE REPAIR IN PATIENTS WITH SYNDROMIC RS

The pathogenical heterogeneity of RS also complicates the associated treatment of cleft palate repair in these patients. Thus, meaningful evaluation of RS-associated cleft palate repair outcomes requires categorization of whether RS occurs in the presence of a syndrome or other congenital anomalies (syndromic RS/RS-plus), or not as an isolated entity (isolated RS) **(Chapter 2).** It is believed that the palatal shelves are intrinsically normal in isolated RS. All patients undergoing cleft palate repair may develop complications that affect velopharyngeal mechanism that can include scarring, palatal movement restriction, or nerve damage. Patients with RS and a syndromic diagnosis might have intrinsic developmental malformed palatal shelves and underlying intrinsic tissue characteristics that can affect the velopharyngeal mechanism, creating further challenges in cleft palate repair and subsequently achieving adequate speech outcomes.

These intrinsic factors can affect speech in distinct manners aside from the cleft palate, such as connective tissue diseases (collagen mutations) in Stickler syndrome (Patel et al. 2012; Basta et al. 2014; Jackson et al. 2020), hypotonia in 22q11.2 deletion syndrome (Widdershoven et al. 2008; Solot et al. 2019), palatal agenesis in Nager syndrome, nervous system disorders such as Moebius syndrome, mandibular hypoplasia in Treacher Collins syndrome or developmental disorders associated with other associated syndromes (Patel et al. 2012; Basta et al. 2014).

Future perspectives

Speech in patients with syndromic RS should preferably be investigated in future studies by differentiation based on etiological diagnosis, as emphasized in **chapter 2**, rather than investigate a heterogeneous group of "syndromic RS" patients (Basta et al. 2014; Jackson et al. 2020) This means international collaborations have to be made to combine patient's data with RS with similar syndromic diagnosis, to draw conclusions on speech outcomes in these syndromic patients (Patel et al. 2012; Basta et al. 2014).

CLEFT PALATE REPAIR TECHNIQUES

Two major cleft palate repair techniques, the straight-line repair with intravelar veloplasty and the Furlow Z-plasty technique are being used in patients with a cleft palate. Many articles have demonstrated good speech outcomes for both techniques. Controversy considering what technique results in optimal speech outcome remains, and 2 recent systematic reviews were not able to draw definite conclusions for patients with cleft palate only (Timbang et al. 2014; Stein et al. 2019). In patients with RS, the cleft palate anatomy and possible airway compromise can make cleft palate repair more challenging and more prompt for individualized treatment protocols. With respect to surgical technique for cleft palate repair**,** in **chapter 8**, tendency to use straight line repair with intravelar veloplasty in RS at UCSF is emphasized because of wider clefts and because it reduces the risk of worsening airway compromise as opposed to primary Furlow Z-plasty repair, in which greater lengthening, thickening and more posterior position of the velum occurs.

SPEECH OUTCOMES WITH OR WITHOUT TONGUE-LIP ADHESION IN PATIENTS WITH RS

In **chapter 8** the effect of TLA on the long-term speech and articulation outcomes of patients with RS after cleft palate repair has been investigated. This was performed by assessing not only hypernasality, VPI and the need for speech improving operations, but also different groups of articulation errors. The studied protocol in the Amsterdam Medical Center, location VU included the Von Langenbeck repair with intravelar veloplasty in all consecutive patients with RS or ICP. If the cleft palate anatomy didn't allow one stage closure of the hard and soft palate, repair of the hard palate was performed at a later stage. Patients with RS had higher rates of hypernasality and needed more speech improving operations to resolve VPI compared to patients with ICP between the age of 3 to 6 years old. Patients with isolated RS had similar speech outcomes to patients with ICP, which is all in line with the findings in **chapter 8.** The surgical procedure TLA did not affect long-term velopharyngeal function. However, patients with RS and a TLA demonstrated higher rates of anterior-oral articulation errors that might be related to long-term different positioning of the tongue after TLA. Possible causes of this altered tongue placement could be scarring, neural injury caused by the pullout suture (dysphagia), long-term positioning of the tongue in a lower anterior position, or altered motoric brain innervation. Therefore, it is emphasized that cleft speech pathologists should be more aware of these anterior-oral articulation errors in patients with a history of TLA, in order to improve long-term articulation outcomes.

SURGICAL MANAGEMENT FOR VPI

In the surgical management for VPI three distinct categories are available: 1. palate re-repair with muscle repositioning that includes secondary intravelar veloplasty, secondary Furlow Z-plasty and buccal myomucosal flaps, 2. pharyngoplasty procedures including pharyngeal flap or sphincter pharyngoplasty, and 3. posterior pharyngeal wall augmentation. In current practice for patients with cleft lip and/or palate a pharyngeal flap is the most common procedure (64%), followed by sphincter pharyngoplasty (24%), palate muscle repositioning (8%), and posterior pharyngeal wall augmentation (4%) (de Blacam, Smith, and Orr 2018). There is not yet a consensus regarding the specific choice of posterior pharyngeal flap versus sphincter pharyngoplasty for surgical treatment of VPI. Some centers/surgeons prefer one specific technique as the treatment of choice for velopharyngeal insufficiency regardless of velopharyngeal closure pattern (Armour et al. 2005). However, others advocate the importance preoperative assessment of the velopharyngeal closing pattern by nasopharyngeal endoscopy to choose what surgical technique is best suitable to resolve VPI (Gart and Gosain 2014). The sphincter pharyngoplasty seems suitable for coronal and circular patterns of closure with adequate velar motion, while the posterior pharyngeal flap is best suitable for a sagittal closure pattern with good lateral pharyngeal wall motion (Huang, Lee, and Rajendran 1998; Armour et al. 2005; Gart and Gosain 2014).
For all three categories of surgical techniques in patients with cleft palate there is a concern UAO/OSA development post-operatively in varying degrees (de Blacam, Smith, and Orr 2018).

Two randomized clinical trials compared pharyngeal flap versus sphincter pharyngoplasty and found the same speech outcomes for both techniques (Abyholm et al. 2005; Ysunza et al. 2002). Clinically significant OSA was found rare and no differences were found between both procedures (Abyholm et al. 2005). It is known that the success or failure of the pharyngeal flap and sphincter pharyngoplasty has been attributed to the specific tailoring of each surgical technique with preoperative surgical planning based on individual anatomy, together with the referring diagnosis in each individual patient with VPI (Shprintzen 1988; Ysunza et al. 2002).

UNILATERAL BUCCAL FLAP AS NEW SURGICAL TREATMENT FOR VPI

Considering that pharynoplasties like the pharyngeal flap and the sphincter pharyngoplasty alter the anatomy of the lateral pharyneal walls and posterior pharynx by creating a permanent narrowing of the oropharynx, and the possible increased risk of UAO/OSA postoperatively, a new surgical technique for the treatment of VPI was investigated in **chapter 7.** This technique includes an extensive repositioning of the levator veli palatini, unilateral myomucosal buccinator flap procedure and the

incorporation of an oral mucosa Z-plasty. This new technique is an alternative for the bilateral myomucosal buccinator flaps to lengthen the soft palate (Hill et al. 2004; Mann et al. 2011). This unilateral myomucosal buccinator flap results in less operating time for patients. The incorporation of the oral mucosa Z-plasty (and if needed a nasal mucosa Z-plasty) increases the exposure to the levator muscle to optimize muscular reconstruction and will increase the length of the soft palate. It could avoid the need for a bite block postoperatively to protect the buccal flap pedicle, and most importantly, an extra procedure to divide the flap pedicle at a later stage can be prevented, since the flap will fit nicely in between the two limbs of the Z-plasty. Additionally, by using a unilateral myomucosal buccinator flap the other contralateral flap is still available as a possible salvage option if VPI is persistent.

