Airway obstruction in Robin sequence:

Evaluating longitudinal evolution

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

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November 2019

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Abstract

Airway obstruction of various degrees is one of the most important problems in infants with Robin sequence. Various tools are used to evaluate airway obstruction in these infants and monitor treatment, but polysomnography is the gold standard. Routine use of polysomnography is however limited by cost and availability. The general purpose of the study was to document the evolution of airway obstruction in the first 18 months of life in a cohort of infants afflicted with Robin sequence. More specifically, we wanted to determine whether night-time pulse oximetry, an inexpensive and widely available technology, could be used as a surrogate for polysomnography in identifying obstructive apnea in infants with Robin sequence.

METHODS

This is a retrospective cohort study for all patients admitted in the neonatal period with a final diagnosis of Robin sequence at the Montreal Children's Hospital from 2003 to 2018. All data was thoroughly review from medical records for infants qualifying as Robin sequence: association of micro-retrognathia, glossoptosis and airway obstruction. We also reviewed all polysomnography and oximetry test and extracted the following standard data: Apnea hypopnea index (AHI) and mixed obstructive AHI (MOAHI) from polysomnography and Desaturation index (drops by ≥3%/hour, DI ≥3%; drops by ≥4%/hour, DI ≥4%; and time spent <90%) from the oximetry done at the time of polysomnography. A MOAHI ≤5 events/hour was used to separate infants with no/mild obstruction from those with moderate/severe obstruction (MOAHI >5 events/hour).

Analysis of data for the correlations was obtained through linear regression models with prediction equations; agreement was judged using the intraclass correlation coefficient and Bland-Altman plots. Next, generalized linear models and receiver-operator characteristic curves were used to determine the diagnostic accuracy of the desaturation index and to select a cut-off value. Statistical significance was set at a p value of <0.05.

RESULTS

The cohort of patients was comprised of sixty infants (34 males, 56.7%). With the stepwise approach to management, treatment consisted of: no intervention, n = 10; prone positioning, n = 26; nasopharyngeal airway, n = 4; low flow oxygen: n = 1; and surgery: tongue

lip-adhesion (TLA), n = 9; mandibular distraction osteogenesis (MDO), n = 9; and tracheostomy, n = 1.

We reviewed 57 polysomnographies in 29 infants; many infants with very mild obstruction in the neonatal period and normal evolution did not require a polysomnography. However, of the 97 tests that could have been done according to the institution protocol, only 59% were done. The tests done were useful to identify moderate to severe obstruction in 38.6% of cases.

When we compared oximetry to polysomnography, there was a strong correlation between DI ≥3% and MOAHI data (correlation coefficient: 0.721, $p<0.001$). All infants with a DI ≥3% <10 events/hour had no or mild obstructive apnea (MOAHI <5 events/hour, 100% negative predictive value). In patients with MOAHI >5 events/hour, all had a DI ≥3% >7 events/hour (100% sensitivity). Finally, in infants who had serial oximetry in the first 6 months of life to follow evolution, significant obstruction at age 10-12 months (moderate or severe obstructive index) was associated with an elevated value of the DI ≥3% at age 5 to 6 months (>10 events/hour).

CONCLUSION

In our cohort of infants with Robin sequence, a cohort having the characteristics of other larger cohorts, oximetry can identify the infants with no or mild obstructive apnea thereby decreasing the demand for polysomnography. Oximetry could be also a solution to serial evaluation of infants in the first several months of life to avoid adverse outcome and organize rapid intervention.

Résumé

L'obstruction des voies aériennes de divers degrés est l'un des problèmes les plus importants chez les nourrissons avec séquence de Robin. Divers tests sont utilisés pour évaluer l'obstruction des voies respiratoires chez ces nourrissons et suivre leur évolution, mais la polysomnographie est l'étalon-or. L'utilisation courante de la polysomnographie est toutefois limitée par le coût et la disponibilité. Le but général de l'étude était de documenter l'évolution de l'obstruction des voies respiratoires dans les 18 premiers mois de vie dans une cohorte de nourrissons atteints de séquence de Robin. Plus précisément, nous voulions déterminer si l'oxymétrie nocturne, une technologie peu coûteuse et largement disponible, pourrait être utilisée comme substitut à la polysomnographie dans l'identification de l'apnée obstructive significative chez les nourrissons atteints de séquence de Robin.

METHODOLOGIE

Il s'agit d'une étude de cohorte rétrospective incluant tous les patients admis dans la période néonatale avec un diagnostic de séquence de Robin à l'Hôpital de Montréal pour enfants de 2003 à 2018. Toutes les données ont été soigneusement examinées à partir des dossiers médicaux pour les sujets se qualifiant comme séquence de Robin : association de micro-rétrognathie, glossoptosis et obstruction des voies aériennes. Nous avons également passé en revue tous les tests de polysomnographie et d'oxymétrie et extrait les données standard suivantes : Indice d'apnée/hypopnée; indice d'apnée/hypopnée obstructive (IAHO); indice d'apnée centrale; indice de désaturation (baisses de ≥3 %/heure; baisse de ≥4 % /heure) et temps passé à <90 %. Un IAHO à <5 événements/heure a été utilisé pour séparer les nourrissons sans obstruction ou avec obstruction légère de ceux qui ont une obstruction modérée/grave (IAHO ≥5 événements/heure).

L'analyse des données pour les corrélations a été obtenue par des modèles de régression linéaire avec des équations de prédiction ; l'accord a été jugé en utilisant le coefficient de corrélation intraclasse et le Bland-Altman. Ensuite, des modèles linéaires généralisés et des courbes caractéristiques récepteur-opérateur (ROC) ont été utilisées pour déterminer l'exactitude diagnostique de l'indice de désaturation et pour sélectionner une valeur de coupure. Le niveau de signification statistique a été fixée à une valeur p de <0,05.

RESULTATS

La cohorte était composée de 60 nourrissons (34 garçons, 56,7 %). Avec l'approche progressive de la prise en charge, le traitement se composait de : aucune intervention, n = 10 ; positionnement sur le ventre, n = 26; voie respiratoire nasopharyngée, n = 4; faible débit d'oxygène: n = 1; et la chirurgie : adhérence des lèvres à la langue, n = 9; distraction mandibulaire, n = 9 ; et la trachéotomie, n = 1.

Nous avons passé en revue 57 polysomnographies chez 29 nourrissons ; les sujets avec obstruction légère en période néonatale et une évolution normale n'ont pas eu de polysomnographie. Toutefois, sur les 97 tests qui auraient pu être effectués selon le protocole de l'établissement, seulement 59 % ont été effectués. Les tests effectués ont été utiles pour identifier des obstructions modérées à graves dans 38,6% des cas.

Lorsque nous avons comparé l'oxymétrie à la polysomnographie, il y avait une forte corrélation entre l'indice de désaturation de ≥3 % (DI ≥3 %) et l'IAHO (coefficient de corrélation : 0,721, p 0,001). Tous les nourrissons ayant un DI ≥3 % de <10 événements/heure n'avaient pas d'obstruction ou des obstructions légères (IAHO <5 événements/heure, valeur prédictive négative à 100 %). Chez les patients avec IAHO ≥5 événements/heure, tous avaient un DI ≥3 % qui était à ≥7 à événements/heure (100 % de sensibilité). Enfin, chez les nourrissons qui ont eu une oxymétrie sérielle au cours des 6 premiers mois de vie pour suivre leur évolution, une obstruction importante à l'âge de 10-12 mois à la polysomnographie (indice obstructif modéré ou grave) a été associée à une valeur élevée de DI ≥3 % à l'âge de 5 à 6 mois (>10 événements/heure).

CONCLUSION

Dans notre cohorte de nourrissons avec séquence de Robin, une cohorte ayant les caractéristiques d'autres cohortes avec beaucoup plus de sujets, l'oxymétrie peut identifier les nourrissons sans apnées obstructives ou avec apnées légères, diminuant la demande pour la polysomnographie. L'oxymétrie pourrait également être une solution de rechange à la polysomnographie pour l'évaluation en série des nourrissons dans les premiers mois de la vie afin d'éviter les complications et d'organiser une intervention rapide.

Acknowledgements

I would like to thank and acknowledge my indebtedness to my supervisor Dr. Aurore Côté and my co-supervisors Dr. Mirko Gilardino and Dr. Lucie Lessard who made this work possible. Your continuous mentorship, support and supervision have been invaluable throughout all stages of this work.

Special thanks are given to the departments of Experimental surgery, and Plastic and reconstructive surgery at McGill university. Most of all, I would like to thank each member of my committee who has provided me expert guidance and taught me a great deal about scientific research notably Dr. Peter Davison, Dr. Evelyn Constantin and Dr. Jacques Lapointe. Also, I wish to extend my gratitude to our program coordinator Ms. Sharon turner for her continuous help since the first day. Moreover, I would like to extend my gratefulness and gratitude to my friends and colleagues who were of great support during the period of my master's notably: Dr. Andrew Gorgy, Dr. José Ramirez, Dr. Alex Viezel-Mathieu, Dr. Alain Azzi, Dr. Ahmed Al-Qattan and all the plastic surgery residents at McGill University.

I would like to thank also 2 symbols of inspiration for me throughout my studies, Prof. Nivaldo Alonso and Dr. Endrigo Bastos, my mentors in Brasil. They always believed in my craniofacial career providing me all the support needed to reach this goal.

Completing this work would have been all more difficult were it not for the support and love provided by my family members. My wife, Myriam MacDonald Galli has been extremely supportive of me throughout the entire process and has made countless sacrifices to help me get to this point. My parents, Neide and Cesario, deserve special thanks for their continuous support and encouragement since day one. My siblings, Guta, Marcelo and Gustavo, you have been so generous in your love and encouragement despite the long distance between us. Last but not least, I would like to express my gratefulness to the late Felix for always being there for me.

Contribution to original knowledge

To the best of our knowledge, the present study is the first on infants with Robin sequence to use parameters on oximetry (a simple, widely available test that can be done at home) to correctly identify infants who might not need polysomnography (a test difficult to obtain and done only in pediatric tertiary centres, with long waiting list). Indeed, we found that the desaturation index on the oximetry correlated well with the index of obstruction on the polysomnography; a cut-off value was identified to make sure that a negative oximetry corresponded to a negative polysomnography (negative predictive value of 100%); as well all positive polysomnography for moderate and severe obstruction were identified on the oximetry (100% sensitivity).

As a second novel contribution, also related to the use of oximetry, we were able to identify, with serial recordings, which infants had likely persistent obstruction at key points in the first year of life; this will enable physicians to act upon rapidly to correct the situation.

Author contribution and statement of originality

The work described in this project was performed by the author and his supervisor Dr. Aurore Côté, and it is novel and original. Rafael Galli under the supervision of his supervisors designed, conducted, coordinated and carried out studies for his project. In particular, Rafael Galli did the chart review at Medical record and online (for the electronical chart) and gathered all the data from these charts including all demographics, evolution, special tests including polysomnography data and treatment. Marie-Ange Picard Ruel (Research summer student) extracted all the oximetry data from patients on home oximeters and created the database that was later analysed by Rafael Galli. Dr. José Ramirez helped in conducting the statistical analysis of this work.

Chapter 1

Thesis Introduction

Robin sequence is a rare condition afflicting newborn infants. Airway obstruction is a cardinal feature of Robin sequence. These infants could present in the neonatal period with severe repetitive episodes of airway obstruction and intervention is needed urgently to improve their condition. The interventions could include invasive procedure such as surgery on the mandible or tracheostomy. Much has been written concerning the management of these infants in the neonatal period and several reviews are available with a consensus on the investigation and some consensus on management in the neonatal period. There is however a paucity of data exploring objectives criteria to determine the effectiveness, in the medium or long term, of interventions made to solve the problem of airway obstruction in infants afflicted with Robin sequence. Infants with Robin sequence will eventually have growth of the mandible and usually will improve after the first year of age, even those with the most severe obstruction. Some authors have nevertheless shown a persistence of the obstructive apnea. This is important as persistent airway obstructions can have lifelong consequences. There is however very little data on the evolution of airway obstruction in the first 6-18 months of life in Robin sequence.

Polysomnography (complex multichannel overnight study) has been identified as the gold standard evaluation test to diagnosed obstructive sleep apnea in infants, children and adults as well. Unfortunately, this test is often difficult to obtain in a timely manner in infants and children as it is performed only in tertiary pediatric centres and is time consuming. The waiting list for the test could be up to one year. Considering the difficulties in obtaining objective data by the gold standard test, there is a need to look at alternatives to polysomnography, namely oximetry (recording of Hb-O_2 saturation in oxygen). This test is gaining in acceptance with older children with obstructive sleep apnea but very few data have been published for the age group during which it is most crucial for infants with Robin sequence.

General objective of the research

The general objective was to study the evolution of obstructive sleep apnea in the first 18 months of life in a cohort of infants afflicted with Robin sequence.

More specifically, we wanted to

1. Describe a cohort of infants afflicted with Robin sequence and followed at the Montreal children's Hospital in recent years.

2. Describe the usefulness of timely polysomnography to identify suboptimal outcome in infants with Robin sequence in the first 18 months if life.

3. Correlate the results of polysomnography with oximetry data and determine if we could identify a cut-off value on oximetry parameters that would identify infants not needing polysomnography.

4. Report on the evolution of oximetry over time in the first 18 months of life and determine if we could identify suboptimal outcome.

Chapter 2

Comprehensive review of the relevant literature

2.1 Description of Robin Sequence (RS)

What is Robin sequence

Pierre Robin (a French stomatologist) originally described in 1923 the triad of mandibular hypoplasia, glossoptosis and airway obstruction (Robin 1923, Robin 1934). This constellation of physical findings became known as Pierre Robin syndrome until 1976 when Cohen introduced the term anomalad, defined as ‘‘a malformation together with its subsequent derived structural changes’’. To reflect the fact that these anomalies occur as a developmental sequence, the name was changed to Pierre Robin sequence. Linguistic purists argue that by convention the first names are not used in an eponym, and the currently accepted term is Robin sequence (Evans, Rahbar et al. 2006) and we will use it throughout the document. Even though a cleft palate is absent in Robins' original description, some clinicians also include it as part of the definition. However, there is no clear, unanimous definition of RS. In our review of cases at our institution, we did not use cleft palate as part of the definition of RS.

Incidence

Many countries have reported on the incidence of RS. Scott in 2014 reported that from 1,654,805 in-hospital births in North America between 2006 and 2009, 529 were born with RS. Of those, there were 302 isolated RS (1.8 in 10,000) and 227 syndromic RS (1.4 in 10,000). This was a higher incidence than in previous studies. (Scott and Mader 2014) In Europe, the incidence varies from 1 in 8060, in Germany (Vatlach, Maas et al. 2014) to 1/8500 in the UK (Bush and Williams 1983) and 1/14,000 in Denmark (Printzlau and Andersen 2004). This wide interval is seen mostly because of regional variations between different centers in distinct parts of the world. There's also no clear consensus on the precise definition of the disease itself, so the incidence reported by each center varies accordingly to the definition and criteria included in the different search strategies. Cleft palate is associated with RS in 66%–90% of cases and there is still debate whether it should be included in the definition of RS.

The diagnosis of RS initiates an evaluation to determine whether this is an isolated occurrence or a known association or syndrome. Isolated RS accounts for 20%–40% of all cases depending on the series (Bush and Williams 1983, Cohen, Greathouse et al. 2017). The most common syndromes associated with RS are Stickler (34%) and velocardiofacial syndrome (11%).

Mortality

Mortality rates for RS have been published from various countries over times. For Canada (cohort spanning 1964 to 1991) the rate was 22.8% (Caouette-Laberge, Bayet et al. 1994); it was 21% in a study from the United Kingdom spanning 1960 through 1982; (Bush and Williams 1983); in the Unites States in a study spanning 2001 to 2012, the rate was 16.6% (Costa, Tu et al. 2014). In more recent times, the rate was 3.6% in The Netherlands (1997-2011) (van Nunen, van den Boogaard et al. 2014). In that Dutch cohort, although the overall mortality rate was 3.6% there was no mortality in isolated RS; infants with cardiac or central nervous system anomalies had the highest mortality (40.6% in infants with cardiac anomalies, for instance).

Pathophysiology

RS has been associated with a range of syndromes and chromosomal anomalies, but the underlying pathogenesis of the sequence and the pathophysiological processes leading to it have yet to be fully elucidated, despite significant progress in the last decade, especially in genetics. Various genetic associations have been made with RS and the diversity of these associations highlights the fact that there are numerous ways to arrive at a common phenotype: the Robin sequence, as reviewed by Tan et al. (Tan, Kilpatrick et al. 2013).

RS represents an embryological sequence in which the primary abnormality seems to be a lack of mandibular growth, with a retro positioned tongue resulting in a physical obstruction. The mandible houses the tongue; if mandibular growth is restricted, the developing tongue will likely be pushed upwards and backwards into the mouth. The risk of developing a cleft palate seems to be related to the length of the mandible. Indeed, Hermann et al.(Hermann, Darvann et al. 2014) showed a doubling of the risk of cleft palate per millimeter reduction in mandible size.

Currently, there are three major hypotheses to explain the sequence of events in RS: (a) hypoplastic mandible; (b) oropharyngeal and muscular deficiencies; (c) compression of the mandible in utero.(Cote, Fanous et al. 2015)

The **hypoplastic mandible** theory is the one mostly retained in the literature and the one that has been demonstrated in animal models (mostly murine). While the maxilla and mandible share early origins within the first branchial arch, the subsequent development of the mandible is quite different from the maxilla. The maxillary skeleton forms in intimate association with the rest of the craniofacial complex and brain and there is no cartilage component formed in the maxillary primordia. In contrast, the mandible forms in relative isolation and the first mandibular skeletal element to form is the cartilaginous rod known as Meckel's cartilage.(Bhaskar, Weinmann et al. 1953) The primary defect of the mandible in RS is thought to be in this cartilage, the embryonic structure involved in its formation and growth. The subsequent mandibular hypoplasia is thought to lead to a small mouth volume, abnormal position of the tongue, and the secondary impairment of palatal closure.(Hanson and Smith 1975)

In the **oropharyngeal and muscular deficiency** hypothesis, it is believed that hypotonia of the oropharyngeal muscles could result in hypoplasia of the mandible. (Tan and Farlie 2013, Tan, Kilpatrick et al. 2013)The persistence of feeding issues for weeks to months in infants afflicted with RS in which respiratory compromise has resolved suggests anomalies in pharyngeal tone and motility. Fetal oral muscular activity, including swallowing movements, is thought to be required for normal growth of the mandible. A number of neuromuscular abnormalities are associated with micrognathia and diagnosed with RS (Renault, Flores-Guevara et al. 2000, Baujat, Faure et al. 2001, Abadie, Morisseau-Durand et al. 2002, Abadie and Couly 2013). Those include (but are not restricted to) Congenital Myotonic Dystrophy, Carey-Fineman-Ziter syndrome, Moebius syndrome and Moebius sequence. (Tan and Farlie 2013, Tan, Kilpatrick et al. 2013)

Finally, the **mandible compression** theory probably plays a role in a small proportion of infants born with RS, in particular those having experienced a pregnancy associated with fetal constraint such as oligohydramnios or twin pregnancies. Indeed, a higher incidence of twins has been reported in RS when compared to the general population. (Cote, Fanous et al. 2015) Early in fetal development (first few weeks), the head is in a flexed position on the thorax and the mandible is therefore apposed against the chest. There is later a progressive

extension of the fetal head (full at the 12th week of gestation). Head extension is believed to favor mandibular growth. If head extension is limited by the presence of oligohydramnios, multiple fetuses, uterine abnormalities, a small or malformed uterus, there might be restriction of growth, which in turn can lead to restriction in growth of the mandible. (Cohen 1976, Sadewitz 1992),

The hypoplastic mandible theory has gained a great deal of support and was first hypothesized by Robin himself. The relationship between Meckel's cartilage and mandibular outgrowth has been the subject of considerable experimental work and palatal shelf obstruction by the tongue is similarly well supported. However, the diversity of genetic conditions associated with RS indicates that there might be several pathways to reach the same developmental outcome. This does not exclude alternative etiologies and although less well-established, the oropharyngeal and muscular deficiency theory is a highly plausible explanation for RS.(Tan, Kilpatrick et al. 2013)

Genetic basis

As highlighted in recent reviews on the genetics of RS, the medical community is only starting to learn about the potential genes involved in mandibular growth and their implication. There are more than 50 described disorders associated with Robin sequence. (Tan, Kilpatrick et al. 2013) (Logjes, Breugem et al. 2018)

There are several genetic defects, which will trigger a sequence of events leading to RS. Indeed, a recent literature review on ontogeny of RS (Logjes, Breugem et al. 2018) identified numerous genes that are implicated in RS and they are classified as follows: Collagen and bone development: 12 genes including the COL11A1 and 2 involved in various forms of Stickler syndrome; metabolic disorder 2 genes; Neuromuscular disease: 3 genes; Neural crest development: 5 genes including the 22q11.2 (Velocardiofacial syndrome), TCOF1 and POLR 1C and 1D involved in Treacher-Collins syndrome; Pharyngeal arch developments: 3 genes; RNA related genes: 6 genes; and other not yet classified: 10 genes. There are also identified defects in ubiquitous cellular processes resulting in RS-related conditions like Treacher-Collins syndrome and Miller syndrome, for instance.

Very interesting work is being conducted in order to better understand the role of SOX9. The SOX9 gene provides instructions for making a protein that plays a critical role during embryonic development. The SOX9 protein is especially important for development of

the skeleton and plays a key role in the determination of sex before birth. The SOX9 protein binds to specific regions of DNA and regulates the activity of other genes, particularly those that control skeletal development and sex determination. This gene, a critical chondrogenic regulator, has been linked to non-syndromic RS in families with more than one member affected (Benko, Fantes et al. 2009), lending support to the mandibular hypoplasia hypothesis. Furthermore, more recent work has shown that multiple non-coding elements contribute to the craniofacial regulation of SOX9 expression; in RS, these craniofacial regulatory elements are the site of deletions, contributing to the typical phenotype (Gordon, Attanasio et al. 2014, Cote, Fanous et al. 2015). Mutations in the SOX9-regulated collagen genes COL2A1, COL11A1, and COL11A2 are associated with Stickler syndrome, one of the frequent syndromic RS. (Logjes, Breugem et al. 2018)

Among the syndromes responsible for RS, Stickler syndrome (SS) and 22q11.2 deletion syndrome (22qDS)/velocardiofacial syndrome (VCFS) are the most frequent and the prevalence varies significantly in the literature probably owing to small cohorts studied. Holder-Espinasse et al. (Holder-Espinasse, Abadie et al. 2001) found no cases of 22qDS in their cohort of 110 patients with RS. In contrast, Shprintzen (Shprintzen 1992) reported VCFS in 11% of 100 patients with RS.

Stickler syndrome is associated with mutations in COL genes (COL2A1, COL9A1, COL11A1, and COL11A2)(Acke, Dhooge et al. 2012); velocardiofacial syndrome arises from a microdeletion of chromosome 22q11.2(Buchanan, Xue et al. 2014); and Treacher Collins syndrome is associated with mutations in the TCOF1, PLOR1C, and POLR1D genes (Trainor and Andrews 2013, Buchanan, Xue et al. 2014, Kadakia, Helman et al. 2014, Cote, Fanous et al. 2015).

Eventually, it might be possible to correlate the genotype with the phenotypic characteristics and have a better understanding of the evolution and the prognosis for airway obstruction, feeding and development in those with a specific genotype identified(Cote, Fanous et al. 2015). The diagnosis of syndromic RS has an impact on medical treatment, including airway and feeding management, because the literature suggests that infants with syndromic RS have more severe disease and need more aggressive management than those with isolated RS(Izumi, Konczal et al. 2012). Better genetic characterization, especially if rapidly available in the neonatal period, likely will be an advantage in future.

2.2 Airway obstruction

Obstructive apnea is defined by the American Thoracic Society as having prolonged partial upper airway obstruction (obstructive hypopnea) and/or intermittent complete obstruction (obstructive apnea) that disrupts sleep patterns and ventilation during sleep (George 1996, Garg, Afifi et al. 2017). During obstructive apnea, respiratory effort is preserved or increased at times of apnea, as the infant attempts to overcome obstruction.

The infant is particularly vulnerable to obstruction due to anatomical considerations: face shape, large tongue relative to the oral cavity as compared to older children and adults and obligate nasal breathing. In infancy, causes of obstructive sleep apnea are predominantly anatomical for example those with laryngomalacia, macroglossia or craniofacial disorders such as Robin sequence, craniosynostoses, mid-face hypoplasia, and those with choanal atresia (Cielo, Montalva et al. 2016) (Patwari and Sharma 2019) (Virbalas and Smith 2015).

Obstructive apneas are much more prevalent in sleep. Sleep is a distinct physiological state with changes in brain activity, muscle tone and autonomic function (cardiac and respiratory control) as compared with wakefulness. Sleep and breathing are intrinsically related functions, and this relationship is very important in newborns and infants who sleeps for much longer periods than older children and adults and have a higher proportion of REM sleep (Urquhart and Tan 2016). In addition, the predominance of rapid-eye movement sleep (REM sleep) is associated with marked decrease in muscle tone in general, which includes the muscles of the upper airway, which in turn, may exacerbate obstruction.

Obstructive sleep apnea has a very high prevalence in RS, being between 85 and 100% in infants referred for evaluation in a tertiary care facility (Anderson, Sedaghat et al. 2011, Daniel, Bailey et al. 2013). Infants with Robin sequence are classically described as developing airway obstruction soon after birth(Dennison 1965). There are infants, however, that have a delayed presentation and airway obstruction become evident only in the first or second month of life. Ogborn and Pemberton (Ogborn and Pemberton 1985) reported that 30% of their cases did not present in the immediate neonatal period. Similarly, Wilson et al. noted that upper airway obstruction might appear over the first month of life (66% in that cohort) (Wilson, Moore et al. 2000).

Late onset upper airway obstruction, particularly after initial hospital discharge, has potentially serious consequences. Indeed, deaths caused by sudden deterioration in the degree of upper airway obstruction in the Robin sequence have been reported by Caouette-

Laberge et al. (Caouette-Laberge, Bayet et al. 1994). These reports of late clinical presentation of upper airway obstruction in the Robin sequence highlights the need for close prospective respiratory monitoring of all such infants.

Evaluation for airway obstruction

Given the very high prevalence of obstructive apnea in newborn with RS, a thorough evaluation is needed. There are many ways to evaluate airway obstruction and we have divided it into clinical and objective evaluation. Objective evaluation includes, blood gases, physiological recordings of respiration and oxygenation and endoscopic evaluation of the upper and lower airways

Clinical evaluation

It could be difficult to evaluate airway obstruction solely with clinical criteria in infants, and especially in those with RS. Snoring, a cardinal manifestation of airway obstruction in children and adults, is not always present in infants with RS in part due to the wide U-shape cleft palate. Anderson et al. (Anderson, Sedaghat et al. 2011) reported that only 50% of the infants with severe airway obstruction had snoring. Often, difficulties in feeding and lack of appropriate weight gain are the only clinical signs of persistent airway obstruction. These difficulties, however, could also be due to a more general central nervous system problem, as presented by some authors (Abadie and Couly 2013). Clearly, clinical evaluation cannot be the sole evaluation, even in mild cases.

Objective evaluation

There are a few tests available to evaluate the presence of airway obstruction: measuring blood gases, monitoring oxygenation by pulse oximetry, performing a polysomnography (multichannel recording with sensors for airflow, respiratory movements, transcutaneous PCO_2 and SpO_2 and with recording of sleep states by EEG, electro-oculogram and electromyogram) and evaluation by upper and lower airway endoscopies.

Blood gases. Measurement of capillary blood gases (CBG) is a good tool to evaluate rapidly the presence of airway obstruction. Infants with repeated airway obstructions, even those with only brief repeated obstructions, have increase in PCO_2 and HCO_3. CBG entails blood procurement and serial measurements are usually done during hospital admission.

A recent study (Fahradyan, Azadgoli et al. 2018) has shown that the most reliable test to predict the physiologic effects of obstructive apnea in newborn with RS is the capillary blood gas showing an increase in PCO2 values. The authors showed that a pCO_2 of 49.5 has the best specificity (100%) and sensitivity (72.6%) profile in terms of need for definitive airway intervention.

Serial CBG measurement are however not practical in the home setting. Obviously, other tests are also available and should be used to better characterize the airway obstructions and the impact on oxygenation.

Oxygenation monitoring. Oxygenation status is routinely done by estimating the Hb saturation in oxygen by pulse oximetry (SpO_2). SpO_2 monitoring is non-invasive through the skin with a sensor place on the extremities (usually the foot in newborns). It will identify the episodes of drops in oxygenation. It is known that infants with airway obstruction will have drops in oxygenation at the time of obstruction (partial or complete) and these drops are more important in infants than older children and adults (Horemuzova, Katz-Salamon et al. 2000) and (Marcus 2001). Normative data of oxygenation measured by pulse oximetry are available for infants in the first year of life (Poets, Stebbens et al. 1991, Poets, Stebbens et al. 1996, Hunt, Corwin et al. 1999, Beresford, Parry et al. 2005, Hunt, Corwin et al. 2011, Brockmann, Poets et al. 2013).

Traditionally, oximetry was considered a poor predictor of airway obstruction except for the most severe cases. This was well recognized for children with adenotonsilar hypertrophy and a normal study result did not eliminate the need for a polysomnography. This is changing now as recently presented in a systematic review of the literature (Kaditis, Kheirandish-Gozal et al. 2016). Indeed, the desaturation index (number of event below a certain level/hour of recording) is now considered as a good surrogate for the obstructive apnea index of polysomnography in children. There is however no data evaluating the use of the desaturation index in infants with airway obstruction.

Oximetry has many advantages as it is a simple test, easily performed by non-professionals (parents) with the need of brief training only; it can be done at home and can be done repeatedly. In addition, prolonged continuous monitoring with oximeters is feasible and our group has published the largest experience on the subject (Gelinas, Davis et al. 2008), showing the feasibility, good compliance to the use of the monitor and excellent results that can be obtained, including changes in management based on the results.

Infants in the first few months of life have central events with drops in oxygenation, which is not seen in older infants and children. The problem with oximetry is that it cannot help differentiating drops in oxygenation due to central vs. obstructive events.

Polysomnography. Polysomnography (PSG) is still the gold standard for the diagnosis of obstructive sleep apnea (Marcus, Brooks et al. 2012). Central apnea can be differentiated from obstructive apnea on PSG. Normative values and criteria for obstructive and central apnea are now available for infants (Brockmann, Poets et al. 2013) and longitudinal data in infants with Robin sequence have been published (Lee, Thottam et al. 2015).

PSG is done in a sleep laboratory during a full night of sleep and is a complex test needing qualified and highly trained personnel. For infants and children, the test is available only in tertiary pediatric hospitals. Everywhere in Canada (and in many other regions of the world), there is a long waiting list (sometimes up to one to two years) for the test. Urgent cases are prioritized, but in cases where regular follow-up is needed, it is difficult to get timely serial evaluations.

Airway endoscopy. An airway endoscopy entails the direct evaluation of the airway (upper and lower) with a fiberoptic device helping in visualization of the anatomy. Upper airway endoscopy is essential to appreciate the degree of glossoptosis if any (one of the criteria to diagnose Robin sequence). It is also useful to assess any degree of nasal or choanal stenosis or choanal atresia. Careful examination of the mouth is also possible for any other anomaly as buco-pharyngeal membranes. In addition, it permits the visualization of the vocal cord, their movements and any presence of laryngomalacia or other supraglottic anomaly. Lower airway endoscopy allows the evaluation of the subglottic space for the presence of any stenosis and to evaluate the presence of tracheomalacia or bronchomalacia as well as possible compression of the major airway by extrinsic factors.

Classification of Robin sequence

There have been many attempts over the years at classifying Robin sequence especially as it pertains to feeding complications and, more recently, to the intervention needed to relieve airway obstruction.

Couly (Couly, Cheron et al. 1988) established the first classification of RS which was published in 1988; this classification was later revised by Caouette-Laberge in 1994 (Caouette-Laberge, Bayet et al. 1994). Patients were evaluated for their respiratory and nutritive problems. Cole et al. (Cole, Lynch et al. 2008) published a new more detailed classification in 2008 but still with only the consequences of the airway obstruction on feeding. The last two published classifications, by Cote et al. (Cote, Fanous et al. 2015) in 2015 and Li et al. (Li, Poon et al. 2017) in 2017 added to their grading system what intervention is needed to relieve airway obstruction. In addition, Cote et al. went a step further classifying separately the respiratory issues and feeding issues as in some cases, the severity of feeding issues might be greater than that of the respiratory issues. The different classifications with their details are given in Tables (2.1 to 2.4).

Interestingly, there are not many publications that attempted to determine objectively the degree of severity in RS as it relates to one or several of these classifications. A recent publication (Manica, Schweiger et al. 2018) correlated the results of polysomnography with the clinical manifestations of the classification of Cole. They found that oximetry-based parameters (time < 90% and desaturation index ≥4%) had significant high correlation with the grade on the classification, the higher the low oxygenation index, the higher the grade of clinical severity.

2.4 Airway obstruction

Consequences of airway obstruction

The immediate consequences of airway obstruction in the neonatal period are hypoxemia and hypercapnia and failure to feed adequately by mouth (often exacerbated if there is a cleft palate). Some newborns will need medical intervention immediately after birth to avoid serious consequences; those includes placement of a nasopharyngeal airway, endotracheal intubation to bypass the obstruction. In the short term, hypercapnia and failure to thrive is the most important manifestation of repeated airway obstruction in newborns with RS.

In longer term, untreated repeated airway obstructions lead to persistent failure to thrive and eventually cardiovascular complications. There is, in addition, ample evidence that behavioral problems and neurocognitive deficits are more prevalent in children with

obstructive sleep apnea (Grigg-Damberger and Ralls 2012, Marcus, Brooks et al. 2012, Chan, Shi et al. 2014, Horiuchi, Oka et al. 2014).

Many authors have described neurocognitive deficits of various severities in children afflicted with RS (Caouette-Laberge, Bayet et al. 1994, Abadie, Morisseau-Durand et al. 2002, Smith, Walker et al. 2014). Neurocognitive deficit is thought to be due to repetitive hypoxia with sleep disturbance, although an underlying disorder involving the central nervous system (with associated poor control of facial movements, breathing and swallowing) may play a role as well (Abadie, Morisseau-Durand et al. 2002). Interestingly, a group from Germany (Drescher, Jotzo et al. 2008) compared cognitive function and global development in 34 children with RS treated according to a protocol aimed at preventing airway obstruction and the consequent repetitive hypoxia by using an orthodontic device and compared the results to those of 34 control (normal) subjects. Both groups had cognitive function within normal limits, with no significant difference between groups. It is important to mention, however, that the orthodontic device is not used in severe cases. The patients with severe airway obstruction are those at the highest risk of developing impaired cognitive function secondary to repetitive hypoxia. There is so far no long term study examining the neurodevelopmental outcome of infants with severe obstruction who were treated with different strategies and for which there is objective data on the presence or absence of airway obstruction and its severity.

Intervention to correct airway obstruction

The two immediate goals of the treatment for Robin sequence in the neonatal period are relief of upper airway obstruction and improvement in feeding. The natural history of patients with RS is an improvement with growth, for both the airway obstruction and feeding difficulties. Along with growth, airway obstruction improves as the mandible grows and the coordination of the parapharyngeal muscles improves in conjunction with voluntary tongue control. All centres that have published algorithms and clinical practice guidelines advocate conservative management initially for newborns with Robin sequence and this will be continued in those who demonstrate adequate growth and mild or no airway obstruction; this is reviewed in a recent systematic review of the literature by Gomez et al. (Gomez, Baron et al. 2018). Conservative or nonsurgical treatments include prone positioning, installation of

a nasopharyngeal airway (NPA) and continuous positive airway pressure (CPAP) applied to the airways.

Four surgical treatment modalities are available when conservative management fails or for newborns with very severe obstruction who need urgent intervention: tongue-lip adhesion, sub-periosteal release of the floor of the mouth, mandibular distraction osteogenesis (MDO) and tracheostomy. The indications for surgical intervention are often subjective and are usually based on the preference of surgeons coupled with clinical experience as recently shown in a survey in the USA (Scott and Mader 2014). Prior studies have developed grading systems, clinical criteria, and algorithms to aid in therapy selection, but these systems remain incomplete in identifying those patients who will likely improve without surgery. Overall, little consensus exists regarding objectively proven clinical parameters for choosing between operative and non-operative airway management. And some authors presenting their data on conservative management and its success have used adult criteria for evaluation of airway obstruction, criteria in the range that would be representing severe obstruction in infants and young children (Albino, Wood et al. 2016).

Non-surgical intervention

Most infants with Robin sequence are believed to not require surgical intervention for respiratory compromise. In a recent publication, Cote et al. reviewed the literature up to 2015 on the intervention in RS and had data on 1425 infants with RS in 14 different cohorts. They calculated that 68% of the infants with Robin sequence were treated without surgery. The range of use of different strategies was as follows: prone position from 19% to 73%, naso-pharyngeal airway from 0% to 61% and CPAP from 0 to 91%. The wide range between centers is certainly a reflection of the familiarity with a technique, especially for the use of a nasopharyngeal airway and CPAP. We will now review the different non-surgical interventions available.

Prone position. As early as the 1920s and 1930s, Lenstrup (Lenstrup 1925) as well as Eley and Farber (Eley and Farber 1930) had described a few cases of micrognathia and cleft palate and had proposed treatment options which included prone positioning in order to improve breathing and feeding (Cote, Fanous et al. 2015). Dennison, in 1965, believed that surgery had little to offer in the treatment of Pierre Robin Syndrome and he reported the treatment

of his patients with “Elastoplast Cap Suspension” in the prone position associated with tube feeding and skilled nursing (Dennison 1965). Currently, positioning the infant in the prone or side position is generally agreed to be the first-line and simplest management option for airway obstruction. Placing the infant prone is thought to allow the mandible and tongue to fall forward and reduce airway obstruction at the tongue-base level.