In 83% of all 42 consecutive patients with a cleft lip and/or palate sufficient speech outcome was achieved postoperatively, with significant improvements in resonance and level of intelligibility respectively evaluated by the parents and the speech pathologists. The other 17% remaining patients needed a pharyngeal flap to resolve persistent VPI. This group consisted of 4 patients with bilateral cleft-lip-palate, 3 patients with unilateral cleft-lip-palate, and none had a palatal cleft only. All consecutive patients were included, irrespective of the gap size found during nasopharyngoscopy preoperatively, however, patients with bilateral cleft-lip-palate and a wide velar gap were found less suitable for this unilateral technique and therefore bilateral myomucosal buccinator flaps are preferred. Although, a small number of 5 patients with RS were included, this new technique seems also suitable for this patient population since all of them had sufficient speech outcome.

Future perspectives

This new technique can be classified in the palate re-repair with muscle repositioning group, since a more physiological result is achieved when reconstructing the soft palate, and is line in with the protocol in **chapter 8** that assessed the VPI treatment by use of the secondary Furlow Z-plasty. Despite the previous mentioned benefits of this palate re-repair with muscle repositioning techniques, they have not been widely adopted, with 8% of patients receives palate-re-repair while 88% will undergo pharyngoplasty if surgical treatment for VPI is indicated (de Blacam, Smith, and Orr 2018). A systematic review and meta-analysis found these palate re-repair techniques to result in a complete resolution of VPI in 61% and 21% needed additional surgery to treat persistent VPI (Kurnik et al. 2020). However, the combination of adding new and well vascularized tissue by a myomucosal buccinator flap to the soft palate, repositioning of the levator muscle and the oral Z-plasty, makes this a promising and distinct technique, compared to the other palate re-repair techniques.

VPI MANAGEMENT IN PATIENTS WITH RS

Airway at time of cleft palate repair in patients with RS

In patients with RS, cleft palate repair can be compromised as breathing issues might occur, ranging from very mild to life threatening. Some recent reports demonstrated that airway-related problems after primary cleft palate repair are significantly more often seen in patients with RS compared to ICP-patients (Costa, Murage, et al. 2014; van Lieshout et al. 2016; Naros et al. 2021). These patients can have a restricted upper airway at baseline and are more likely to develop respiratory distress due to palatal and lingual swelling postoperatively. They are also at risk to develop more severe airway-related problems, such as stridor, re-intubation or tracheostomy with prolonged hospital stay and unplanned admission to an intensive care unit.

PSG is considered the gold standard to diagnose UAO/OSA in infants and children with RS (Kaditis et al. 2016; 2017). In addition, PSG assessment is necessary because the absence of clinical respiratory distress or snoring does not indicate the absence of UAO/OSA (Anderson et al. 2011; MacLean et al. 2012; Cielo et al. 2016; Manica et al. 2018). PSG is found an effective preoperative screening tool for patients with RS being considered for cleft palate repair to minimize postoperative airway compromise (Costa, Murage, et al. 2014; van Lieshout et al. 2016; Naros et al. 2021). Some even suggest the use of preoperative PSG with a palatal plate in order to simulate a closed palate before continuing with surgical repair (van Lieshout et al. 2016).

In **chapter 8** the airway of the patients with RS was clinically assessed before cleft palate repair and in case of a clinical suspected compromised airway, a supplemental PSG was performed. The perioperative protocol included repair of the cleft palate if the patients with RS were cleared regarding breathing based on PSG, home oximetry findings, or clinically judgement alone. This resulted in a cleft palate repair beyond 12 months of age in 43% in patients with RS, including both isolated and non-isolated cases. Based on this preoperative protocol, the palate was closed significantly later in patients with RS (14 months) compared to patients with ICP (11 months). As demonstrated in **chapter 8** this resulted in no direct postoperative airway compromise in any of the patients with RS.

Airway at time of speech improving operations in patients with RS

The airway in patients with RS should also be taken in consideration when speech surgery to resolve VPI is indicated. In some patients with RS the airway compromise can still be apparent far beyond infancy, for example in those who had severe neonatal airway compromise or in those who still demonstrate significant micrognathia (Witt et al. 1996; van Lieshout et al. 2017). It is believed that pharynoplasties like the pharyngeal flap and the sphincter pharyngoplasty alter the anatomy of the lateral pharyneal walls and posterior pharynx by creating a permanent narrowing of the oropharynx, and the possible increased risk of UAO/OSA especially in patients with RS.

As mentioned before, PSG is still considered the gold standard to diagnose UAO/OSA in infants and children with RS (Kaditis et al. 2016; 2017). Objective assessments of UAO/OSA by PSG are essential to the airway evaluation in RS and to assessing the impact of speech improving operations on breathing. The spectrum of UAO/OSA in patients with RS is broad and can change over time (Anderson et al. 2011a; MacLean et al. 2012; Cielo et al. 2016; Manica et al. 2018). This was emphasized in **chapter 8** by the fact that in follow-up, 8 patients with RS had UAO/OSA confirmed by PSG at a median age of 4.8 years (range: 2.9-6.3 years).

Objective data from PSG on the development of UAO/OSA in patients with RS after speech improving operations are scare. There are a few reports that clinically demonstrated some potential airway hazards. Pharyngeal flap complications in relatively old reports including small sample sizes varied from UAO/OSA that resulted in extended hospital stay in each one patient with RS (age 4.5 years) (Kravath et al. 1980; Shprintzen 1988), in direct postoperative UAO/OSA in 4 of 5 patients with RS that disappeared spontaneously within a few months (mean age 7 years) (Sirois et al. 1994), UAO/OSA that required flap take-down in 1 of 6 patients with RS (mean age 7 years) (Lehman, Fishman, and Neiman 1995) and in 6 of 7 patients with isolated RS (older than 5 years) (Abramson, Marrinan, and Mulliken 1997) to even death in one patient with RS at age of 7 years because of severe UAO/OSA that did not resolve 3 days after flap division (Jackson, Whitaker, and Randall 1976). Recent work in larger cohorts reported the pharyngeal flap to be a safe intervention regarding post-operative UAO/OSA combined in a total of 21 patients with RS (de Buys Roessingh et al. 2008; Goudy, Ingraham, and Canady 2011; Patel et al. 2012), with only one patient requiring a secondary enlargement of 1 lateral port because of unilateral nasal obstruction (de Buys Roessingh et al. 2008). Post-operative airway compromise after sphincter pharyngoplasty is reported in 5 out of 11 patients with RS and treated with CPAP successfully in all patients (Witt et al. 1996). However, none of this research presented objective PSG outcomes after these speech improving operation techniques. A secondary Furlow Z-plasty appeared to have the least impact on the airway based on postoperative PSG data followed by sphincter pharyngoplasty and pharyngeal flap in patients with cleft lip and/or palate (Abdel-Aziz et al. 2018). In **chapter 8**, the secondary Furlow Z-plasty demonstrated to be 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. Therefore, more obstructive pharyngoplasty procedures including pharyngeal flap or sphincter pharyngoplasty in patients with RS could be avoided without compromising speech outcome. Concerning surgical recovery and postoperative risk of UAO/OSA, some recent reports also suggest the secondary Furlow Z-plasty be to often more suitable than pharyngoplasties in patients with RS (Black and Gampper 2014; Gustafsson et al. 2020; Ahti et al. 2020). Only 1 study has been published on a direct comparison of VPI outcomes between both categories of surgical techniques, so no consensus has yet been emerged (Dailey et al. 2006). The new technique investigated in **chapter 7** that includes a unilateral myomucosal buccinator flap and an oral mucosa

Z-plasty demonstrated sufficient VPI resolution. The results of the protocol in **chapter 8** also demonstrate that the secondary Furlow Z-plasty in both isolated and syndromic RS, and a tertiary sphincter pharyngoplasty in syndromic RS, are suitable procedures to achieve adequate VPI resolution.

Future perspectives

Studies with objective assessment by PSG of the airway in patients with RS related to speech improving operations are awaited. Until now, clinical decision making for speech improving operations in patients with RS is based on expert opinion or surgeons' preferences.

Although PSG is considered the gold standard to diagnose UAO/OSA, it is expensive and time consuming, which means that in many centers it is not standardized as a postoperative outcome measurement and screening tool for UAO/OSA (de Blacam, Smith, and Orr 2018). As alternatives, a number of screening tools have been developed and validated recently including the I'M SLEEPY questionnaire (Kadmon, Chung, and Shapiro 2014), the 22-item Pediatric Sleep Questionnaire (Chervin et al. 2007; Mitchell et al. 2015), and Sleep Clinical Record (Villa et al. 2013). All these screening tools have the potential to avoid undue delay in setting the diagnosis and treatment of UAO/OSA, especially when speech improving operations are indicated. It is hoped that future studies will test the implication of these screening tools in the RS population, while normative, age depended PSG data are hopefully on the way (**chapter 4**).

While more objective screening studies on UAO/OSA related to speech improving operations are awaited, cleft surgeons should be aware that improvements in speech after pharyngoplasty techniques may change airway dynamics and increase the risk of the development of UAO/OSA in patients with RS. In addition, future research should be focussed on direct comparisons on pharyngoplasties versus re-palate repair techniques (**chapter 7**: the unilateral buccal flap technique & **chapter 8**: secondary Furlow Z-plasty) investigating both VPI and objective breathing outcomes by PSG.

QUALITY OF LIFE OUTCOMES IN SURGICAL TREATMENT OF PATIENTS WITH RS

In addition to the traditional clinical treatment evaluations, proxy and patient-reported outcome itself is being increasingly acknowledged as useful in assessing the result of interventions. One example of this is health-related quality of life, that is described as a multidimensional concept, which assesses physical, psychological, and social parameters (Guyatt, Feeny, and Patrick 1993). Clinicians should be aware that interventions might affect many aspects of the daily life of their patients, and that proxy and patient-reported outcome can be evaluated by assessing health-related quality of life. Implementing the research question *"what matters to patients?"* should be one of the main questions in future research, apart from objective outcome measurements. This could also lead to a more shared decision-making approach in the treatment of RS.

In **chapter 10**, this research question was assessed for the first time in RS, by comparing changes in health-related quality of life outcomes post-MDO and post-TLA in 31 consecutive patients with RS in two tertiary medical centers (Wilhelmina Children's Hospital and VU Medical Center). The health-related quality of life outcomes outcomes after MDO and TLA were found similar without significant differences. Positive changes in all four domains of the emotion, physical health, learning, and vitality were observed for both surgical interventions. Although MDO is considered a more complex surgical intervention than TLA (including associated complications) this seemed to have less of an impact on health-related quality of life in patients with RS, as demonstrated by the small differences between Glasgow Children's Benefit Inventory (GCBI) questionnaire scores.

Future perspectives

Because these patient and parents' perspective judgments could have a significant impact on deciding for a specific treatment option in patients with RS, it is our hope, that in the future more studies evaluating health-related quality of life in larger RS cohorts will be conducted to identify which procedure is best for the individual patient with RS.

It is desirable that patients with rare congenital anomalies, like RS, won't be left out and will also be included in assessments of proxy and patient-reported outcomes of patients in the spectrum of craniofacial and or cleft lip and/or palate disorders, e.g. the Cleft-Q or the International Consortium for Health Outcomes Measurement (ICHOM) (Arora and Haj 2016; Wong Riff et al. 2018). Future development of these patient-reported outcome instruments for individuals with RS will improve physical, psychological, and social health from the RS patient's perspective.

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12.

CHAPTER 12.
SUMMARY

This thesis was initiated to provide better insight in different treatment aspects for patients born with RS, with a special focus on long-term outcomes. This resulted in that we better understand the etiology of the development of RS, we can better support choices between the different treatment options for the individual patient with RS, and has improved outcome prediction and counseling for patients with RS and their families.

In **chapter 2** better understanding of the pathophysiology in RS was investigated. Different etiologies of the RS phenotype (extrinsic, instrinsic en neurological) were investigated based on embryologic, developmental and genetic mechanisms. A new categorization of patients with RS based on etiological diagnosis was achieved by linking the RS-phenotype to the different embryologic, developmental and genetic mechanisms: *1. Collagen or bone development group* including the Stickler syndrome, Catel-Manzke syndrome, Kniest dysplasia, Osteopathia striata with cranial sclerosis, and the isolated form of RS. 2. *Neural crest group,* including the Treacher Collins syndrome, Miller syndrome and 22q11.2 deletion syndrome. 3. *Neuromuscular group* including congenital myotonic dystrophy, Carey-Fineman-Ziter syndrome and the Moebius syndrome 4. *Metabolic group*, including two types of congenital disorder of glycosylation 5. *Pharyngeal arch group,* including three types of Auriculocondylar syndrome 6. *Transcriptional defects group*, including the Glass syndrome 7. *RNA related group* including Mandibulofacial dysostosis, Acrofacial dysostosis, TARP syndrome, Cerebro-costo-mandibular syndrome and the Richieri-Costa-Pereira syndrome. The increasing use of next-generation exome sequencing provides clinicians access to a more etiological diagnosis. Focusing more on the etiological diagnosis should eventually result in a more personalized approach in each individual patient with RS.

In **chapter 3** greater insight was gained into the mortality rate and the characteristics of deceased patients with RS in a cohort of 103 consecutive patients followed at the Wilhelmina Children's Hospital in Utrecht. A mortality rate of 10% was reported at a median age of 0.8 years with a range of 0.1 – 5.9 years, and nine of these ten patients were diagnosed with an associated syndrome. Of these, seven patients died of respiratory insufficiency due to various causes, with only two related to neonatal tongue related UAO/OSA. This indicates that clinicians should be more aware of respiratory problems in syndromic patients with RS, also after the first year of life. The patients with RS represented a heterogeneous population and were associated with a high level of underlying syndromes. Mortality was significantly associated with syndromic RS and the presence of neurological anomalies. A multidisciplinary approach in all patients born with RS, including genetic testing and examination of neurological anomalies in a standardized way, is crucial to identify patients with underlying syndromes potentially associated with increased mortality. Extensive examination (including re-examination in follow-up) of the possible genetic diagnosis and congenital anomalies in a standardized way in all patients with RS is recommended.