Since the 1990s, prone position has been associated with sudden infant death syndrome (SIDS). In Canada, a large campaign to discourage the prone sleeping position has been launched in the early 1990s and there was a subsequent > 50% decline in the number of sudden infant death syndrome (Gilbert, Fell et al. 2012). Parents all over the world are now advised to place newborns supine to sleep. To address Robin sequence patients, Cole et al. proposed side positioning in these infants (Cole, Lynch et al. 2008) and have used that strategy in their less severe group.

Nasopharyngeal airway. Tongue-base airway obstruction may be relieved as the NPA breaks the seal between the tongue and posterior pharynx. The procedure involves placement of a tube (usually a modified endotracheal tube) into one nasal passage, with the tip positioned in the distal oropharynx, beyond the area of obstruction. At the time of the procedure, flexible nasopharyngoscopy through the tube can be performed to visualize the position of the distal tip of the NPA above the level of the glottis or distal oropharynx.

When used appropriately, it is believed to solve a significant amount of airway obstruction (Parhizkar, Saltzman et al. 2011) (Abel, Bajaj et al. 2012) Drago Marquezini Salmen and Lazarini Marques 2015). The main advantages of this intervention are that the NPA can be placed without anesthesia, and these patients may be discharged home and followed as outpatients. Furthermore, the NPA can be removed without anesthesia. Disadvantages are the cosmetic appearance of the NPA, the possible negative impact on oral feeding and the additional home care required from the parents. Indeed, in one of the study (Wagener, Rayatt et al. 2003), all infants were cared for in the hospital’s long-term care unit, as opposed to being discharged home following appropriate parent teaching.

Clearly, the nasopharyngeal airway at home necessitates documentation that airway obstruction is relieved, committed parents and a dedicated readily available team for support. Furthermore, the treatment usually spans several months as reviewed in Cote et al. (Cote, Fanous et al. 2015).

Continuous Positive Airway Pressure (CPAP). Continuous positive airway pressure is a non-invasive modality that is used for maintenance of airway patency during the whole breathing cycle and has been shown to reduce the work of breathing and to improve gas exchange and clinical outcomes (Leboulanger, Picard et al. 2010). CPAP has been used in Robin sequence infants in very few centers with the expertise of this equipment in young infants.

The major advantage of continuous positive airway pressure is that this treatment can be applied on demand. The extension of continuous positive airway pressure as routine care became possible because of the availability of well-adapted, well-tolerated industrial nasal masks for this age group, enabling this technique to be used on a larger scale (Amaddeo, Abadie et al. 2016).

One complication of CPAP use in very young infants is the secondary maxillary growth delay (Li, Riley et al. 2000). No information regarding this important issue was given in those studies. This possibility must be kept in the clinician's mind when choosing this type of management that will likely be long (Fauroux, Lavis et al. 2005, Amaddeo, Abadie et al. 2016).

Surgical intervention

In their review of the literature on the different interventions in RS, Cote et al. reported data on 452 infants treated with surgical intervention. The range of use of different surgical options was as follows: for tongue-lip adhesion, from 0 to 27%, mandibular distraction osteogenesis, from 0 to 55% and tracheostomy, from 0 to 34%. Clearly again, the wide range per center reflected the familiarity of the different centers with the techniques.

Tongue-lip adhesion (glossopexy). Glossopexy was described as early as 1911 by Shukowsky (St-Hilaire and Buchbinder 2000), but the concept of tongue-lip adhesion for relief of obstructive apnea related RS was first introduced by Douglas (Douglas 1946). Routledge, in 1960, reported on a modification of the tongue-lip procedure that helped to decrease significantly many of the complications reported with the Douglas technique. Transverse incisions were done along the anterior tongue and the posterior lower lip, the adhesion shaped by suturing the wound edges to one another and hold by a retention suture from the dorsum of the tongue to the chin. Several alterations of the Routledge procedure have been described. Randall reported in 1977, moving the retention suture to the posterior aspect of

the tongue, by this way providing, during healing, better support of the tongue base. Argamaso, in 1992 (Argamaso 1992), described another modification with an internal retention suture looped around the mandible and sutured to the muscularis propria of the tongue. The addition of muscle sutures avoided the complications of tongue laceration and dehiscence of the glossopexy (Kirschner, Low et al. 2003). Many centers still used preferentially that surgical technique.

Release of the floor of the mouth. This surgical option is not widely used with only a few centers in the world preferentially using it. Originally described by Delorme et al. (Delorme, Larocque et al. 1989), this procedure entails the release of the genioglossus muscle from its mandibular insertion on the floor of the mouth to allow for better anterior movement of the tongue. This technique is still in use at the CHU-Ste-Justine in Montreal. Complications of this technique are not well described in the literature.

Mandibular distraction osteogenesis. Mandibular distraction osteogenesis was successfully employed first in children with various conditions to avoid tracheostomy or to decannulate children with long-standing tracheostomy. Following these initial reports, MDO has been used in progressively younger patients, including in newborns with RS.

The surgical approach includes bilateral osteotomies at the ramus and/or the body of the mandible and insertion of distraction devices, which can be internal or external with transcutaneous pins. External hardware has the main advantage of being easy to regulate the angle vector and easy removal in a second surgery. On the other hand, it can be displaced with trauma by the infant and are associated with more scarring. Internal hardware is in general better tolerated by the patient, although need extensive dissection for removal under general anesthesia. There are 3 steps that follow the osteotomies: latency (early osteotomy healing); activation (depending on age and local center protocol, the device opens the area of the osteotomy at a rate of 1 to 2 mm/day, as the mandible is elongated); and consolidation (bone healing of the gap after end of distraction with the hardware in place). The main gain of infant bone manipulation is the increased airway patency as glossoptosis is diminished, which is obtained with the displacement of the floor-of-mouth and tongue mandibular attachments.

A challenging decision is regarding the timing of intervention of MDO in infants with Robin sequence (Tahiri, Greathouse et al. 2015). Generally, it depends on the severity of the airway obstruction and on the surgical expertise of the craniofacial team. Up to the present time, there are no clear and well-defined protocols to decide on the best timing of this procedure.

Because MDO is a relatively new technique for RS, the role of mandibular growth after distraction has still been an unanswered question in the literature. Nevertheless, the current recommendation is to do an overcorrection of the mandibular position in order to maximize the airway size (Miloro 2010). It is well known now that mandibular growth stay deficient in infants with Robin sequence (Daskalogiannakis, Ross et al. 2001, Staudt, Gnoinski et al. 2013).

The most frequent complication in mandibular distraction is infection, with a rate of 18.5% in a survey of craniofacial surgeons over the world (over 3000 cases) (Mofid, Manson et al. 2001). Local infections, usually associated to the pin site, are successfully treated with oral antibiotics and local wound care. Only 1% of them involved the bone. Initial improper adjustment of the distractors can lead to malocclusion. Another complication seen is hardware dislodgement and/or failure, with a rate reported of 7.5%. When using mainly external distractors, unaesthetic scars may be seen and revision surgery may be necessary (Murage, Costa et al. 2014).

As for all other interventions, further treatment might be necessary if mandibular distraction is ineffective to improve infants with RS. In that case, tracheostomy will likely be needed (Murage, Costa et al. 2014). Intervention in the neonatal period does not seem to be associated with more complications than intervention later on (Lee, Eisig et al. 2019).

Tracheostomy. The last surgical option for airway management for RS children with severe upper airway obstruction is tracheostomy. Described by Asclepiades as early as 100 BC, tracheostomy is the surgical creation of an opening into the trachea (Goodal 1934). It progressed from a treatment for urgent relief of immediate upper airway obstruction to respiratory toilet and supported ventilation, mainly when no other treatment options are successful. Tracheostomy is often performed for infants whose severe airway obstruction and underlying clinical condition do not respond to the conservative measures as well as to

the available surgical therapies, such as TLA and MDO (Evans, Sie et al. 2011). These infants often have multilevel airway obstruction including obstruction in the lower airways.

Tracheostomy achieves control of the airway but is associated with significant morbidity. When compared to the adult population, tracheostomy in children is related with a higher morbidity and mortality. Ozmen et al. have described the complications of tracheostomy, which include tracheal infections and subglottic stenosis. (Ozmen, Ozmen et al. 2009) In addition, tracheostomy generates high cost for care (family and institution).

2.5 Outcomes in Robin sequence

Because RS is often a challenging medical and surgical condition, it is especially important to look at the outcomes in these patients. Currently, there is a paucity of studies directly comparing the different treatment strategies with outcomes; and the existing ones are limited by variations in the group selection, and the severity of airway obstruction (Zhang, Hoppe et al. 2018).

There have been several clinical practice guidelines developed for RS to help in deciding which strategies to use in the neonatal period. There is much less available on the strategies once patients are sent home after non-surgical or surgical treatment. Very few centers have done serial objective evaluations to determine adequacy of treatment in the long term.

Prone position

Many centres use clinical monitoring coupled with the absence of alarms on the oximeter in the nursery and the normalization of the PCO_2 to judge success of the prone position during the initial hospital admission. In a prospective study, Marques et al. (Marques, de Sousa et al. 2001) reported that prone positioning alone was successful in 40.3% of patients; syndromic patients did less well than their nonsyndromic counterparts. Caouette-Laberge et al.(Caouette-Laberge, Bayet et al. 1994), in a series of 125 Robin sequence patients, successfully used prone positioning treatment in 44.8%. (Evans, Rahbar et al. 2006) Meyer et al.(Meyer, Lidsky et al. 2008) reported success with nonsurgical airway intervention in 70% of infants with isolated RS. However, these were often based solely on clinical evaluation.

Daniel et al. studied infants with polysomnography in the neonatal period. All infants had obstructive sleep apnea with a minority having a mild degree (13%). Therefore, the infants though to be fine in the prone position all had at least a mild degree of obstruction. A more recent study by Coutier et al. (Coutier, Guyon et al. 2019) examined the evolution of obstructive sleep apnea and sleep quality also with polysomnography in patients studied supine and prone; the age was between 1 month and 2 months. In their group, most of the infants (2 out of 3 infants) still had severe obstructive sleep apnea (mixed obstructive apnea-hypopnea index > 10 events/hour) in the prone position.

Nasopharyngeal airway

For the use of nasopharyngeal airway, some centers have reported their experience(Marques, Sousa et al. 2001, Abel, Bajaj et al. 2012). Abel et al.(Abel, Bajaj et al. 2012), for instance, studied their patients with oximetry to categorized the degree of obstruction. However, they used the criteria published for detecting mild, moderate or severe airway obstruction in children with adenotonsilar hypertrophy (Nixon, Kermack et al. 2004). Infants with a less severe degree of obstruction were therefore likely missed. They later studied their patients with polysomnography to document improvement. They reported no obstruction in 5 of the 63 infants (8%) treated with NPA, mild obstruction in 39 (62%) and 19 infants (30%) had persistent moderate obstruction with no patients having severe obstruction. They also used polysomnography to determine the timing of removal of the NPA. Nevertheless, in their cohort of 63 infants, the NPA was required for an average of 8 months (range 6 weeks to 27 months). This has been the experience of others that also reported that the NPA is often needed for months (Marques, Sousa et al. 2001, Wagener, Rayatt et al. 2003).

Marques et al. (Drago Marquezini Salmen and Lazarini Marques 2015) analyzed the evolution of a large series of severe cases of children with RS treated exclusively with NPA in their center. They did not use polysomnography to identify persistent airway obstruction but oximetry (Marques, Peres et al. 2004, Marques, Bettiol et al. 2008, Drago Marquezini Salmen and Lazarini Marques 2015).

All that data on the use of NPA emphasizes the need to use adequate data to diagnose airway obstruction and the need as well for adequate prolonged follow-up.

CPAP

Daniel et al. from Australia (Daniel, Bailey et al. 2013) and Fauroux et al. from France (Amaddeo, Abadie et al. 2016) published the largest experience on the treatment of Robin sequence with CPAP as their first initial management modality. The former group (n=39) reported that 2 of their 10 infants with mild to moderate obstruction and 16 of the 29 with severe obstruction could be discharged home on CPAP. Fauroux et al. (n=44) had 4 of their 4 infants with moderate obstruction and 5 of the 9 with severe obstruction that went home successfully with CPAP. The remaining 31 were classified as mild and were treated with prone position or had no clinical upper airway obstruction. Both groups assessed their cohorts with objective polysomnography data but failed to provide data on follow-up regarding the resolution of airway obstruction (Daniel, Bailey et al. 2013, Amaddeo, Abadie et al. 2016). Duration of non-invasive continuous positive airway pressure ranged from 4 weeks to more than 4 months, showing that non-invasive continuous positive airway pressure is necessary only during a critical window of a maximum of 6 months in most patients. This relatively short period restricts the potential side effects of long-term non-invasive continuous positive airway pressure already described.

Subperiosteal release of the floor of the mouth

Caouette et al. (Caouette-Laberge, Borsuk et al. 2012) have followed their patients with serial polysomnography following their surgical procedure (sub-periosteal release of the floor of the mouth). The results were used to guide the therapy (utilization and cessation of CPAP, supplemental oxygen or prone position). Many infants still had significant airway obstruction for a prolonged period as judged by the range of values provided for the apnea-hypopnea index and the additional treatment done (CPAP or supplemental oxygen).

Tongue-lip adhesion

We found two studies from the same group (the latest one with longer follow-up) evaluating the persistence of airway obstruction post tongue-lip adhesion in infants with RS (Resnick, Dentino et al. 2016, Resnick, Calabrese et al. 2018). These authors described improvement in all infants but persistent airway obstruction (more than mild severity) in 50% and 47% respectively. The patient with no or minor obstructions post-surgery were followed from 15 to 28 months in the first study and up to 5 years in the second study, which is excellent and should have uncovered ongoing problems of obstruction.

Mandibular distraction osteogenesis

A few studies evaluated the outcome of mandibular distraction in small cohorts, usually at a single institution (Denny and Amm 2005, Genecov, Barcelo et al. 2009, Miloro 2010, Resnick, Calabrese et al. 2018). All showed positive outcome immediately after distraction and extubation or cessation of other therapy.

Some other studies have shown objective improvement in the size of the airway by different means post MDO. Denny et al. in 2001, (Denny, Talisman et al. 2001), used cephalometric studies to assess infants born with micrognathia pre and post mandibular distraction. The authors observed the normalization of maxillary-mandibular relationship and a 67.5% mean augmentation in the cross-sectional airway area, when it was compared with the effective airway space before the procedure. As well, mandibular lengthening and volume increase are associated with airway obstruction improvement in infants who were submitted to MDO, after analysis of the results from 3-dimensional CT scans (Roy, Munson et al. 2009).

Comparison of MDO to other surgical options. In their review, (Zhang, Hoppe et al. 2018) use the avoidance of tracheostomy, having reached full oral feed at follow-up and rate of second intervention for recurrent obstruction as outcome measure for comparison between the two procedures. Whereas 95% of subjects avoided tracheostomy in the MDO group, it was 89% in the TLA group. Eighty-seven percent of subjects treated with MDO achieved full oral feeds at latest follow-up while it was 77% in subjects treated with TLA. The rate of second intervention for recurrent obstruction ranged from 4% to 6% in MDO studies, compared to a range of 22% to 45% in TLA studies. In a recent retrospective study from Resnick, there was successful resolution of obstructive apnea in RS infants in 72% (n=31) of their cohort treated with MDO, accordingly to objective polysomnography data (pre and post operative) (Resnick, Calabrese et al. 2018).

Al-Majed et al. In their systematic review of the literature (Almajed, Viezel-Mathieu et al. 2017) gathered information on airway obstruction with both TLA and MDO using polysomnography data. MDO was associated with the lowest percentage of significant airway obstruction post-procedure (3.6%) compared to 50% for infants who underwent TLA.

For longer follow-up data (past the neonatal period), we have the study of Flores et al. (Flores, Tholpady et al. 2014) who did serial polysomnography in infants having undergone tongue-lip adhesion and mandibular distraction osteogenesis. The timing of PSG was in the pre and post-operative period (usually shortly after birth) and at one year of age. Infants in the TLA group still had more severe obstruction by PSG criteria at one year of age than the MDO group.

The comparison of mandibular distraction osteogenesis and tracheostomy shows an overall increase in complications, hospital stay and costs with tracheostomy. Paes et al., (Paes, Fouche et al. 2014), in their retrospectively studied isolated RS patients younger than 6 months in a 14 years survey; they observed 4 times more complications after tracheostomy than after MDO. Airway infections presented in all cases after tracheostomy and none of the MDO patients had this complication. Finally, Kohan et al. noted a 14.7-fold increase in costs, associated only to pneumonia, when they analyzed both procedures (Kohan, Hazany et al. 2010).

2.6. Summary and Gaps in knowledge

Robin sequence is a relatively rare disease associated with airway obstruction in the neonatal period. Mortality from that condition has decreased in the past few decades but is considered significant for infants with associated anomalies, especially cardiac and central nervous system anomaly.

There are a few theories to explain Robin sequence, all occurring in fetal life and leading to a sequence of events that leads to small mandible, glossoptosis and airway obstruction. Genetic factors play a very important role as well (gene involved in mandibular growth and development).

In infants with airway obstruction, there are several ways to evaluate the presence of airway obstruction and its severity. This goes from a simple blood gas analysis to multichannel recording of various parameters (polysomnography) and includes airway endoscopy of upper and lower airways. The goal of the investigation is to choose the most appropriate strategy to relieve the airway obstruction.

Non-invasive strategies include positioning, the installation of a nasopharyngeal airway and continuous positive airway pressure. The last two are not used by many centers as they involved much commitment from parents and often long hospitalisation.

Four different types of surgery are used when the non-invasive strategies fail: tongue lip adhesion, release of the floor of the mouth (rarely used outside 2 or 3 centres in the world), mandibular distraction osteogenesis and tracheostomy. Tracheostomy is used in last resort at the present time, when mandibular distraction has failed or has contraindications.

The outcome of infants treated with different strategies and in term of identification of persistent airway obstruction post treatment and in the long term has not been studied in detail. The prone positioning, which is widely used, has not been much studied as to its efficacy and the few studies having reported polysomnography (gold standard for identifying airway obstruction) have revealed a high proportion of infants with persistent, sometimes severe events. The nasopharyngeal airway technique has been studied for its efficacy; often infants treated with that method have severe obstruction and need the artificial airway for months. For infants treated with tongue-lip adhesion and studied with polysomnography, 50% had persistence of obstruction and needed additional treatment (only one study). The technique of mandibular distraction osteogenesis has been better studied with polysomnography, but usually shortly after surgery only; for longer follow-up, some authors have used adult parameters on polysomnography.

There are two major gaps identified in our literature review

- What is the natural history of airway obstruction in infants with RS in the first year of life? And, in infants receiving various treatments (invasive and non-invasive), what is the evolution of obstruction over time?

- Because polysomnography (the gold standard test) is not widely available, is there an alternative to serial polysomnography for follow-up of airway obstruction?

Table 2.1 Classification of Couly et al. modified by Caouette-Laberge et al.

Grade	Baseline state	Nutrition
1	Adequate respiratory dynamics in prone position and regular feeding.	No special requirement
2	Adequate respiratory dynamics in prone position but feeding difficulties	Often necessary to use gastric tube
3	Endotracheal intubation	Always need gastric tube

Table 2.2 Classification of Cole et al.

Grade	Baseline state	Nutrition
1	Micrognathia, palatal cleft and mild glossoptosis. No major airway obstruction when supine.	Nutrition is satisfactory.
2	Micrognathia, palatal cleft and medium grade glossoptosis. Intermittent evidence of mild obstruction while supine, none on side.	Often require nasogastric tube for few months to restore ventilation dynamics.
3	Micrognathia, severe glossoptosis, palatal cleft, and moderate or severe obstruction of the upper airways. Moderate to severe respiratory distress when supine; evidence of airway obstruction remains when nurse on side.	Respiratory dysfunction and glossoptosis do not provide normal nutrition and patient need to be fed through a nasogastric tube.

Table 2.3 Li et al. Vancouver classification

Grade	Baseline state	Intervention needed to relieve obstruction
0	Micrognathia and maxillo-mandibular discrepancy less than 10 mm, mild glossoptosis, no respiratory dysfunction, normal feeding.	Non-surgical treatments and improve the clinical conditions with prone position
1	Micrognathia and maxillo-mandibular discrepancy less than 10 mm. There is a moderate or severe degree of glossoptosis and difficulty in feeding which require the use of the nasogastric tube. There are no respiratory diseases, but oxygen desaturations can be found also in prone position.	Surgical repositioning of the tongue (tongue-lip adhesion) may be a good solution
2	Micrognathia is more pronounced and the discrepancy between maxilla and mandible is 10 mm. Severe degree of glossoptosis is associated to the oxygen desaturation also in prone position and the difficulty in feeding which requires the use of the nasogastric tube. There are some alterations in ventilatory dynamics.	Elective surgical treatment is mandibular distraction osteogenesis
3	Micrognathia is severe and airways are strongly compromised.	Tracheostomy is often required

Table .4 Classification of Cote et al.

Grade	Baseline state	Intervention needed to relieve obstruction
Respiratory classification		
0	Asymptomatic in supine position	None
1	Airway obstruction when supine	Prone or side positioning
2	Airway obstruction in supine and prone positions	Nasopharyngeal airway, CPAP, other non-surgical measures including orthodontic appliance
3	Persistent airway obstruction following non-surgical measures, or need for endotracheal intubation	Needs a surgical intervention, but not tracheostomy.
4	Multilevel airway obstruction; syndromes or associated condition not likely to improve with mandibular distraction alone	Needs a tracheostomy
Feeding classification		
0	Feeding well, appropriate weight gain	None or may need special feeding bottle for cleft palate
1	Feeding difficulties, prolonged feeding time	Increased calories or temporary gavage feeding
2	Impossibility to feed orally (motor inability or risk of aspiration); or inappropriate weight gain despite intervention	Gavage feeding (nasogastric or gastrostomy) for a prolonged period

Classification: Couly et al. (Couly, Cheron et al. 1988);
Caouette-Laberge et al. (Caouette-Laberge, Bayet et al. 1994)
Cole et al. (Cole, Lynch et al. 2008)
Li et al. (Li, Poon et al. 2017)
Cote et al. (Cote, Fanous et al. 2015)

Chapter 3

Methods

3.1 Design

This is a retrospective cohort study for all patients admitted in the neonatal period with a final diagnosis of Robin sequence at the Montreal Children's Hospital

3.2 Study Population

Identification of cases

Patients with Robin sequence followed at the Montreal Children's Hospital

Following approval from the McGill University Health Centre Ethics board (IRB 15-423-MUHC), we contacted the personnel in charge of research studies at our medical records centre to discuss the search strategy to identify all the patients. The final search strategy included the following key word for diagnosis: "pierre robin sequence" or "micrognathia" or "retrognathia". In addition, we added the following codes in the search: K07.09: Anomaly of jaw size, unspecified and K07.19: Anomaly of jaw-cranial base relationship, unspecified. All patients identified as having at least 1 of these features were included in the search if they were born between January 1st 2003 and December 31st 2018. Once created, the database obtained by the research archivist was sent to us for review.

Inclusion criteria

- All infants who satisfied the criteria recognized for the diagnosis of Robin sequence: micro/retrognathia, glossoptosis and airway obstruction.

Exclusion criteria

- Patients who were continuously on oxygen therapy for the first few months of life.
- Syndromic patients for which marked hypotonia is part of the manifestation of the syndrome; hypotonia often leads to recurrent drops in oxygenation in infants.
- Patients with heart disease associated with hypoxemia (shunt).
- Patients with significant parenchymal lung disease as this decreases pulmonary reserve and will lead to more severe hypoxemia with any obstruction.

3.3 Conduct of the project

3.3.1. Chart review

Initial review

We reviewed the original databases obtained from the search strategies and merged them in a single database. We then removed the double entries. The paper charts were then requested for those infants admitted in earlier years for which no electronic medical record was available. For the other infants, we had access to the electronical records.

The RS diagnosis was assigned to those with micrognathia on physical examination, glossoptosis (on physical examination and confirmed on upper airway endoscopy), and signs of airway obstruction including observed apneic events with hypoxemia, recorded events assessed through measurement of Hb-O_2 saturation by pulse oximetry (SpO_2) and abnormality of blood gazes (hypercapnia).

Thorough review of medical chart

We collected the following data:

a) General information: gender, gestational age, associated syndrome, presence of cleft palate, length of first admission and readmission;
b) Type and duration of respiratory support: mechanical ventilation, non-invasive ventilation, use of nasopharyngeal airway, supplemental oxygen, high flow air with nasal cannula and prone positioning;
c) Feeding: need for increased caloric intake, nasogastric feeding and duration; need for gastrostomy feeding;
d) Endoscopic procedures: upper airway endoscopy and bronchoscopy (dates and results);
e) Surgical procedures and type: tracheostomy, mandibular distraction, tongue-lip adhesion, supraglottoplasty and others related to airway management.

Review of physiological studies

Capillary blood gases

All results of blood gases were available in the electronic medical record (OACIS). We considered that the blood gases were abnormal if PCO_2 was higher than 47, and HCO3 higher than 28.

Review of cardiorespiratory and oxygenation investigation and follow-up

The data collected from the recording equipment used for cardiorespiratory studies done in the hospital had been stored on the server of the Respiratory Medicine Division at the MCH. Data is available since 2000 for the three-channel cardiorespiratory recordings and since 2003 for the oximetry recordings. Data on oximetry results from home monitoring is also available for infants who went home on a pulse oximeter. Indeed, at clinic visits, the memory of the oximeter is downloaded and stored for analysis. We had requested access to the database on the Respiratory Medicine server to obtain the files containing these recordings.

Cardiorespiratory recordings. We used the Synergy software, which is provided with the equipment for review and analysis of the data. We collected data on the presence and severity of apnea and bradycardia. The cardiorespiratory recording permits only the identification of central apnea as respiration is obtained through chest wall motion and chest wall motion is totally absent with central apnea. Obstructive events could not be identified, as they are associated with chest wall movement (to overcome the obstruction).

A significant central apnea was an apnea > 20 seconds or shorter apnea with significant drop in SpO2, that is below 80% for longer than 10 seconds. A significant bradycardia was defined as a drop in heart rate that would represent a 30% drop in cardiac output in a newborn, that is below 80 bpm for > 10 seconds. (Eichenwald 2016) Periodic breathing was defined as three or more episodes of central apnea lasting at least 4 seconds, separated by no more than 30 seconds of normal breathing (Berry, Budhiraja et al. 2012).

Oximetry recordings. We used the Profox oximetry software© (widely used throughout university centers and for clinical studies in the Respiratory Medicine Division at MCH) for re-analysis of all data. The data collected were as follows*:* average SpO_2 value, % time spent below 90%, desaturation index and nadir value of SpO_2. The desaturation index (DI) is the number of drops in SpO_2 below a certain level/hour. In the literature, both the number of drops ≥3% (D I≥3%) and the drops ≥4% (DI ≥4%) have been used (Kaditis, Kheirandish-Gozal et al. 2016).

The criteria for normal/abnormal study used in the neonatal period were according to published normative data for newborns (Poets, Stebbens et al. 1991, Poets, Stebbens et al. 1991, Poets, Stebbens et al. 1992, Poets, Stebbens et al. 1996, Brockmann, Poets et al. 2011, Terrill, Dakin et al. 2015, Wellington, Campbell et al. 2016, Flint 2018). The normative data were as follows: average SpO2: ≥95%; time spent <90%: <5%; desaturation index <80%: <5 events/hour; desaturation index ≥ 4%, <2519 events/hour and desaturation index ≥3%, <25 events/hour (Brockmann, Poets et al. 2013, Evans, Karunatilleke et al. 2018).

For follow-up after the newborn periods, we used the following criteria obtained in the first 3 months of age: average SpO2: ≥95%; time spent <90%: <0.2%; desaturation index ≥4%: <10 events/hour, desaturation index ≥3%: <16 events/hour (Poets, Stebbens et al. 1991, Brockmann, Poets et al. 2013) (Evans, Karunatilleke et al. 2018).

Polysomnography studies

Most infants had one to two polysomnography studies in the first year of life and a follow-up study after closure of cleft palate early in the second year of life. PSG results are available in the hospital chart. We extracted the following information: apnea-hypopnea index (AHI), mixed obstructive apnea–hypopnea index (MOAHI), central apnea index (CAI), respiratory arousal index (RAI). For CO_2 recording (transcutaneous) we extracted the peak CO_2, and average; the presence of CO_2 retention was defined as CO_2 levels higher than 50 mmHg for at least 25% of TST. From the oximetry recording done at the same time, we extracted the average SpO_2, percentage of SpO_2 below 90%, SpO_2 nadir and desaturation index (≥ 3% and ≥ 4%). Before July 2015, only the DI ≥4% was available and after that date, only the DI ≥3% was available (change in the recommendation of the American association of

sleep Medicine (AASM) (Berry, Budhiraja et al. 2012, Brockmann, Poets et al. 2013, DeHaan, Seton et al. 2015).

The degree of obstructive sleep apnea was divided according to the Apnea-hypopnea index: normal: <1 ev/hour; mild: 1-5 ev/hour; moderate: 6-10 ev/hour; severe: >10 ev/hour. Normative values for infants were according to international standards (Berry, Budhiraja et al. 2012, Brockmann, Poets et al. 2013, DeHaan, Seton et al. 2015).

Identification of the severity of airway obstruction

Patients were classified regarding their clinical data and effect of therapy. Infants that had only mild signs of airway obstruction, a normal oximetry, blood gases were classified as mild, and according to the institution protocol, they had no treatment. Moderate cases were those who needed to be treated with the strict prone position for normalization of their respiratory parameters. Any infant that needed a nasopharyngeal airway to improve significantly severe obstruction on respiratory assessment, and all patients who had surgery (TLA, MDO or tracheostomy), were classified in the severe category.

Data analysis

We used mostly descriptive statistics for reporting the data in the whole cohort as no analysis was required. For comparisons between groups, when applied, we used analysis of variance. Post-hoc tests were not always possible because of the small number of subjects. Data was expressed as the mean and standard deviation or proportions, as appropriate. Statistical analysis was performed using the statistical package R v.3.3.2 and Rstudio v1.0.153.

Correlation between DI ≥3% and DI ≥4% with AHI or MOAHI was obtained through linear regression models. From these models, prediction equations for were derived. Agreement rate between the predicted Apnea/Hypopnea or MOAHI and the real values were tested using the intraclass correlation coefficient (ICC) and Bland-Altman plots. Next, generalized linear models and receiver-operator characteristic (ROC) curves were used to determine the diagnostic accuracy of the desaturation index and select a cut-off value. Statistical significance was set at a p value of <0.05.

Chapter 4

RESEARCH FINDINGS

4.1 Part I DESCRIPTION OF COHORT OF INFANTS AFFLICTED WITH ROBIN SEQUENCE AND FOLLOWED AT THE MONTREAL CHILDREN'S HOSPITAL

4.1.1 Description of our cohort, investigation and management

From the databases obtained from Medical records at our institution (2003-2018), and after removing double entries obtained under different search terms, we had a total of 97 patients identified in the study period. Thirty-six (36) were excluded because of not matching the diagnosis criteria for RS; these usually had isolated micrognathia with no glossoptosis or airway obstructions. From the remaining 61, one was very sick with multiples other issues, could not be off mechanical ventilation and deceased on initial admission. We were therefore left with sixty infants (34 males, 56.7%) admitted for investigation. A cleft palate was present in 46 (76.7%), usually a wide U-shaped (Veau II) cleft. All the details of the cohort and the investigation is given in Table **(4.1.1)**

4.1.2 Syndromic vs. non-syndromic Robin sequence

All infants were evaluated by the Medical Genetic service and appropriate testing was done (which varied over the years, being much more detailed in later years). Twenty-nine infants had non-syndromic RS, 18 had a syndrome identified and the remaining 13 had associated congenital anomalies but no specific syndrome was identified. The most common syndrome identified was Stickler, in 6 cases.

4.1.3 Evaluation of airway obstruction by endoscopy

All infants had initial upper airway endoscopy by the Otolaryngology service to determine if they had glossoptosis and to evaluate for the presence of other upper airway anomalies. Nine infants were found to have associated laryngomalacia which was severe in 2 infants (supraglottoplasty was done in both), 4 had pharyngomalacia, 4 had buccopharyngeal membranes that limited severely mouth opening (release was done before any other intervention), and 2 infants had significant choanal stenosis that needed repair.

Twenty-five infants underwent bronchoscopy as part of the initial investigation; all patients judged to have severe obstruction had a bronchoscopy. The evaluation was normal in 14 of the 25 infants. The most frequent abnormalities found was tracheomalacia in 11 infants, being severe in 2 cases and further associated with bronchomalacia in 1 case. Three infants had subglottic stenosis in addition to tracheomalacia.

4.1.4 Evaluation of ventilation and oxygenation

All infants had serial measures of capillary blood gases to evaluate hypoventilation. PCO2 was initially elevated in 40 infants (66.7%). It was corrected either with time or after intervention.

All 60 infants had bedside monitoring of oxygenation with a pulse oximeter. Fifty-five of the 60 infants were evaluated with continuous oximetry recording overnight in addition to bedside monitoring. Of these 55 infants who were evaluated with recordings, 51 (92.7%) had an abnormal study with 13 infants having only mild anomalies (slightly elevated desaturation index or % time spent below 90%). In the other 38 infants, the repetitive drops in SpO2, in addition to the signs of hypoventilation, strongly suggested significant obstructions.

Cardiorespiratory recording was done in all 55 infants with anomalies on the oximetry recording, in order to evaluate for the presence of central apnea. None of the infants had prolonged central apnea (duration > 15 seconds) and there were no infants with significant bradycardia (heart rate < 60 bpm). Eight infants had significant periodic breathing with periodic drops in SpO2 explaining a significant proportion of the drops in oxygenation (more than 50%).

4.1.5 Severity of airway obstruction and treatment

Based on clinical observation, results of capillary blood gases and oximetry results, 17 infants (28.3%) were classified as having mild obstruction, 19 (31.7%) having moderate obstruction and 24 (40%) having severe obstruction Table **(4.1.2.)**.

The protocol in our institution always involved the least invasive technique initially with escalation of treatment if the strategy fails. Ten infants in the mild group of severity patients needed no treatment, having very mild obstruction in supine position and a normalized PCO2 within a few days. Those were followed at least once in the first two months of life (at our institution or by their primary care givers) to ensure they were evolving well and gained weight.

Thirty infants were treated conservatively, 7 in the mild category, 22 in the moderate category and 1 in the severe category. The most frequent non-invasive treatment was prone positioning (26 infants) and the other 3 patients were treated with a nasopharyngeal airway. In the mild and moderate category, 17 infants were later discharged home with the strict prone position and were under surveillance with a home oximeter. The infant in the severe category had multiple medical issues and was treated with low-flow oxygen.

The infants with severe obstructions were still symptomatic in strict prone position and some needed a nasopharyngeal airway with or without supplemental oxygen, and some were treated with CPAP or high flow air by cannula for prolonged period awaiting further investigation or surgery. Twenty patients required surgical management of the airway. Tongue lip adhesion, n = 10, one after prolonged used of a nasopharyngeal airway. Mandibular distraction osteogenesis, n = 9. Tracheostomy, n = 1. The median age at surgery was 25.5 days (interquartile range: 21.0 to 55.3 days). Those who had a delay for the intervention were complex cases for which there were associated findings or who needed a prior surgery (3 patients, one for bucopharyngeal membrane release, one for choanal stenosis repair and one for supraglottoplasty). The details are given in Table **(4.1.2.)**. Of the infants who had a surgical procedure, 14 went home on an oximeter monitor, at least transiently post-operatively. In the case of infants having had TLA, those who needed to sleep in the prone position (4 infants) had an oximeter at home for surveillance.

The success rate for treatment of airway obstruction was the lowest for TLA and highest for MDO. Details are given in Table **(4.1.2.)** and Figure **(4.1.1)**. Successful single-

procedure airway management was achieved in 2 of the 9 patients who had TLA; the other infants needed either prone position after TLA or further surgery. The nine patients with initial MDO all improved of the airway obstruction for months; one patient needed CPAP for recurrence of airway obstruction post palatal closure.

4.1.6 Feeding issues

In our cohort of 60 infants, 7 had no feeding issues at all, 27 needed increased calories in the first few weeks or temporary gavage feeding in hospital, and 24 infants (40%) went home with gavage feeding; of those, 7 eventually had a gastrostomy.

The severity of feeding problems was not always correlated with the severity of the respiratory problems. Indeed, of the 17 infants with mild airway obstruction, 11 had some trouble with oral feeding and 5 eventually went home with gavage feeding. Not surprisingly, all infants with severe airway obstruction could not feed orally until the respiratory situation improved.

Table 4.1.1 . Description of the cohort in the neonatal period

	N of infants
Total cohort	**60**
Prematurity	7 (1.7%)
Male gender	34 (56,7%)
Cleft palate	46 (76.7%)
Genetic evaluation	**60**
Non-syndromic	29 (48.3%)
	15 (25.0%)
Syndromic[1]	16 (26.7%)
RS plus[2]	
Ventilation and oxygenation	
Blood gases	**60**
PCO2 abnormal[3]	40 (66.7%)
Oximetry	**55, significant anomaly in 69.1%**
Normal	4
Mildly abnormal[4]	13
Abnormal	38
Cardiorespiratory recording	**55**
Normal[5]	47
Increased periodic breathing[6]	8 (14.5%)
Upper airway endoscopy	**60, abnormal in 21.7%[7]**
Laryngomalacia	4
Pharyngomalacia	4
Bucopharyngeal membranes	4

[1] 6 infants with Stickler syndrome, 3 Treacher-Collins syndrome, 2 Van der Woude syndrome (siblings), and 1 each with Hallermann-Streiff syndrome, Peter + syndrome, Toriello-Carey syndrome, Trisomy 9 mosaicism.