The systematic review of the literature conducted in **chapter 4** and the discussion in **chapter 5** demonstrated a lack of standardized use and implementation of objective measurements (polysomnography, oximetry and blood gas) in the assessment

and treatment indications of UAO/OSA in patients with RS. A wide variation in interpretation and reporting of these measurements was observed. Polysomnography was the most commonly used measurement, but polysomnography type and other essential variables (like indication, age, body position, duration, technique, and OSA scoring protocol), and interpretation of results had variations or were missing. Although oximetry was less commonly used as an outcome measure, parameters from oximetry were frequently used to define treatment thresholds for UAO/OSA interventions. In total, 34 different definitions for treatment threshold were identified. Based on these findings, a list of minimal reporting for future studies using polysomnography in patients with RS was purposed. Until measures and metrics are systematically assessed and reported, front-line physicians rely on limited evidence and thus variations in clinical practice will persist. Precise reporting of objective measurement techniques to assess airway obstruction, guide decision making and evaluate outcomes is necessary in this high-risk population.

Up until now cleft surgeons focused purely on the perfect muscle reconstruction in the treatment of patients with a cleft palate, however, for a dynamic cleft palate repair an anatomical insight in the nerves innervating the soft palate muscles is important. The innervation of the tensor veli palatini - levator veli palatini - and palatopharyngeus muscle was investigated in **chapter 6**. Most likely the lesser palatine nerve and the pharyngeal plexus (vagus nerve and the glossopharyngeal nerve) dually innervate the levator veli palatini - and palatopharyngeus muscles. The lesser palatine nerve innervates the small inferior-velar part of the levator veli palatini muscle and the anterior part of the oral part of the palatopharyngeus muscle, together referred to as the anteromedial region of the soft palate muscles. The pharyngeal plexus innervates the bigger superior part of the levator veli palatini muscle and the nasal and remaining oral part of the palatopharyngeus muscle, also referred as the posterolateral region of the soft palate muscles. The pharyngeal plexus nerves enter these muscles from the lateral side. The pharyngeal plexus plays a major role in innervating the levator veli palatini - and palatopharyngeus muscle and receive its motor-fibres from the accessory nerve. However, since the type of nerve fibres of the lesser palatine nerve is unclear, the role of the facial nerve in motor-innervating the soft palate is uncertain. The remaining other soft palate muscle, the tensor veli palatini muscle, is innervated by the mandibular nerve. This information is valuable to cleft surgeons and will likely allow improvements in cleft palate repair and subsequently decrease the incidence of VPI.

The use of palate re-repair techniques with muscle repositioning are emerging in the surgical management for VPI. Speech outcomes of a new technique that includes a levator muscle reconstruction with an oral Z-plasty and a unilateral myomucosal buccinator flap was investigated in **chapter 7.** This unilateral myomucosal buccinator flap procedure demonstrated similar results compared to the bilateral myomucosal buccinator flaps procedure, to whereas it results in less operating time for patients. The incorporation of the oral mucosa Z-plasty (and if needed a nasal mucosa Z-plasty) increased the exposure to the levator muscle to optimize muscular reconstruction

and increased the length of the soft palate. It could impede the need for a bite block postoperatively to protect the buccal flap pedicle, and most importantly, an extra procedure to divide the flap pedicle at a later stage could be prevented, since the flap fitted nicely in between the two limbs of the Z-plasty. Additionally, by using a unilateral myomucosal buccinator flap the other contralateral flap is still available as a possible salvage option if VPI is persistent. This technique showed to be an effective and safe procedure and became a valuable adjunct to the armamentarium of the cleft surgeon in the management of VPI following primary palatoplasty.

In **chapter 8** long-term speech outcomes and outcome predictors for VPI in all consecutive RS and ICP patients treated and followed at the Craniofacial Center of the University of California San Francisco were investigated. The investigated protocol includes a one stage straight-line repair with intravelar veloplasty or Furlow Z-plasty repair depending on cleft palate and airway characteristics. In addition, the development of UAO/OSA after cleft palate repair, and the outcomes of a secondary Furlow Z-plasty and a tertiary sphincter pharyngoplasty to resolve VPI in patients with RS, were investigated. Long-term speech outcomes could be achieved by the median follow-up of more than 8 years.

Patients with RS were found to have features that required individualized treatment protocols and that could affect surgical and speech outcomes compared to patients with ICP. Patients with RS have wider and more severe cleft palate anatomy and airway compromise that resulted in delayed repair and greater use of straight-line repair with intravelar veloplasty.

Clinical assessment of the airway in patients with RS before cleft palate repair was performed and in case of a clinical suspected compromised airway, a supplemental polysomnography was performed. In this way, patients with RS were cleared regarding breathing based on polysomnography, home oximetry findings, or clinically judgement alone. As a result, the palate was closed significantly later in patients with RS (14 months) compared to patients with ICP (11 months). This perioperative airway protocol was demonstrated to be safe as no direct postoperative airway compromise in any of the patients with RS occurred. However, the at-risk airway in RS was confirmed by a number of patients with RS that had UAO/OSA confirmed by PSG in follow-up at a median age 5 years.

Despite different cleft palate etiology and the presence of several other RS associated variables, **chapter 8** demonstrated that cleft palate anatomy is the only independent variable predictive for VPI in patients with RS compared to patients with ICP. Age at repair, syndromic RS compared to isolated RS, isolated RS compared to ICP and initial tongue-lip adhesion in RS were not predictive.

Patients with isolated RS attain similar long-term VPI outcomes compared to patients with ICP, though patients with syndromic RS require secondary Furlow Z-plasty procedures more often to resolve VPI than patients with isolated RS.

Utilizing the Furlow Z-plasty as secondary procedure (after primary straight-line repair with intravelar veloplasty) resulted in normal velopharyngeal function in the majority of patients with RS and the avoidance of obstructive speech operations.
Chapter 8 resulted in improved preoperative predictability of speech outcomes after cleft repair for patients with RS and their families.

In **chapter 9** the effect of tongue-lip adhesion in the neonatal period was assessed on the long-term speech and articulation outcomes of all consecutive patients with RS that underwent cleft palate repair by Von Langenbeck technique with intravelar veloplasty at the Amsterdam Medical Center Location VU. These outcomes are compared to patients with RS and a cleft palate who required positioning alone and with patients with ICP who all were treated according to the same protocol.
Patients with RS demonstrated to have higher rates of hypernasality and needed more speech improving operations to resolve VPI between the age of 3 to 6 years old compared to patients with ICP. Patients with isolated RS were found to have similar speech outcomes compared to ICP, however, patients with syndromic RS needed more speech improving operations compared to patients with isolated RS.
In patients with RS the findings demonstrated that the surgical procedure tongue-lip adhesion does not affect long-term velopharyngeal function. Patients with RS that had a tongue-lip adhesion had no differences in any articulation errors groups (passive, non-oral, posterior-oral) compared to patients with RS without a tongue-lip adhesion, except for the anterior oral articulation errors. This might be related to a different positioning of the tongue in these patients with RS after tongue-lip adhesion.
In patients with RS and a history of tongue-lip adhesion, cleft speech pathologists (as part of the multidisciplinary cleft team) should be more aware of this phenomenon in order to improve long-term articulation outcomes.

In addition to the traditional clinical evaluations, proxy and patient-reported outcomes are being increasingly acknowledged as useful in assessing the result of surgical interventions. In **chapter 10**, two surgical treatments for UAO/OSA in RS were compared on health-related quality of life outcomes in two tertiary medical centers: The Wilhelmina Children's Hospital using mandibular distraction osteogenesis and the Amsterdam Medical Center Location VU using tongue-lip adhesion. The health-related quality of life outcomes after mandibular distraction osteogenesis and tongue-lip adhesion were found similar without significant differences. Positive changes in all four domains of the emotion, physical health, learning, and vitality were observed for both surgical interventions. These patients reported findings could contribute to the debate regarding the use of mandibular distraction osteogenesis versus tongue-lip adhesion as surgical treatment in RS.

ADDENDUM

SUMMARY IN DUTCH

LIST OF ABBREVIATIONS

PORTFOLIO: PUBLICATIONS & PRESENTATIONS

ACKNOWLEDGEMENTS

ABOUT THE AUTHOR

SUMMARY IN DUTCH

Deze PhD thesis is geïnitieerd om meer inzicht te verkrijgen in de verschillende behandelaspecten van patiënten geboren met Robin sequentie met een speciale focus op lange termijn uitkomsten van verschillende behandelingen. Het heeft ertoe geleid dat we de etiologie van het ontstaan van Robin sequentie beter begrijpen, de verschillende behandelopties beter kunnen onderbouwen voor de individuele patiënt en heeft de voorlichting en verwachtingen voor specifieke behandelingen van patiënten met Robin sequentie en hun families verbeterd.

In **hoofdstuk 2** is de huidige kennis van de pathofysiologie van RS uitgebreid onderzocht. Verschillende etiologiën van het RS-fenotype (extrinsiek, intrinsiek en neurologisch) zijn onderzocht, gebaseerd op embryologische, ontwikkelings- en genetische mechanismen. Een nieuwe categorisatie van patiënten met RS gebaseerd op etiologische diagnose, was mogelijk door het RS-fenotype te linken aan de verschillende embryologische, ontwikkelings- en genetische mechanismen: 1. Collageen of bot ontwikkelingsgroep zoals het Stickler syndroom, Catel-Manzke syndroom, Kniest dysplasie, Osteopathia striata met craniale sclerose en de geïsoleerde vorm van RS. 2. Neurale lijst groep, zoals het Treacher Collins syndroom, Miller syndroom en het 22q11.2 deletie syndroom. 3. Neuromusculaire groep zoals congenitale myotonische dystrophie, Carey-Fineman-Ziter syndroom en het Moebius syndroom 4. Metabolische groep, zoals twee types van congenitale afwijkingen van de glycosylatie 5. Pharyngeale arch groep, zoals drie types van het Auriculocondylar syndroom 6. Transcriptionale defecten groep, zoals het Glass syndroom 7. RNA gerelateerde groep zoals Mandibulofaciale dysostose, Acrofaciale dysostose, het TARP syndroom, het Cerebro-costo-mandibulaire syndroom en het Richieri-Costa-Pereira syndroom. Het toegenomen gebruik van de "next generation exome sequencing" zorgt ervoor dat clinici steeds meer toegang hebben tot een meer etiologische diagnose voor patiënten met RS. Meer aandacht voor de etiologische diagnose zal uiteindelijk resulteren in een meer gepersonaliseerde aanpak en behandeling van iedere individuele patiënt met RS.

In **hoofdstuk 3** is meer inzicht verkregen in het mortaliteitspercentage en de karakteristieken van overleden patiënten met RS in een cohort van 103 opeenvolgende patiënten behandeld in het Wilhelmina Kinderziekenhuis in Utrecht. Een mortaliteitspercentage van 10% werd gevonden op een mediane leeftijd van 0.8 jaar (0.1 – 5.9), en negen van deze tien patiënten waren gediagnostiseerd met een onderliggend syndroom. Hiervan bleken 7 patiënten overleden te zijn als gevolg van respiratoire insufficiëntie met variërende oorzaken, waarvan er maar 2 direct gerelateerd waren aan de kenmerkende neonatale bovenste luchtwegobstructie bij RS. Clinici moeten zich bewuster zijn van respiratoire problemen in syndromale patiënten met RS, niet alleen in de neonatale periode, maar ook na het eerste levensjaar.
Patiënten met RS vormden een heterogene patiëntengroep en waren geassocieerd met een hoog aantal onderliggende syndromale diagnoses. Mortaliteit was significant

geassocieerd met de diagnose van een onderliggend syndroom en de aanwezigheid van neurologische aangeboren afwijkingen.
Een multidisciplinaire aanpak van alle patiënten die geboren worden met RS, inclusief genetisch testen en onderzoek van neurologische aangeboren afwijkingen in een gestandaardiseerde manier is essentieel om de patiënten met RS te identificeren met onderliggende syndromale diagnoses die potentieel geassocieerd zijn met een hoger risico om te overlijden. Het wordt aanbevolen aan betrokken clinici om uitgebreid onderzoek te verrichten (en dit te herhalen in follow-up) naar mogelijke genetische diagnoses en andere aangeboren afwijkingen op een gestandaardiseerde manier van alle patiënten die geboren worden met RS.

De systematische review van de literatuur die uitgevoerd is in **hoofdstuk 4** en in de discussie in **hoofdstuk 5** toonde het gebrek aan het gestandaardiseerde gebruik, en implementatie van objectieve metingen (polysomnografie, oximetrie en bloedgas analyse) in de aanpak en indicatiestelling voor behandeling van bovenste luchtwegobstructie van patiënten met RS. Er werd een grote variatie gevonden de interpretatie en rapportage van de waardes verkregen van deze objectieve metingen. Polysomnografie was de meest gebruikte meting, maar het type polysomnografie inclusief andere essentiële variabelen (indicatie, leeftijd, lichaamspositie, duur, techniek en OSA-scoringsprotocol) en interpretatie van resultaten, varieerden of ontbraken. Alhoewel oximetrie minder wordt toegepast voor evaluatie van behandelingen, worden de parameters van oximetrie wel frequent gebruikt om een indicatie te stelling voor bovenste luchtwegobstructie behandelingen. In totaal werden er 34 verschillende behandelindicaties geïdentificeerd gebaseerd op deze objectieve metingen. Voor toekomstige studies die bovenste luchtwegobstructie middels polysomnografie van patiënten met RS willen onderzoeken, werd er een lijst voorgesteld met minimale variabelen die gerapporteerd dienen te worden. Totdat deze metingen en de uitkomsten hiervan systematisch op dezelfde manier worden beoordeeld en worden gerapporteerd, hebben clinici gelimiteerd wetenschappelijk bewijs voor de behandeling van bovenste luchtwegobstructie van patiënten met RS en zal de grote variatie in behandeling blijven bestaan. Transparante rapportage van de objectieve metingen ter beoordeling van de bovenste luchtweg en het evalueren van behandeluitkomsten is essentieel voor een optimale behandeling van deze hoog risicopatiënten.