[2] These infants had associated anomalies but no specific syndrome identified on investigation

[3] We defined abnormality of blood gases as PCO_2 higher than 47 with HCO_3 higher than 28 on more than one test.

[4] Mild increase in desaturation index or % time spent below 90% SpO_2

[5] No significant apnea and bradycardia

[6] We defined periodic breathing as three or more episodes of central apnea lasting at least 4 seconds, separated by no more than 30 seconds of normal breathing.

[7] All infants had glossoptosis to qualify for the definition of Robin sequence; we defined 'abnormal' if there was an associated anomaly in addition to glossoptosis. Some infants had more than one anomaly.

Choanal stenosis	2
Bronchoscopy	**25, abnormal in 44%[8]**
Tracheomalacia	11
Bronchomalacia	1
Subglottic stenosis	3
Feeding evaluation	**60, severe difficulties in 18.3%%**
No anomaly	7
Mild difficulties[9]	22
Needed gavage feeding at home	11

[8] Some infants had more than one anomaly.
[9] Increased calories in feedings or temporary gavage feeding

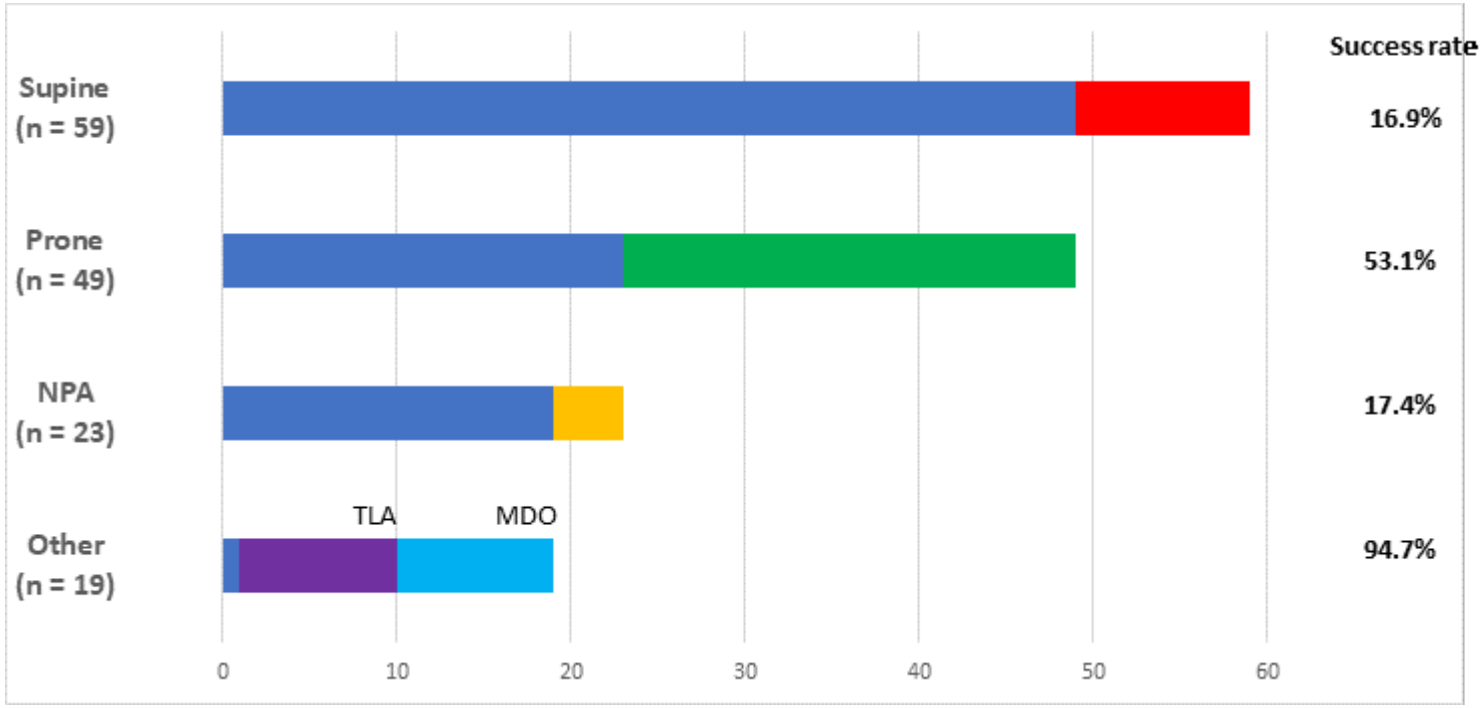


Fig 4.1.1. Success rate of treatment for airway obstruction

The % at the right of the bar graph indicates the success of the treatment attempted. For the category 'Other' the % represent the sum of the two treatments (TLA and MDO).

All infants 59 were originally tried supine, if failure the next step was the prone position; with failure of the prone position most children had a nasopharyngeal airway in place. With failure, surgical treatment was the treatment of choice.

Table 4.1.2 Severity of the airway obstruction and management

Severity	Initial treatment		Further treatment			
	Procedure	N	Procedure	N	Procedure	N
Mild n = 17 (28.3%)	None, supine position	10	-		-	
	Prone position	7	-		-	
Moderate N = 19 (31.7%)	Prone position	19	-		-	
Severe N = 24 (40.0%)	NPA	4	TLA	1	-	
			MDO	1		
	TLA	9	Prone position	4	-	
			BiPAP	1	-	
			MDO	2	CPAP	1
					BiPAP	1
	MDO	9	CPAP	1	-	
	Tracheostomy	1	-		-	
	Supplemental oxygen	1	-		-	
	Total	60	Total	10	Total	2

BiPAP: Bilevel positive airway pressure; CPAP: Continuous positive airway pressure;

NPA: Nasopharyngeal airway; MDO: Mandibular distraction osteogenesis; TLA: Tongue lip adhesion;

4.2 Part II. USE OF TIMELY POLYSOMNOGRAPHY TO MONITOR THE EVOLUTION IN ROBIN SEQUENCE

Our institution' protocol is to perform polysomnography in all infants, first pre-palatal closure and then post palatal closure to identify infants with suboptimal outcome. Polysomnography could also be performed in the first few months of life in infants if there was persistence of high desaturation index on oximetry; the goal is to identify the infants with persistence of significant obstructive sleep apnea. This protocol is largely a consequence of severely restricted access to polysomnography with long waiting list.

4.2.1 Availability of polysomnography

Despite the established protocol for Robin sequence, we discovered that not all infants had a polysomnography, as those with mild severity that had no treatment, were not followed for more than one or two months in our institution; this was the case as well for infants with no cleft palate if they had mild disease. Also, we noticed many cancellations of polysomnography when the infants suffered from upper respiratory tract infections, especially during the winter season. Consequently, surgery for palatal closure occurred without prior polysomnography in infants doing well and with normal or near normal oximetries. The same happened post palatal closure with many tests cancelled repeatedly due to viral respiratory illnesses. In our cohort of 60 patients with Robin sequence, 43 infants (those identified as having a moderate degree of obstruction in the neonatal period) should have had at least 2 polysomnographies (one pre- and one post -palatal closure) and 11 of the infants had in addition a request for the test in the first few months of life as well; this means that 97 studies should have been done in 43 infants. We only identified 57 polysomnographies (58.8%) realized in 31 patients.

Despite the caveats mentioned above, the review of polysomnography data was informative on many aspects. We were interested in all aspects of the polysomnography data in addition to the presence of obstructive apnea, the major manifestation of Robin sequence.

4.2.2 Follow-up of obstructive sleep apnea in the first few months of life

Eleven infants had PSG at an average age of 22.2 ±10.8 weeks (mean ± SD). The reason for the test was a persistently high desaturation index on the oximetry recording (Desaturation index ≥4% higher than 10 events/hour, as per our institution's protocol). The polysomnography was informative in all patients, as detailed in the next Table (**4.2.1)**, and led to important action in five cases and reassurance that the obstructive apnea index was in the mild range for the 6 other infants.

4.2.3 Obstructive sleep apnea pre- and post-palatal closure

Pre-palatal closure. We had 25 studies pre-palatal closure; the average age was 44.7 ± 9.6 weeks. The test was normal or showed mild obstruction in 17 studies (68%). Seven polysomnographies revealed a moderate degree of obstruction. Four infants had been done in wintertime and the infants had repeated viral respiratory illnesses (although they had recuperated at the time of the PSG). There was no delay in palatal closure despite the moderate obstruction, but close follow-up. Two infants did not improve and needed adenoidectomy with normal post procedure polysomnography. One infant still with a nasopharyngeal airway had persistence of severe obstructive sleep apnea OFF NPA and underwent mandibular distraction pre-palatal closure.

Post-palatal closure. We had 22 studies post-palatal closure, age 76.7 ± 13.7 weeks. The test was normal or showed mild obstruction in 13 infants (59%). Three infants had moderate obstruction and were followed clinically with later improvement. Six infants had severe obstructive sleep apnea. Five of the infants had adenoidal hypertrophy on upper airway endoscopy and one had adenotonsilar hypertrophy. Even if the hypertrophy of lymphoid tissue was not major for these infants, they all underwent surgery (adenoidectomy or adenotonsillectomy), and all significantly improved clinically with 4 having a normal follow-up polysomnography; the 2 others had normal oximetry. The other infant needed CPAP.

4.2.4 Central Apnea

Significant central apnea was not common in most of the studies. Indeed, 43 studies (75.4%) showed either no central apnea (index < 1 event/hour, 11 studies) or a mild degree (32 studies). The infants who had moderate central apnea (index between 5 and 10 events per hours, 9 studies, 16%) had non-significant desaturations with the events, hence no intervention required. There were 5 studies in 3 infants with a central apnea index > 10 event/hour. One infant (3 studies) was known for central nervous system disease with syndromic RS and was on oxygen at home (PSG done OFF oxygen). The two other infants had a recent viral infection and moderate or severe obstruction in addition to high central apnea index. Their follow-up study did not show increased central apnea index; therefore, the phenomenon seems to have been transient.

4.2.5 Arousal from respiratory events

Unfortunately, the information on whether the respiratory events were associated with arousal was not available to us for review. We therefore looked at the respiratory arousal index in proportion with the total apnea-hypopnea index, the MOAHI and the CAI and the desaturation index.

We found that the scoring of events depended more on the drops of SpO_2 than on arousals as the desaturation index was much higher than the respiratory arousal index. For the obstructive hypopneas, the arousal index was in the majority less than 50% than the MOAHI (48.0%; 95% confidence interval: 39,6% and 56,4%).

Table 4.2.1 Result of polysomnography and action taken

Findings	N	Action
1st six months (n = 11)		
No or Mild obstruction, presence of central apnea	6	None required, clinical follow-up
Moderate obstruction		
On prone position	2	Treatment of gastro-oesophageal reflux (reflux laryngitis at OTL evaluation)
On back sleeping position	2	Reinforce strict prone position
OFF NPA	1	Continue NPA
Pre-palatal closure (n= 25)		
Normal or mild obstruction	17	None required, clinical follow-up
Moderate obstruction	7	5 improved 2, no improvement, adenoidectomy
Severe obstruction	1	Mandibular distraction osteogenesis
Post-palatal closure (n = 22)		
Normal or mild obstruction	13	No action, clinical follow-up
Moderate obstruction	3	Followed with oximetry, later improved
Severe obstruction	6	5, adenoidectomy or adenotonsillectomy 1, CPAP

Abbreviations. NPA: Nasopharyngeal airway; OTL: Otolaryngology service

4.3 Part III. Correlation between the results of oximetry with parameters of polysomnography

As we have already mentioned in the previous chapter, an additional issue arising was a change in the analysis of the polysomnography data in our institution' Sleep laboratory, in July 2015, to conform to the new rules of the American Association of Sleep Medicine; the new rules were regarding the definition of obstructive hypopnea. This created a problem with our cohort that has a small number of patients with RS. Indeed, we could not group all the patients who had polysomnography. Therefore, we separated the data accordingly: there were 21 polysomnographies performed before July 2015 (Period 1) and 36 performed after July 2015 (Period 2).

We looked at Desaturation Index of 3% (DI ≥3%), Desaturation Index of 4% (DI≥4%) and time spent <90% SpO_2, Apnea Hypopnea Index (AHI), Mixed Obstructive Apnea Hypopnea Index (MOAHI). Firstly, correlation between variables was obtained through linear regression models. Subsequently, we used receiver-operator characteristic (ROC) curves to determine the best cut-off values to correlate with obstructive sleep apnea seen at the time of polysomnography.

4.3.1 The association between DI≥3% and AHI

Linear regression model was obtained to describe the relation between DI3% and AHI ($r2 = 0.943$, $p < 0.001$) **Figure (4.3.1)**. For each 1 unit increase in the DI3% value, there is a 0.66 increase in the AHI value (95%CI 0.61 to 0.72). Because AHI is comprised of both the obstructive and central events, we looked separately at these events and correlated them with the desaturation index.

4.3.2 The association between DI≥3% and MOAHI

The linear regression analysis showed significant association between DI3% and MOAHI (r2 = 0.721, p <0.001) **Figure (4.3.2)**. For each 1 unit increase in the DI ≥3% value, there is a 0.56 (95% CI 0.44 to 0.67) increase in the MOAHI value. From this regression model we were able derive a prediction equation for the MOAHI: DI3 * 0.721 + 0.56. This prediction model has an accuracy of 80% (ICC=0.80) **Figure (4.3.3).**

In order to determine the diagnostic accuracy and identify the cut off value for DI ≥3% that will be most appropriate for clinical use, we used generalized linear models and receiver-operator characteristic curves. We were able to observe a cut off value of DI 3% ≥ 13 which has the best trade-off between sensitivity (78%), specificity (82%), PPV (73%) and NPV (86%) to predict MOAHI > 5 **Figure (4.3.4a**). However, a cut-off value of DI 3% ≥ 7 has a sensitivity (100%), specificity (45%), PPV (54%), and NPV (100%) to predict MOAHI ≥5 **Figure (4.3.4b**).

4.3.3 The association between DI≥3% and MOAHI within the different subgroups

Considering that our sample had 3 distinct subgroups that were each one characterized by the reason for what the test was done, it was decided to perform the same analysis separately. The subgroups were: Diagnostic (n=7), Pre palatal closure (n=12) and Post palatal closure (n=17). After that, the same analysis applied to the complete sample was done to these subgroups in order to determine the association within each one, as well as the most adequate cut off value to increase the sensitivity and NPV of the test, determined by the ROC curve.

The Diagnostic subgroup (n=7) was excluded from the analysis due to a selection bias. According to the protocol of management of these patients, they would only have a PSG done if they had high Desaturation Index, by design. All of the patients composing this subgroup had an

elevated DI3% and all the patients that had low DI3%, didn't need a PSG and hence had not done one at that time. This leaded this subgroup to this severe selection bias not reflecting the reality of this age group, therefore removed.

The linear regression analysis showed no significant associations in the pre palatal closure subgroup between DI3% and MOAHI (n=12) (r^2 = 0.0, p = 0.94) **Figure (4.3.5**). On the other hand, there was a good association within the post palatal closure subgroup (n=17). (r^2 = 0.876, p < 0.001) **Figure (4.3.6)**

When the ROC curve was used to assess the diagnostic performance of a DI3%≥7 on the pre palatal closure subgroup, it was observed a sensitivity of 100%, specificity 22%, PPV 30%, and NPV 100% to predict MOAHI ≥5 **Figure (4.3.7)**. However a cut off value of 10 showed a sensitivity of 100%, with higher specificity of 55%, PPV 43%, and NPV 100% to predict MOAHI ≥5 **Figure (4.3.8)**.

Following, for the post palatal closure subgroup and DI3≥7, a sensitivity of 100%, specificity 80%, PPV 77%, and NPV 100% to predict MOAHI ≥5 was observed**.** However a cut off of 10 gave better metrics with sensitivity of 100%, specificity 90%, PPV 87%, and NPV 100% to predict MOAHI ≥5 **Figure (4.3.9)**.

Combining the Pre and Post palatal subgroups (n=29), a cut-off value of DI3 ≥7 showed a sensitivity of 100%, specificity 52%, PPV 52%, and NPV 100% to predict MOAHI ≥5 **Figure (4.3.10)** However when a cut-off value of DI3 ≥10 was used, a sensitivity of 100%, specificity 73%, PPV 66%, and NPV 100% to predict MOAHI ≥5 was observed **Figure (4.3.11)**

In summary, looking at the same time at the different cut off values of 7 and 10 for the 2 distinct samples, first all the patients, and second pre and post palatal closure subgroups combined, a cut off value of 7 gives the best sensitivity and NPV for the whole sample (n=36) **Figure (4.3.12)** On the other hand, a cut off of 10 gives the best sensitivity and NPV for all the other subgroups combined (n=29), as it can be appreciated in **Figure (4.3.13).**

Finally, to control for the potential effect of age in our study, a multivariable analysis was done between the distinct subgroups. There is no significant association of age with AHI or MOAHI and DI3 (p=0.56, p=0.07, respectively) **Figure (4.3.14)**.

4.2.3 The association between DI≥4% and MOAHI

The linear regression analysis showed no significant association between DI 4% and MOAHI (r2 = 0.144, p=0.074)**.**

4.2.4 The association between time < 90% SpO_2 and MOAHI

The linear regression analysis showed significant association between time < 90% SpO_2 and MOAHI (r^2 = 0.588, p <0.001) **Figure (4.3.15)**. For each 1 unit increase in the time <90% SaO2 value, there is a 7.12 (95% CI 5.3 to 8.8) increase in the MOAHI value. From this regression model we were able derive a prediction equation for the MOAHI: Time <90% SaO2 * 0.588 + 7.12. This prediction model has an accuracy of 9% (ICC=0.09) **Figure (4.3.16)**.

In order to identify a cut off value for time <90% SpO_2 that will be the most appropriate clinically, we also used generalized linear models and receiver-operator characteristic curves. We were able to observe a cut off value of time < 90% SpO_2 ≥ 1 which has the best trade-off between sensitivity (23%), specificity (97%), PPV (83%) and NPV (65%) to predict MOAHI ≥5 **Figure (4.3.17a)**. However, a cut-off value of time <90% SpO_2 ≥1.7 has a sensitivity (19%), specificity (100%), PPV (100%), and NPV (65%) to predict MOAHI ≥5 **Figure (4.3.17b)**.