Tot op heden richten (schisis) chirurgen bij de behandeling van patiënten met een gehemeltespleet zich voornamelijk op een perfecte reconstructie van de musculatuur. Voor een dynamisch herstel van de gehemeltespleet is echter meer anatomisch inzicht nodig in de zenuwen die de zachte gehemelte spieren innerveren. De innervatie van de zachte gehemelte spieren, de tensor veli palatini spier, de levator veli palatini spier en de palatopharyngeus spier, werd onderzocht in **hoofdstuk 6**. Meest waarschijnlijk innerveren nervus palatinus minor en de pharyngeale plexus (bestaande uit de nervus vagus en de nervus glossopharyngeus) beide deze levator veli palatini en palatopharyngeus spier. De nervus palatinus minor innerveert het kleine inferieure deel van de levator veli palatini spier en het anterieure deel van het orale gedeelte van de palatopharyngeus

spier, samen ook wel het anteromediale gedeelte van de zachte gehemelte spieren. De pharyngeale plexus innerveert het grotere superieure deel van de levator veli palatini spier en het nasale en het overige orale gedeelte van de palatopharyngeus spier, samen ook wel het posterolaterale gedeelte van de zachte gehemelte spieren. De zenuwtakjes van de pharyngeale plexus bereiken deze beide zachte gehemeltespieren aan de laterale zijde. De pharyngeale plexus speelt een grote rol in de motorinnervatie van de levator veli palatini spier en de palatopharyngeus spier, en ontvangt zijn motorische vezels van de nervus accessorius. Echter de rol van de nervus facialis in de motorische innervatie de zachte gehemelte spieren via de nervus palatina minor blijft onzeker aangezien het type zenuwvezels van de nervus palatina minor onduidelijk is. De andere belangrijke spier van het zachte gehemelte, de tensor veli palatini, wordt geïnnerveerd door de nervus mandibularis. Deze nieuwe kennis is waardevol voor (schisis) chirurgen en zal hoogstwaarschijnlijk kunnen leiden tot verbeteringen in het operatief sluiten van een gehemeltespleet en aansluitend dus kunnen leiden tot een afname van postoperatieve velopharyngeale insufficiëntie bij patiënten met een gehemeltespleet.

Het gebruik van re-palatoplastiek technieken met levator spier repositie neemt toe in de chirurgische behandeling van velopharyngeale insufficiëntie. De spraakuitkomsten van een nieuwe techniek, een musculus levator veli palatini reconstructie met een orale Z-plastiek en een unilaterale myomucosale buccinator lap, werd onderzocht in **hoofdstuk 7**. Deze unilaterale myomucosale buccinator lap operatie demonstreerde gelijke uitkomsten vergeleken met de bilatereale myomucosale buccinator lap operatie, terwijl het resulteerde in een kortere operatietijd voor patiënten. De toevoeging van de orale mucosa Z-plastiek (en indien nodig ook een nasale mucosa Z-plastiek) verbeterde de toegang tot de musculus levator veli palatini zodat de spierreconstructie optimaal verricht kon worden en het resulteerde in verlenging van het zachte gehemelte. Daarnaast is er vaak geen bijtblok postoperatief meer nodig om de steel van de lap te beschermen en nog belangrijker, is er geen extra operatie nodig om de steel van de lap te klieven omdat de lap netjes tussen de twee lappen van de Z-plastiek past. Tenslotte is bij deze nieuwe operatie de contralaterale buccale lap nog beschikbaar mocht de velopharyngeale insufficiëntie aanhouden. **Hoofdstuk 7** liet zien dat deze nieuwe techniek veilig en effectief is en dat het een waardevolle aanwinst is voor zowel (schisis)chirurgen als voor patiënten in de behandeling van velopharyngeale insufficiëntie na een primaire gehemeltespleetsluiting.

In **hoofdstuk 8** werden de lange termijn spraakuitkomsten en uitkomstvoorspellers voor het ontwikkelen van velopharyngeale insufficiëntie onderzocht in alle opeenvolgende patiënten met RS en geïsoleerde palatoschisis die behandeld werden voor een gehemeltespleetsluiting in het Craniofaciale Centrum van de Universiteit van California, San Francisco. Het toegepaste behandelprotocol bestond uit een rechte-lijn gehemeltespleetsluiting met een intravelaire veloplastiek of een gehemeltespleetsluiting volgens Furlow, afhankelijk van gehemeltespleet en luchtweg karakteristieken. Daarnaast werd ook de ontwikkeling van obstructieve slaapapneu na gehemeltespleetsluiting onderzocht en de uitkomsten van een secundaire Furlow operatie en een tertiaire sfincter

pharyngoplastiek operatie voor de behandeling van velophanrygeale insufficiëntie van patiënten met RS.
De lange termijn spraakuitkomsten konden goed worden onderzocht door de mediane follow-up van meer dan 8 jaar.
Patiënten met RS bleken unieke eigenschappen te hebben die individuele behandelprotocollen noodzakelijk maken en die mogelijk invloed kunnen hebben op de (spraak) uitkomsten in vergelijking met patiënten met een geïsoleerde palatoschisis. Patiënten met RS hebben een bredere en langere gehemeltespleet en mogelijk luchtwegproblematiek dat resulteerde in een latere gehemeltespleetsluiting en meer gebruik van de rechte-lijn gehemeltespleetsluiting met een intravelaire veloplastiek.
Klinische beoordeling van de luchtweg van patiënten met RS werd verricht voorafgaand aan gehemeltespleetsluiting en indien er klinisch een verdenking was op luchtwegproblematiek ondergingen deze patiënten een polysomnografie. Op deze manier werden patiënten met RS goedgekeurd wat betreft de luchtweg gebaseerd op polysomnografie, thuis oximetrie of alleen klinische beoordeling. Dit resulteerde in een significant latere gehemeltespleetsluiting van patiënten met RS (14 maanden) dan in vergelijking met patiënten met een geïsoleerde palatoschisis (11 maanden). Dit perioperatieve luchtweg protocol bleek veilig te zijn aangezien er postoperatief in geen van de patiënten met RS directe luchtwegproblematiek optrad. Echter er bleek bij een klein deel van de patiënten met RS in follow-up rond de mediane leeftijd van 5 jaar alsnog obstructief slaapapneu gediagnosticeerd te zijn met polysomnografie.
Ondanks het feit dat patiënten met RS een andere gehemeltespleet etiologie en andere variabelen geassocieerd met RS hebben, bleek in **hoofdstuk 8** dat de gehemeltespleet anatomie (breedte en lengte) de enige onafhankelijke variabele te zijn voor het voorspellen van velopharyngeale insufficiëntie in patiënten met RS vergeleken met patiënten met een geïsoleerde palatoschisis. Leeftijd ten tijde van sluiting, syndromaal RS vergeleken met geïsoleerd RS, en geïsoleerd RS vergeleken met geïsoleerd palatoschisis, en primaire tong-lip adhesie in RS bleken niet voorspellend te zijn.
Patiënten met geïsoleerd RS bereiken uiteindelijk dezelfde lange termijn spraakuitkomsten als patiënten met een geïsoleerd palatoschisis. Echter, patiënten met syndromaal RS hadden vaker een secundaire Furlow Z-plastiek operatie nodig ter behandeling van velopharyngeale insufficiëntie dan patiënten met geïsoleerd RS.
Het toepassen van een secundaire Furlow Z-plastiek operatie voor de behandeling van velopharyngeale insufficiëntie (na een primaire rechte-lijn gehemeltespleetsluiting met een intravelaire veloplastiek) resulteerde in goede spraakuitkomsten in het merendeel van de patiënten met RS, zodat obstructieve spraak verbeterende operaties (zoals een pharynxlap of een sfincter pharyngoplastiek) van patiënten met RS vermeden konden worden. Deze uitkomsten hebben geresulteerd in een verbeterde preoperatieve voorspelbaarheid van lange termijn spraakuitkomsten na gehemeltespleetsluiting voor patiënten met RS en hun families.