Figures

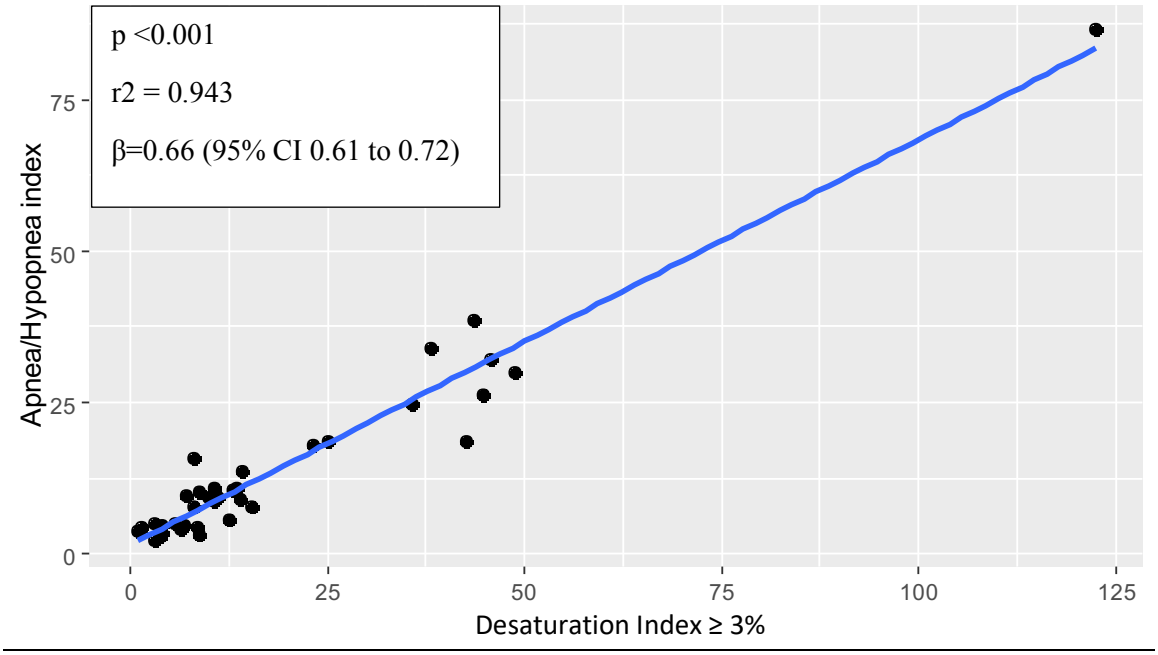


Figure 4.3.1 Linear regression model showing AHI as a function of DI 3%. For each 1 unit increase in the DI ≥3% value, there is a 0.66 increase in the AHI value (95%CI 0.61 to 0.72).

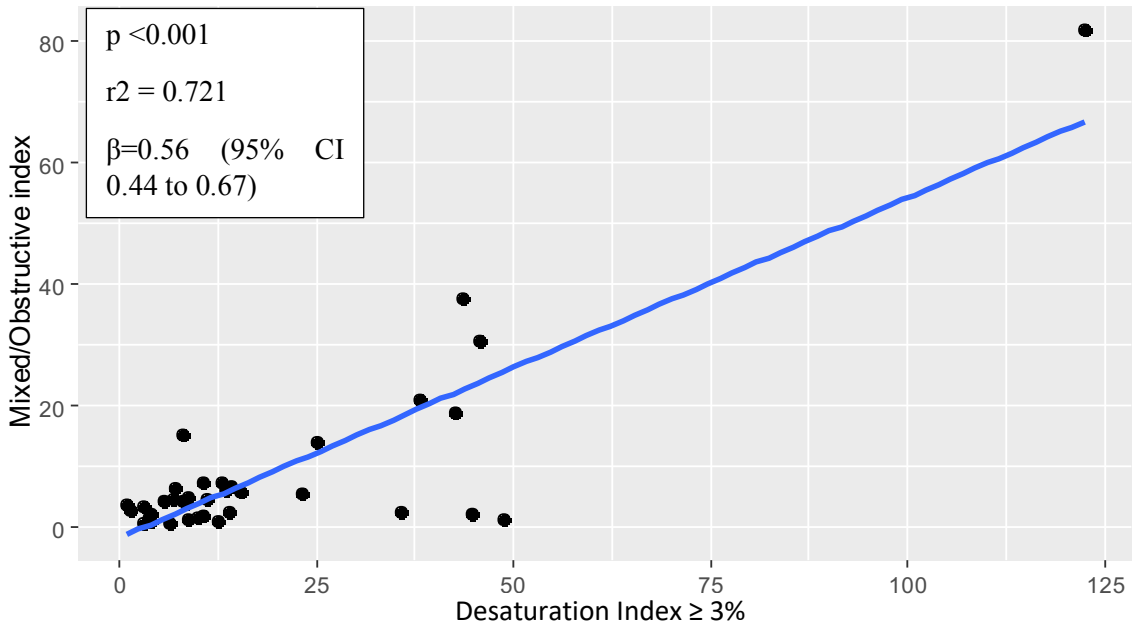


Figure 4.3.2 Linear regression model showing MOAHI as a function of DI 3%. For each 1 unit increase in the DI ≥3% value, there is a 0.56 (95% CI 0.44 to 0.67) increase in the MOAHI value.

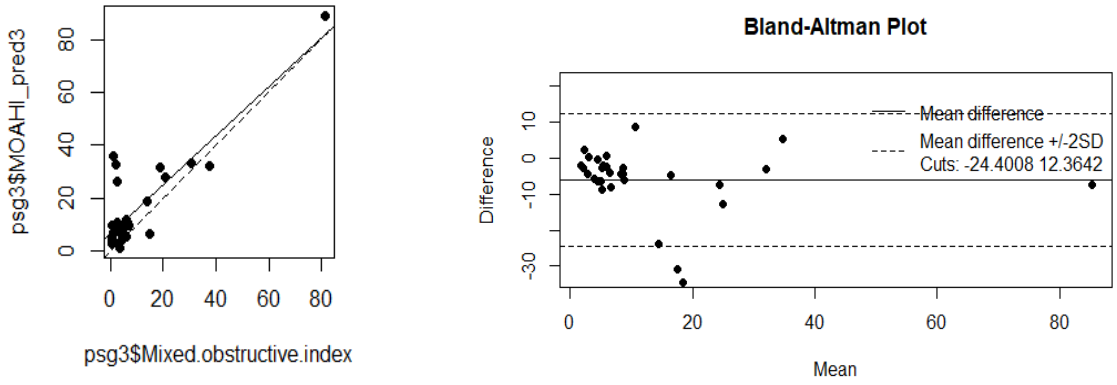


Figure 4.3.3 MOAHI prediction model. we were able derive a prediction equation for the MOAHI: DI3 * 0.722 + 0.57. This prediction model has an accuracy of 80% (ICC=0.80).

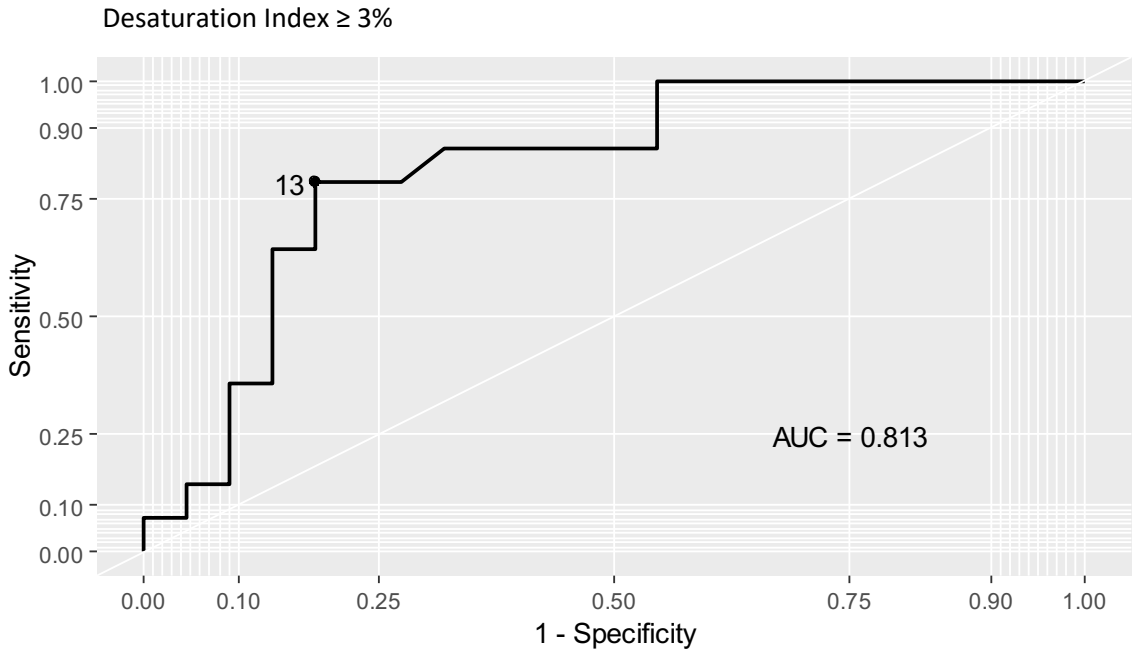


Figure 4.3.4a ROC curve showing a cut-off value of DI3 ≥13 has the best sensitivity (78%), specificity (82%), PPV (73%), and NPV (86%) to predict MOAHI ≥5.

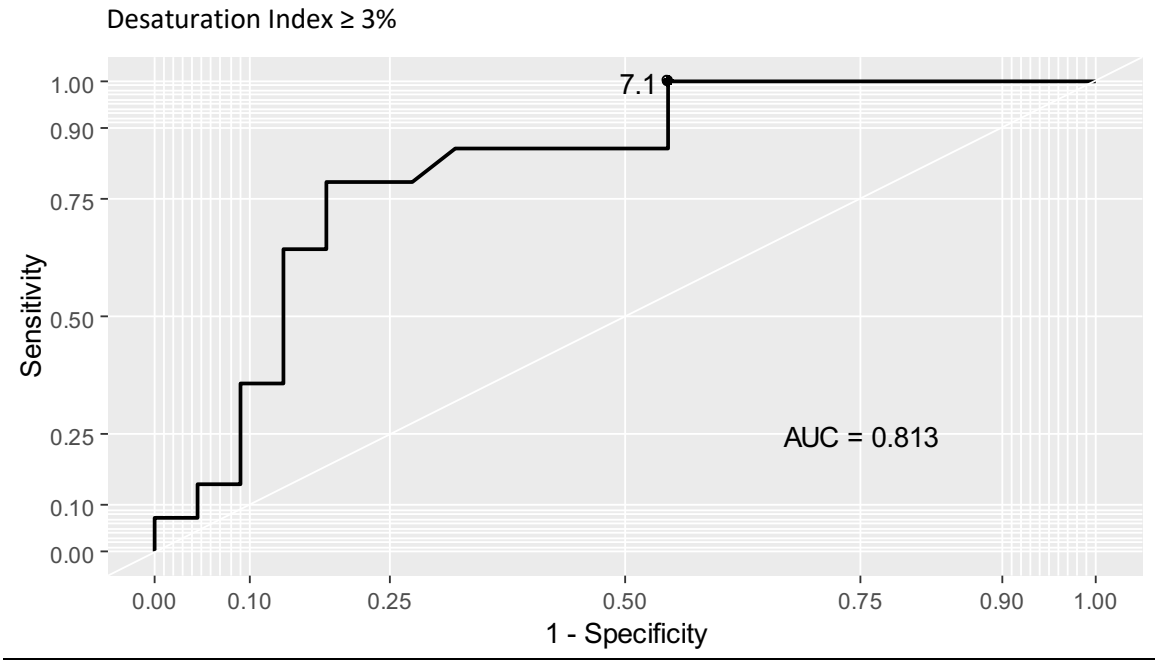


Figure 4.3.4b ROC curve showing a cut-off value of DI3 ≥7 has a sensitivity of 100%, specificity 45%, PPV 54%, and NPV 100% to predict MOAHI ≥5.

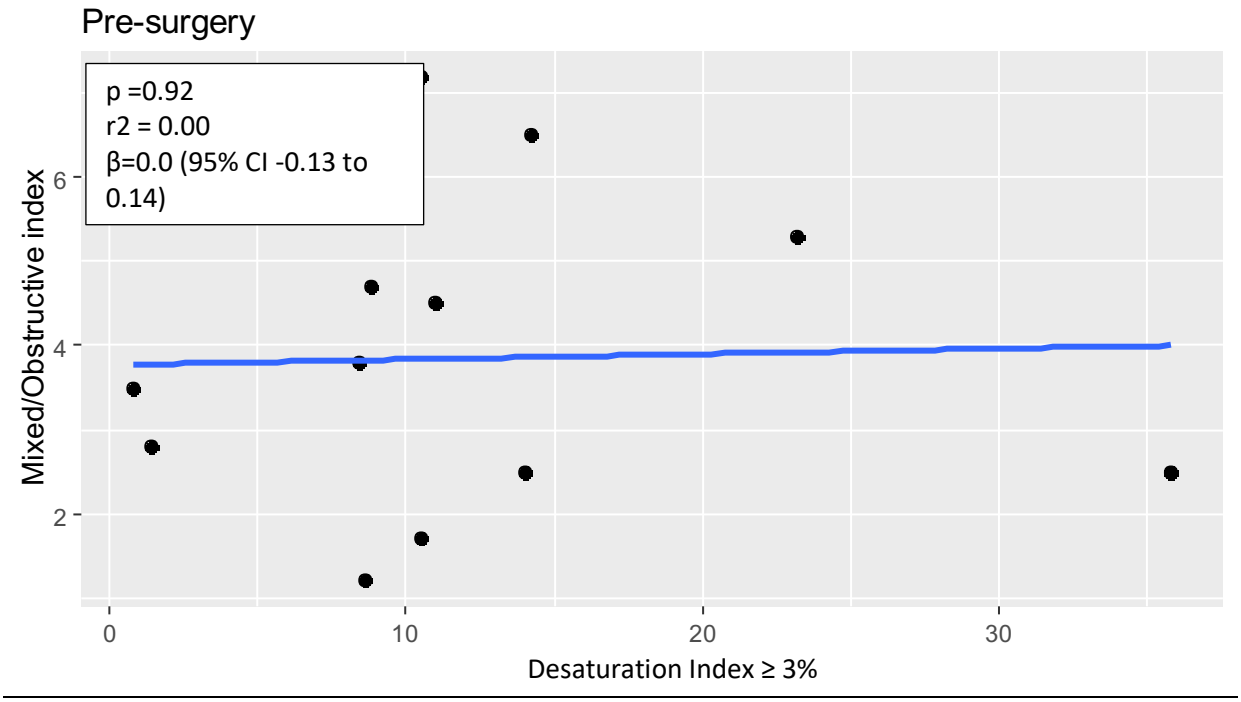


Figure 4.3.5 Linear regression model showing MOAHI as a function of DI 3% in the pre-surgery group. There is no significant association between DI3 and MOAHI (r^2 = 0.0, p = 0.92).

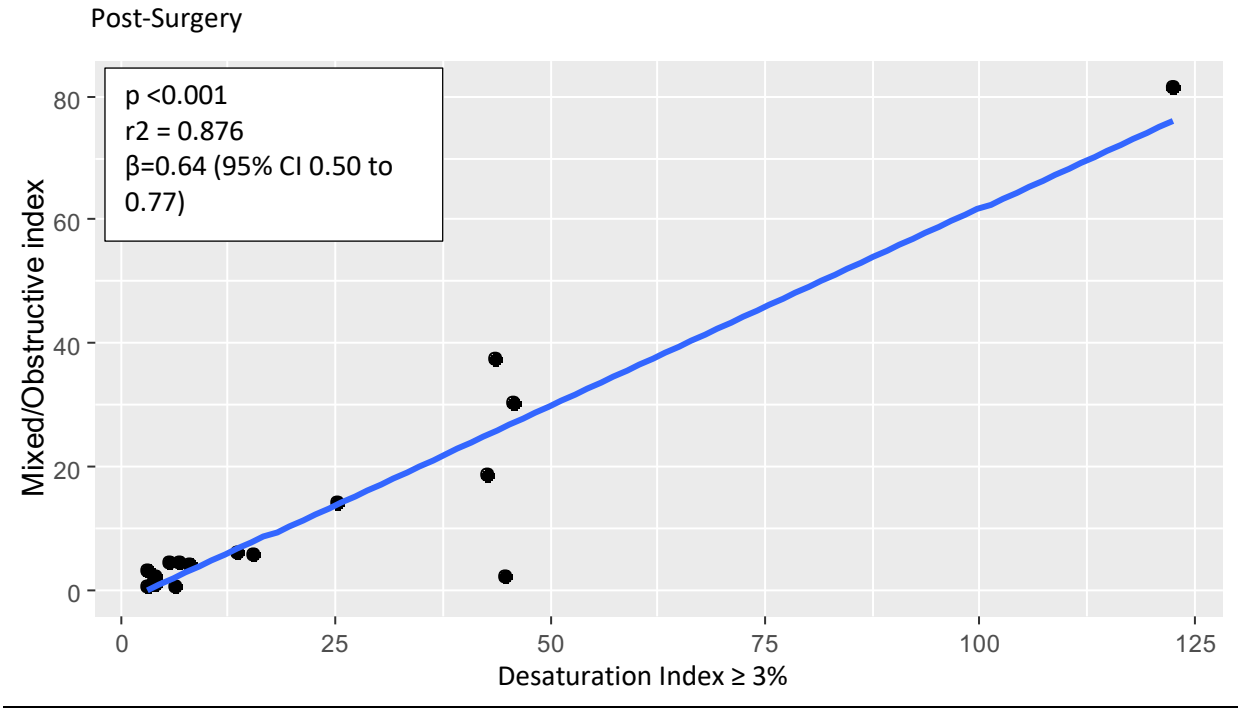


Figure 4.3.6 Linear regression model showing MOAHI as a function of DI 3% in the post-surgery group. There is no significant association between DI3 and MOAHI (r^2 = 0.0, p = 0.92).

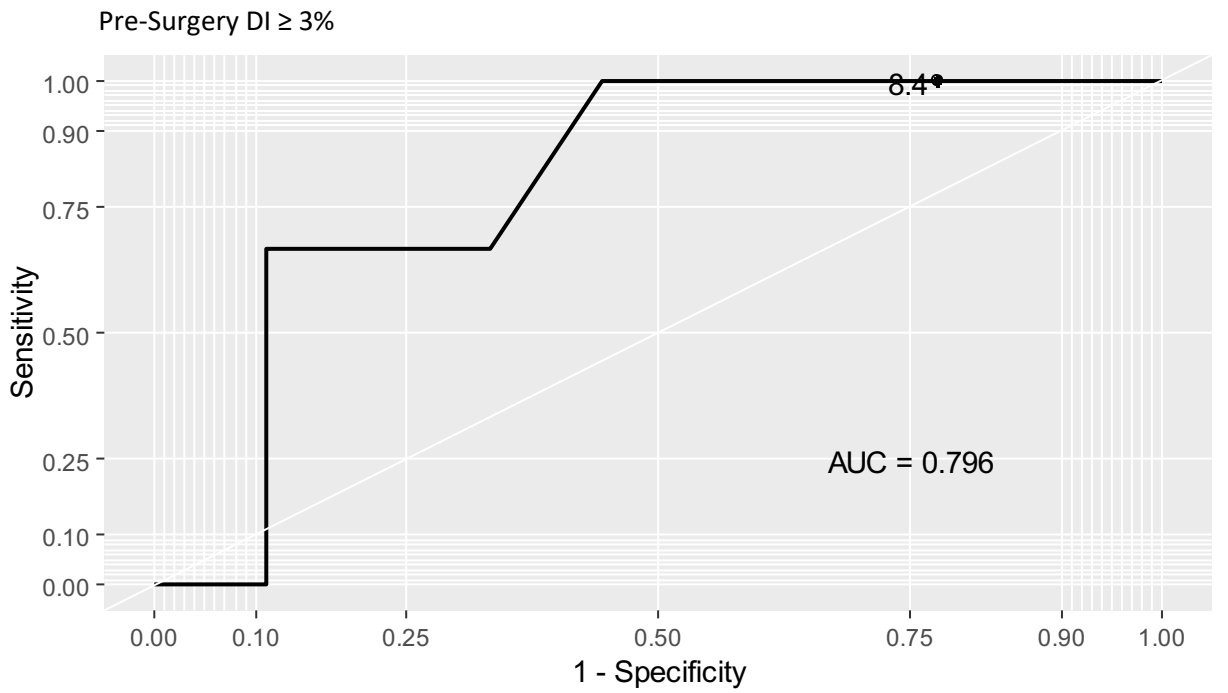


Figure 4.3.7 ROC curve showing a cut-off value of DI3 ≥7 has a sensitivity of 100%, specificity 22%, PPV 30%, and NPV 100% to predict MOAHI ≥5

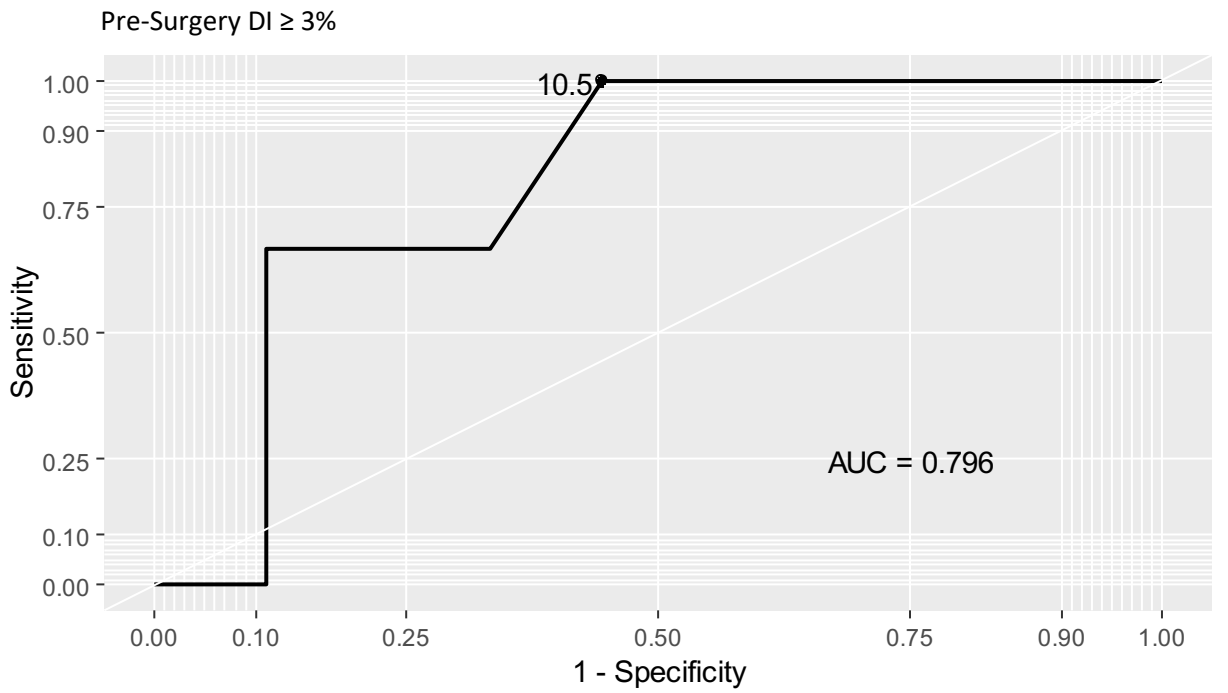


Figure 4.3.8 ROC curve showing a cut-off value of DI3 ≥10 has a sensitivity of 100%, specificity 55%, PPV 43%, and NPV 100% to predict MOAHI ≥5

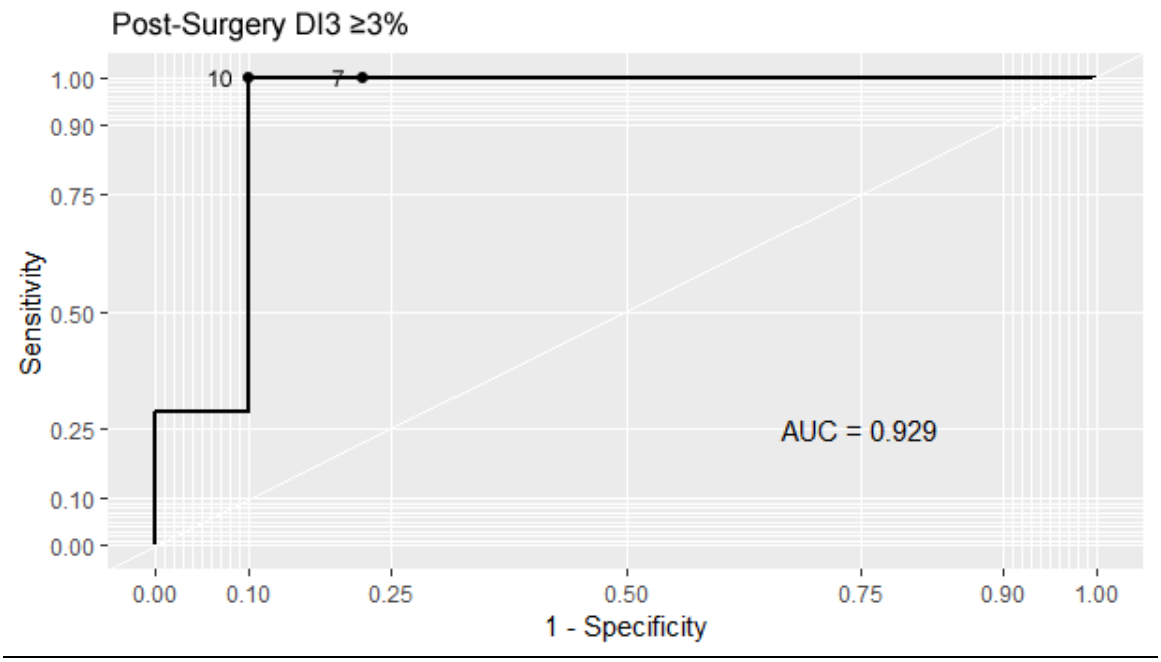


Figure 4.3.9 ROC curve with tables comparing the 2 cut off values. A cut-off value of DI3 ≥7 has a sensitivity of 100%, specificity 80%, PPV 77%, and NPV 100% to predict MOAHI ≥5. A cut-off value of DI3 ≥10 has a sensitivity of 100%, specificity 90%, PPV 87%, and NPV 100% to predict MOAHI ≥5.

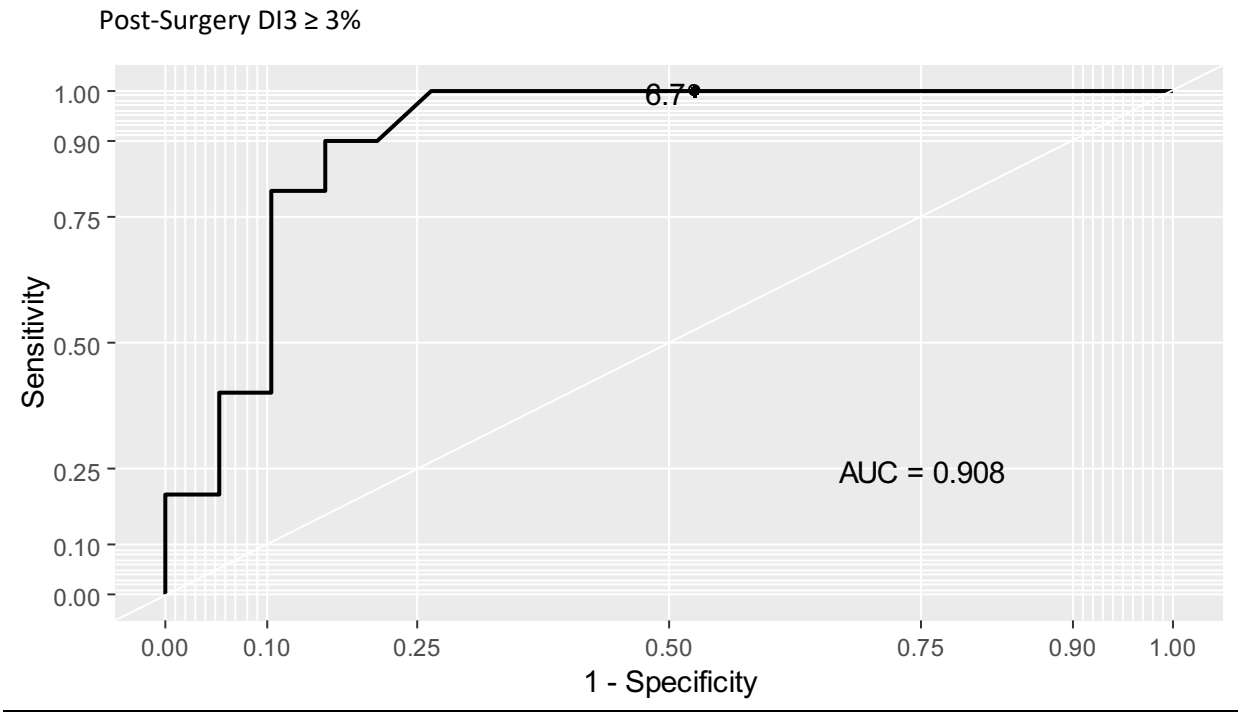


Figure 4.3.10 ROC curve showing a cut-off value of DI3 ≥7 has a sensitivity of 100%, specificity 52%, PPV 52%, and NPV 100% to predict MOAHI ≥5

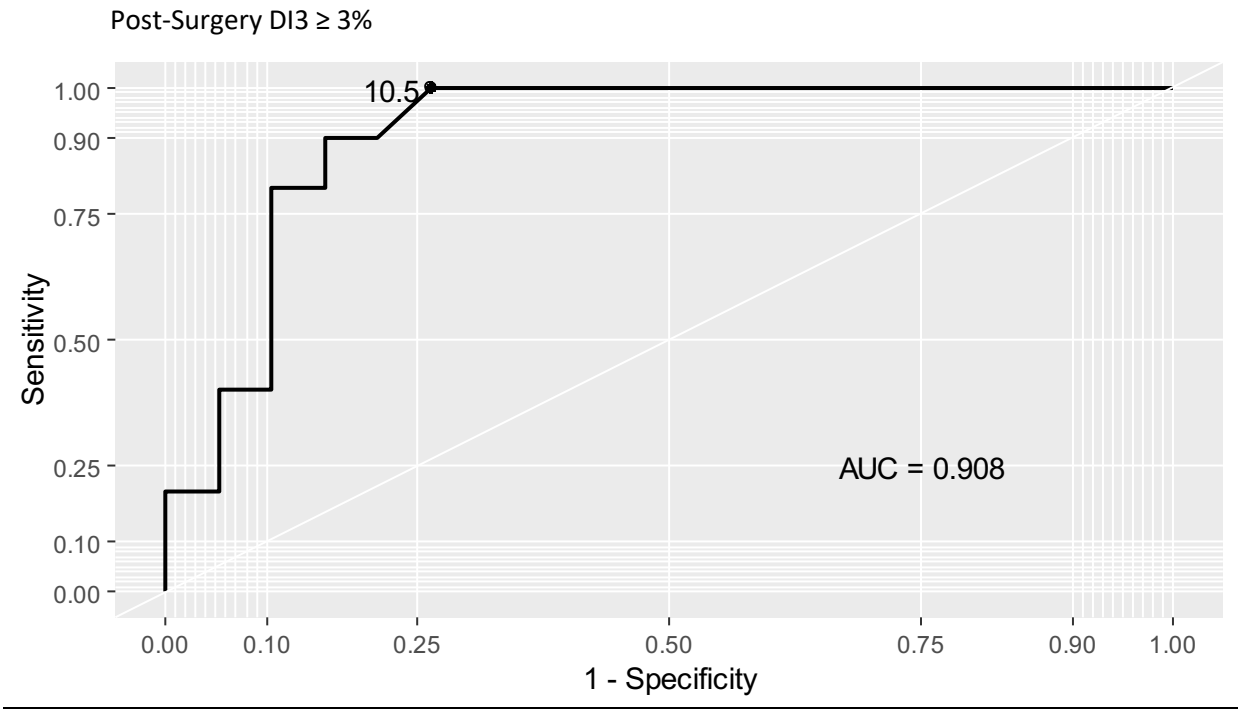
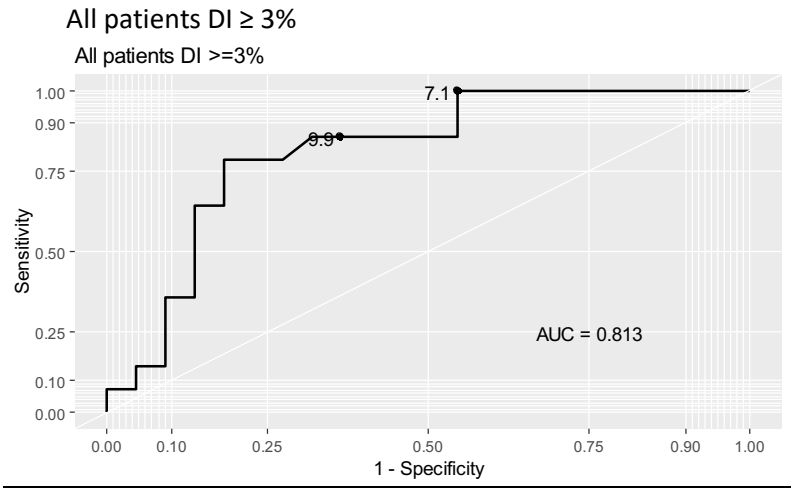


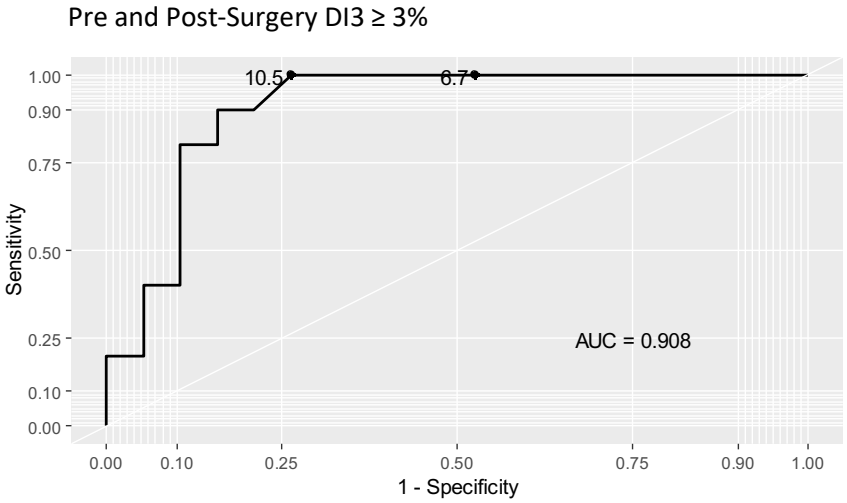
Figure 4.3.11 ROC curve showing a cut-off value of DI3 ≥10 has a sensitivity of 100%, specificity 73%, PPV 66%, and NPV 100% to predict MOAHI ≥5



	MOAHI ≥5	MOAHI <5
DI3 ≥7	14	12
DI3 <7	0	10

	MOAHI ≥5	MOAHI <5
DI3 ≥10	12	7
DI3 <10	2	15

Figure 4.3.12 ROC curve with tables comparing the 2 cut off values for the whole sample (n=36). A cut-off value of DI3 ≥7 has a sensitivity of 100%, specificity 45%, PPV 54%, and NPV 100% to predict MOAHI ≥5. A cut-off value of DI3 ≥10 has a sensitivity of 85%, specificity 68%, PPV 63%, and NPV 88% to predict MOAHI ≥5.



	MOAHI ≥5	MOAHI <5
DI3 ≥7	10	9
DI3 <7	0	10

	MOAHI ≥5	MOAHI <5
DI3 ≥10	10	5
DI3 <10	0	14

Figure 4.3.13 ROC curve with tables comparing the 2 cut off values for the whole sample except the Diagnostic subgroup (n=29). A cut-off value of DI3 ≥7 has a sensitivity of 100%, specificity 52%, PPV 52%, and NPV 100% to predict MOAHI ≥5. A cut-off value of DI3 ≥10 has a sensitivity of 100%, specificity 73%, PPV 66%, and NPV 100% to predict MOAHI ≥5.

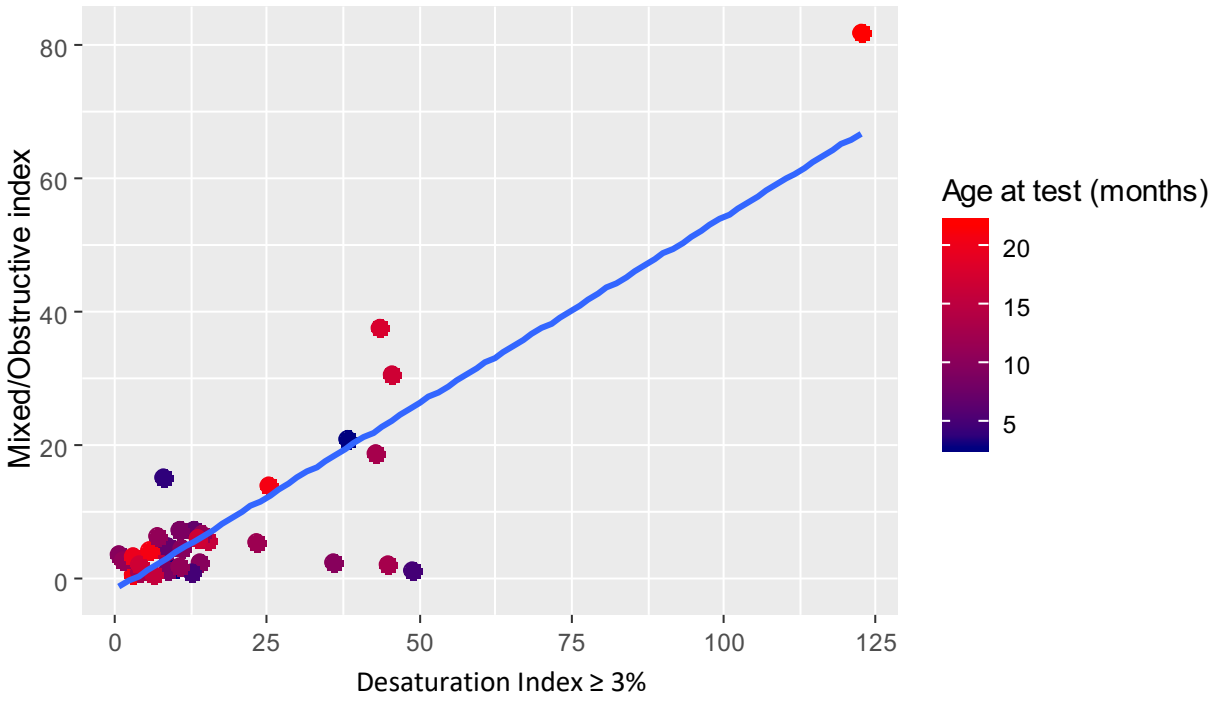


Figure 4.3.14 multivariate analysis showing significant association between DI3 and MOAHI ($p < 0.001$) and no significant association between age at test and MOAHI ($p = 0.07$).