In **hoofdstuk 9** werd het effect van een tong-lip adhesie operatie in de neonatale periode op lange termijn spraak- en articulatie-uitkomsten onderzocht in alle opeenvolgende patiënten met RS die een gehemeltespleetsluiting volgens de Von Langenbeck techniek met intravelaire veloplastiek ondergingen in het Amsterdam Universitair Medisch Centrum, locatie VU. Deze uitkomsten werden vergeleken met patiënten met RS die geen tong-lip adhesie operatie nodig hadden maar enkel positionering in de neonatale periode en met patiënten met een geïsoleerde palatoschisis, die beiden ook een gehemeltespleetsluiting ondergingen. Patiënten met RS bleken vaker hypernasaliteit te ontwikkelen en meer secundaire spraakoperaties nodig te hebben voor de behandeling van velopharyngeale insufficiëntie in de leeftijd van 3 tot 6 jaar, vergeleken met patiënten met een geïsoleerde palatoschisis. Patiënten met geïsoleerd RS bleken dezelfde lange termijn spraakuitkomsten te hebben als patiënten met een geïsoleerde palatoschisis, maar patiënten met syndromaal RS hadden meer secundaire spraak verbeterende operaties nodig vergeleken met patiënten met geïsoleerd RS.
In patiënten met RS bleek een tong-lip adhesie operatie geen invloed op de velopharyngeale functie in de leeftijd van 3 tot 6 jaar te hebben. Patiënten met RS die een tong-lip adhesie ondergingen demonstreerden geen verschil in de verschillende articulatiefouten groepen (passief, non-oraal, en posterieur-oraal) vergeleken met patiënten met RS zonder tong-lip adhesie, behalve in de anterieur-orale articulatiefouten. Dit kan mogelijk gerelateerd zijn aan een andere positionering van de tong in deze patiënten met RS na een tong-lip adhesie. Speciale aandacht vanuit logopedisten (als onderdeel van het multidisciplinaire schisisteam) is er nodig voor deze groep articulatiefouten om zo lange termijn spraak en articulatie uitkomsten te kunnen verbeteren voor patiënten met RS en een tong-lip adhesie.

Naast de traditionele klinische evaluaties worden patiënt gerapporteerde evaluaties toenemend erkend als waardevolle uitkomstmaat ter beoordeling van het effect van chirurgische interventies. In **hoofdstuk 10** werden twee chirurgische behandelingen voor bovenste luchtwegobstructie voor patiënten met RS vergeleken in gezondheid gerelateerde kwaliteit van leven uitkomsten: Mandibulaire distractie osteogenese in het Wilhelmina Kinderziekenhuis te Utrecht en tong-lip adhesie in het Amsterdam Universitair Medisch Centrum. De gezondheid gerelateerde kwaliteit van leven uitkomsten na mandibulaire distractie osteogenese en tong-lip adhesie bleken gelijk aan elkaar te zijn zonder significante verschillen tussen deze twee chirurgische technieken. Positieve veranderingen in gezondheid gerelateerde kwaliteit van leven werden in alle 4 de domeinen: emotie, fysieke gezondheid, leren en vitaliteit voor beide operaties geobserveerd. Deze patiënt gerapporteerde uitkomsten kunnen bijdragen aan de discussie omtrent het gebruik van mandibulaire distractie osteogenese versus tong-lip adhesie in de chirurgische behandeling van patiënten met RS.

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LIST OF ABBREVIATIONS

AHI = apnea-hypopnea index
BIPAP = bilevel positive airway pressure
CPAP = continuous positive airway pressure
ICP = isolated cleft palate
MDO = mandibular distraction osteogenesis
MOAI = mixed obstructive apnea index
NPA = nasopharyngeal airway
OAHI = obstructive apnea-hypopnea index
OSA = obstructive sleep apnea
PEBP = pre-epiglottic baton plate
PSG = polysomnography
PSG NOS = polysomnography not other specified
RS = Robin sequence
TLA = tongue-lip adhesion
UAO = upper airway obstruction
VPI = velopharyngeal insufficiency

PORTFOLIO: PUBLICATIONS & PRESENTATIONS

List of peer reviewed publications

1. Discussion: Robin Sequence: 5-Year Speech Outcomes-A Case-Control Study.
   Logjes RJH, Breugem CC, Pomerantz JH. *Plastic and Reconstructive Surgery 2022*

2. Advantages and disadvantages of mandibular distraction in Robin sequence.
   Breugem CC**, Logjes RJH,** Nolte JW, Flores RL. *Seminars in Fetal-Neonatal Medicine 2021*

3. Discussion: Sleep Outcomes in Neonates with Pierre Robin Sequence Undergoing External Mandibular Distraction: A Longitudinal Analysis.
   Logjes RJH, Maclean JE, Breugem CC. *Plastic and Reconstructive Surgery 2021*

4. A systematic review on objective measurements for airway management in infants with Robin Sequence: What are we measuring?
   Logjes RJH, Maclean JE, de Cort NW, Poets C, Abadie V, Joosten K, Resnick CM, Trindade-Suedam IK, Zdanski C, Forrest C, Kruisinga F, Flores R, Evans K, Breugem CC. *Journal of Clinical Sleep Medicine 2021*

5. Long-term speech outcomes of cleft palate repair in patients with Robin sequence versus isolated cleft palate.
   Logjes RJH, Upton S, Mendelsohn BA, Breugem CC, Hoffman WY, Pomerantz JH. *Plastic and Reconstructive Surgery Global Open 2021*

6. Assessment of Health-Related Quality of Life in Robin Sequence: A Comparison of Mandibular Distraction Osteogenesis and Tongue Lip Adhesion.
   Logjes RJH, Mermans YF, Paes EC, Muradin MSM, Don Griot JP, Breugem CC. *Plastic and Reconstructive Surgery 2019*

7. The Ontogeny of Robin Sequence.
   Logjes RJH, Breugem CC, Van Haaften G , Paes EC, Sperber GH, Van den Boogaard MJH, Farlie P. *American Journal of Medical Genetics part A 2018*

8. Mortality in Robin Sequence: Identification of risk factors.
   Logjes RJH, Haasnoot M, Lemmers PMA, Nicolaije MFA, Van den Boogaard MJH, Mink van der Molen AB, Breugem CC. *European Journal of Pediatrics 2018*

9. Velopharyngeal insufficiency treated with levator muscle repositioning and unilateral myomucosal buccinator flap.
   Logjes RJH, Van den Aardweg MTA, Blezer MMJ, Van der Heul MMB, Breugem CC. *Journal of Craniomaxillofacial Surgery 2017*

10. The innervation of the soft palate muscles involved in cleft palate: A review of the literature.
    Logjes RJH, Bleys RLAW, Breugem CC. *Clinical Oral Investigations 2016*

11. Autologe vetinjectie voor lipcorrectie bij schisispatiënten.
    Logjes RJH, Breugem CC. *Nederlands Tijdschrift voor Plastische Chirurgie 2015*

12. Autologe vetinjectie (lipofilling) van het velum voor spraakverbetering bij schisispatiënten.
    Logjes RJH, Breugem CC, Mink van der Molen AB. *Nederlands Tijdschrift voor Plastische Chirurgie 2015*

13. Patient presenting with sebaceous carcinoma.
    Logjes RJH, Koelemij R. *Snapshot in Surgery in British Journal of Surgery, 2014*

List of oral presentations

Long-term speech in patients with Robin sequence after cleft palate repair and tongue-lip adhesion
Logjes RJH, Mermans JF, Coerts MJ, Breugem CC, JPW Don Griot
- International Cleft World Congres in Edinburgh, UK 11-15th July 2022
- Elective course plastic surgery medical students at Amsterdam UMC NL 9th June 2021
- 78th Annual Meeting American Cleft-Palate Craniofacial Association in Raleigh USA, 1st May 2021
- 35th Annual Meeting of the Dutch Association of Cleft and Craniofacial Anomalies in Zwolle NL, 21th November 2020
- 77th Annual Meeting American Cleft-Palate Craniofacial Association in Portland USA, 2nd April 2020 (cancelled due to COVID-19)
- European Cleft-Palate Craniofacial Association Congress in Utrecht, 15th June 2019

A systematic review on objective measurements for airway management in infants with Robin Sequence: What are we measuring?
Logjes RJH, Maclean JE, de Cort NW, Poets C, Abadie V , Joosten K, Resnick CM, Trindade-Suedam IK, Zdanski C, Forrest C, Kruisinga F, Flores R, Evans K, Breugem CC.
- 78th Annual Meeting American Cleft-Palate Craniofacial Association in Raleigh USA, 1st May 2021
- 35th Annual Meeting of the Dutch Association of Cleft and Craniofacial Anomalies in Zwolle NL, 21st November 2020
- European Cleft-Palate Craniofacial Association Congres in Utrecht, 12th June 2019

Long-term speech outcomes of cleft palate repair in patients with Robin sequence versus isolated cleft palate
Logjes RJH, Upton S, Mendelsohn BA, Breugem CC, Hoffman WY, Pomerantz JH.
- European Cleft-Palate Craniofacial Association Congres in Utrecht, 15th June 2019
- 33th Annual Meeting of the Dutch Association of Cleft and Craniofacial Anomalies in Nijmegen NL, 17th November 2018
- The Annual Meeting of the Dutch Association of Plastic and Reconstructive Surgery in Ede NL, 3th November 2018
- 75th Annual Meeting American Cleft-Palate Craniofacial Association in Pittsburgh USA, 13th April 2018

Assessment of Health-Related Quality of Life in Robin Sequence: A Comparison of Mandibular Distraction Osteogenesis and Tongue Lip Adhesion
Logjes RJH, Mermans YF, Paes EC, Muradin MSM, Don Griot JP, Breugem CC.
- European Cleft-Palate Craniofacial Association Congres in Utrecht, 15th June 2019
- Annual Scientific Meeting Dutch Association of Plastic Surgery in Ede NL, 3rd November 2018
- 32nd Annual Meeting of the Dutch Association of Cleft and Craniofacial Anomalies in Utrecht NL, 18th November 2017
- 2nd International Robin Sequence Consensus Meeting in Toronto Canada, 7th May 2017
- International Cleft World Congres in Chennai India, 8-11th February 2017

Mortality in Robin Sequence: Identification of risk factors
Logjes RJH, Haasnoot M, Lemmers PMA, Nicolaije MFA, Van den Boogaard MJH, Mink van der Molen AB, Breugem CC.
- International Cleft World Congres in Chennai India, 8-11th February 2017
- 2nd International Robin Sequence Consensus Meeting in Toronto Canada, 7th May 2017

Velopharyngeal insufficiency treated with levator muscle repositioning and unilateral myomucosal buccinator flap
Logjes RJH, Van den Aardweg MTA, Blezer MMJ, Van der Heul MMB, Breugem CC.
- 28th EURAPS Annual Meeting in Pisa Italy, 25-27th May 2017
- International Cleft World Congres in Chennai India, 8-11 February 2017
- 31th Annual Meeting of the Dutch Association of Cleft and Craniofacial Anomalies in Utrecht NL, 19th November 2016
- Annual Meeting of the Dutch Association of Plastic and Reconstructive Surgery in Eindhoven NL, 20th May 2016
- 10th European Craniofacial Congres in Gothenburg Zweden, 26th June 2015

The innervation of the soft palate muscles involved in cleft palate: A review of the literature.
Logjes RJH, Bleys RLAW, Breugem CC.
- 31th Annual Meeting of the Dutch Association of Cleft and Craniofacial Anomalies in Utrecht NL, 19th November 2016

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ABOUT THE AUTHOR

Robrecht Johan Hubert Logjes was born on the 30th of September 1992 in Maastricht, The Netherlands, son of Rienie Pierey and Robert Logjes. In his young years he was interested in nature and the human body, which made him decided to study Medicine at the University of Utrecht in 2010 after graduating from the gymnasium at the Porta Mosana College in Maastricht. Throughout his studies he completed multiple rotations abroad including University of Malaya (Kuala Lumpur, Malaysia), Sanglah Hospital (Denpasar, Indonesia) and University of Ruhuna (Galle, Sri Lanka).

In his second year of his studies got in touch with the specialty of Plastic-, Reconstructive-, and Handsurgery during an elective course on the anatomy of the hand. In his third year he started performing research in the field on craniofacial anomalies under the direct supervision of Prof. Dr. C.C. Breugem at the Department of Plastic-, Reconstructive-, and Handsurgery at the University Medical Center Utrecht. He combined his scientific activities with his last 3 years of Medicine, that resulted in this PhD thesis under supervision of Prof. Dr. J.H. Coert and Prof. dr. C.C. Breugem. In his final year of Medicine, he moved to San Francisco for 6 months to conduct a part of this thesis under supervision of Dr. J.H. Pomerantz at the Craniofacial Center of the University of California San Francisco, USA.

Following the completion of his Medical Degree in 2018 he continued his research while working as a non-training resident in general surgery at the Onze Lieve Vrouwen Gasthuis, Amsterdam and the St. Jansdal Hospital, Harderwijk, before he started working as a non-training resident in Plastic-, Reconstructive-, and Handsurgery at Rijnstate Hospital Arnhem in 2021. In December 2021 he was accepted as resident in training in Plastic and Reconstructive Surgery at the University Medical Center Utrecht under supervision of Dr. W. Maarse. As part of this training, he currently works as resident in general surgery under supervision of Dr. D. Boerma at the St. Antonius Hospital, Nieuwegein.