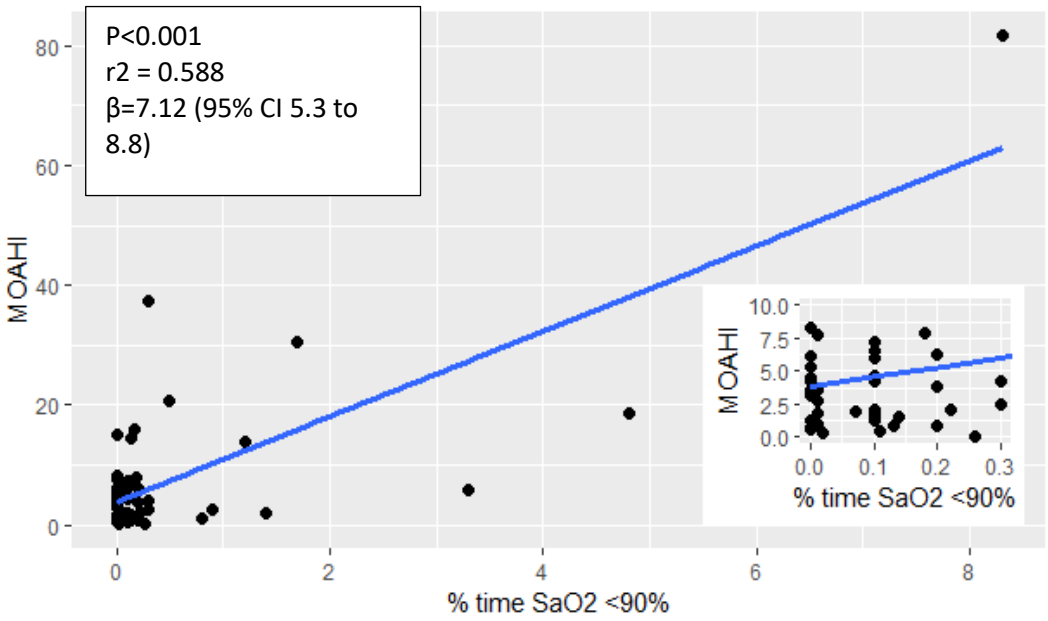


Figure 4.3.15 Linear regression model showing MOAHI as a function of time < 90% SpO_2. For each 1 unit increase in the time <90% SaO2 value, there is a 7.12 (95% CI 5.3 to 8.8) increase in the MOAHI value.

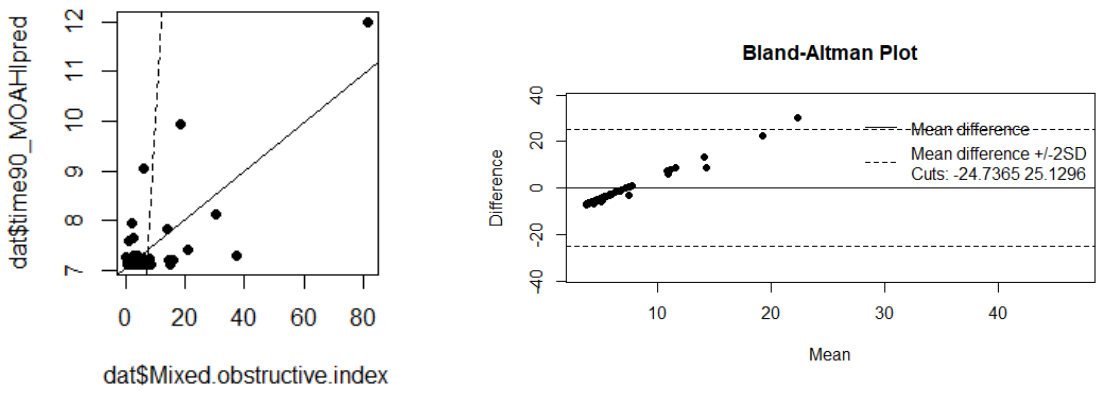


Figure 4.3.16 time < 90% SpO_2 prediction model. From the regression model we were able derive a prediction equation for the MOAHI: Time <90% SaO2 * 0.588 + 7.12. This prediction model has an accuracy of 9% (ICC=0.09)

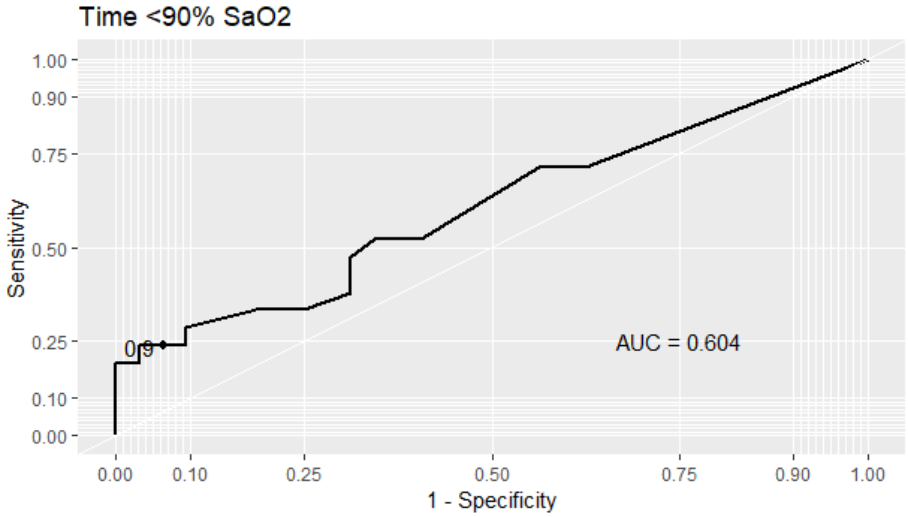


Figure 4.3.17a ROC curve showing A cut-off value of Time <90% SaO2 ≥1 has the best sensitivity (23%), specificity (97%), PPV (83%), and NPV (65%) to predict MOAHI ≥ 5. AUC=0.604

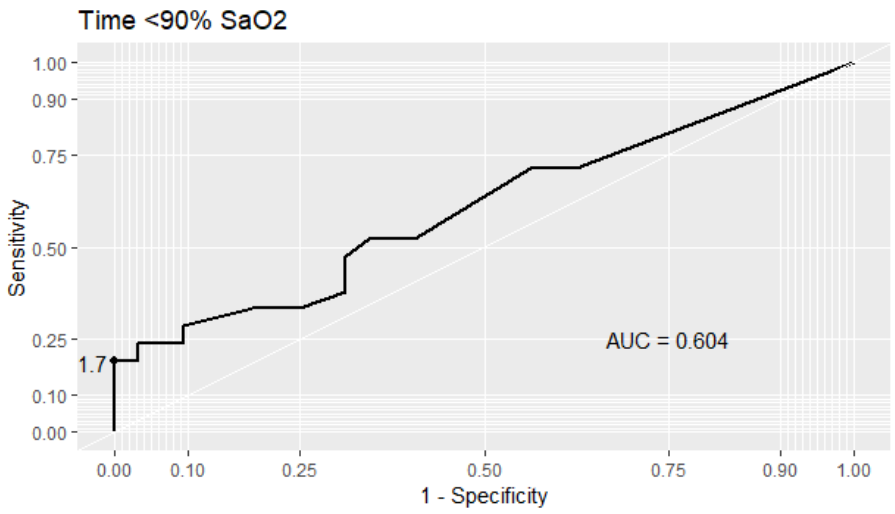


Figure 4.3.17b ROC curve showing A cut-off value of Time <90% SaO2 ≥1.7 has a sensitivity of 19%, specificity 100%, PPV 100%, and NPV 65% to predict MOAHI ≥5. AUC=0.604

4.4 Part IV. EVOLUTION OF OXIMETRY IN THE FIRST SIX MONTHS OF LIFE

The goal of this section is to describe the evolution of upper airway obstruction in the first year of life. The evolution up to the age of 6 months is presented with oximetries, and the desaturation index ≥3% is used as a marker of upper airway obstruction. Indeed, this parameter was shown to be the best parameter correlating with obstructive apnea during polysomnography (preceding chapter). We have however analyzed the data as well with the desaturation index ≥4% and the time spent with SpO_2 <90%. For the evolution at one year of age, we are presenting the data with polysomnography.

For longitudinal evolution, it was important to follow the same group of patients over time. We therefore considered for the analysis only the patients for which we had longitudinal data up to 6 months of age. We identified a total of 32 patients followed in the neonatal period and later at home with a home oximeter for which full data was available. Other patients with mild airway obstruction and not needing the strict prone position were not under home oximeter surveillance and did not have serial oximetries.

4.4.1 Evolution of the desaturation index in the neonatal period

All infants admitted with a diagnosis of Robin sequence were tried first in the prone position as per the institution protocol, if they were symptomatic in the supine position. The goal was to obtain a significant improvement with position with normalisation or near normalisation of the PCO2 and oximetry variables. For our analysis, we divided the groups according to the treatment that showed improvement. The infants treated solely with the prone position will be referred to as the PRONE group. Infants not improved with the prone position had either a nasopharyngeal airway put in place as sole treatment (referred to as NPA group) or had surgery. The two types of surgery, as seen in previous chapters, were either tongue-lip adhesion (TLA group), or mandibular distraction osteogenesis (MDO group).

All the infants in the PRONE group had a significant decrease in the desaturation index ≥3% from 60.8 events/hour (95% Confidence interval [CI]: 48.4 – 73.2) to 40.4 events/hour (95%

CI: 30.4 – 50.4) $p < 0.0001$, t-test for correlated samples. The clinicians at hour institution had judged that the infants who eventually had TLA did not improved sufficiently with the prone position and most had significant hypercapnia, hence they had surgery. This is evident in our analysis presented in Fig **(4.4.1)** In the MDO group, although there was a significant decrease in the desaturation index with the prone position, it stayed high in 50% of the infants and there was persistent hypercapnia (most infants needed CPAP or oxygen administered with the high flow cannula system). Based on this available data, the clinicians decided on surgery. This is also evident from our analysis Fig **(4.4.1)**. All infants eventually improved with their final treatment in the neonatal period. The data is shown in Fig **(4.4.2).**

4.4.2 **Evolution of the desaturation index in the first 6 months of life**

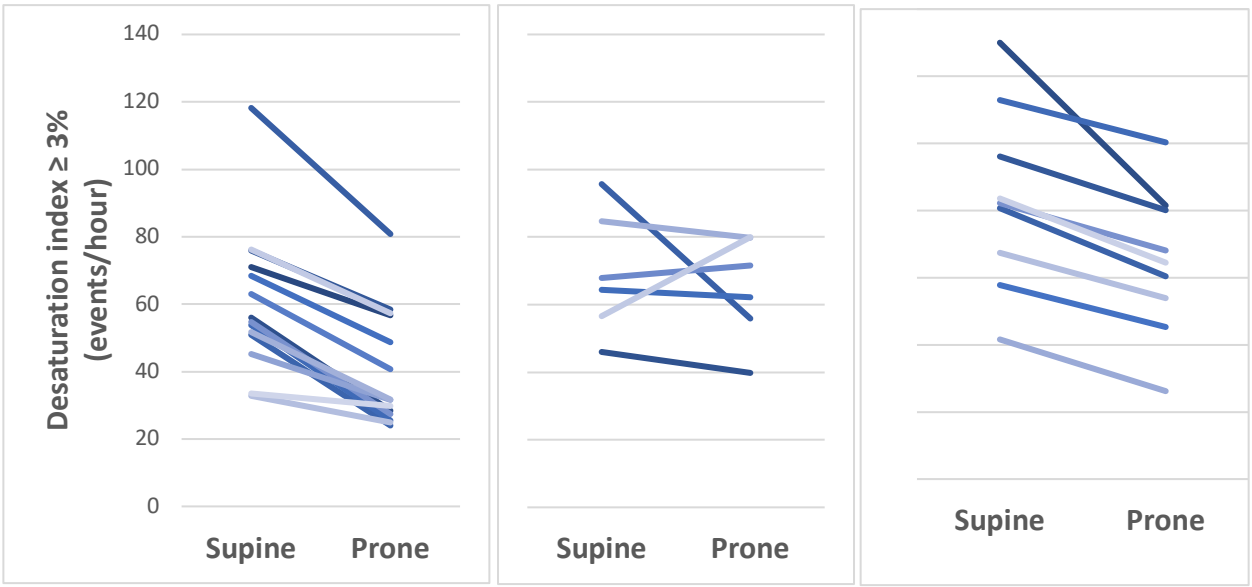
After treatment in the neonatal period (prone position for the group PRONE, insertion of the NPA for the NPA group and after surgery for the two other groups), there was a significant decrease in the desaturation indices and % time spent <90%. We had no data after 2-3 months of age for a few patients in the MDO group, as they were judged normal by the treating physician and sleeping in the supine position. The other groups further decreased their desaturation indices and eventually turned themselves to the supine position with no problems.

Both at 2-3 months and 5-6 months, there was a significant difference between groups (analysis of variance, p< 0.001). Bonferonni correction could not be used for intergroup comparison because of the small number of subjects in the TLA and NPA groups. Despite that, we observed that the values of the desaturation index (both ≥ 3% and ≥ 4%) were much higher in the NPA group as compared to the other groups; it should be mentioned that the data in the NPA group was obtained without the NPA in place to judge if there was enough improvement to stop therapy. The data is presented for the desaturation index ≥3% in Fig **(4.4.3).**

4.4.3 Evolution between 6 and 12 months of age

The evolution in the first 6 months of life was compared with polysomnography data at 10-11 months of age (requested in all infants, pre-palatal closure). In general, the data obtained with oximetry (decrease in the index over time) was in accordance with the polysomnography data in the PRONE, TLA and MDO groups (23 infants) as most (82.6%) had no or mild obstructive sleep apnea at one year of age Table **(4.4.1)**.

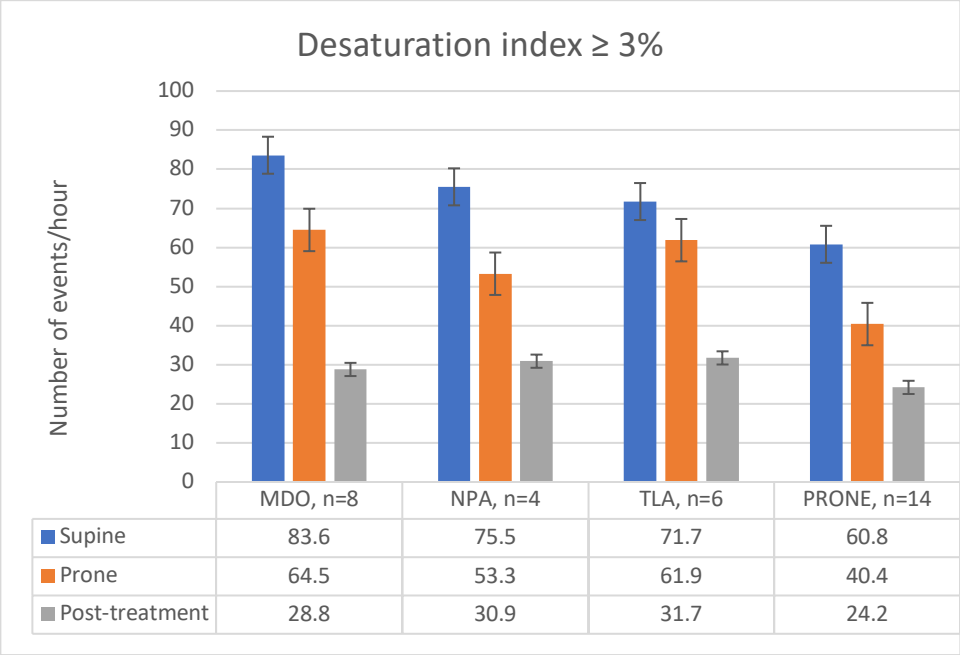
There were a total of 8 infants with moderate or severe obstruction at 10-11 months of age; seven of these 8 infants (87.5%) had elevated desaturation index at 5-6 months of age. In the PRONE group, the three infants with moderate obstruction had a desaturation index ≥3% that was >10 events/hour both at 5-6 months and 10-11 months. All three infants improved over time, two with treatment of nasal obstruction with nasal steroids. In the TLA group, one infant had moderate obstruction at 10-11 months but had a low desaturation index at 5-6 months; this infant was found to have adenoid hypertrophy and improved significantly post-op with a normal polysomnography a few months after. In contrast, in the NPA group, persistence of airway obstruction was the rule at 10-11 months of age (4 out of 4) and the desaturation index had been elevated at 5-6 months of life (> 20 ev/hour); one patient had undergone TLA because of persistent severe obstruction at 6 months of age and had persistent moderate obstruction at one year; he later improved slowly with time with eventually a normal polysomnography. One other patient in that group underwent MDO near one year of age for persistent severe obstruction off NPA; the polysomnography after MDO and palatal closure was normal. The two other infants continued with NPA for moderate obstruction (off NPA) a few more months. In the MDO group, none of the infants had moderate or severe obstruction at the time of polysomnography at 10-11 months of age.



PRONE group TLA group MDO group

Fig 4.4.1. Effect of prone position on the desaturation index in the neonatal period

Individual data presented by groups in number of drops in SpO_2/hour



	MDO, n=8	NPA, n=4	TLA, n=6	PRONE, n=14
Supine	83.6	75.5	71.7	60.8
Prone	64.5	53.3	61.9	40.4
Post-treatment	28.8	30.9	31.7	24.2

Fig 4.4.2. Evolution of the desaturation index in the neonatal period

Data presented as average ± 1 SE. Post treatment represent post-surgery in MDO and TLA groups, post insertion of NPA in the NPA group. For the PRONE group, the data is at one month of age to correspond to the age of the other groups.

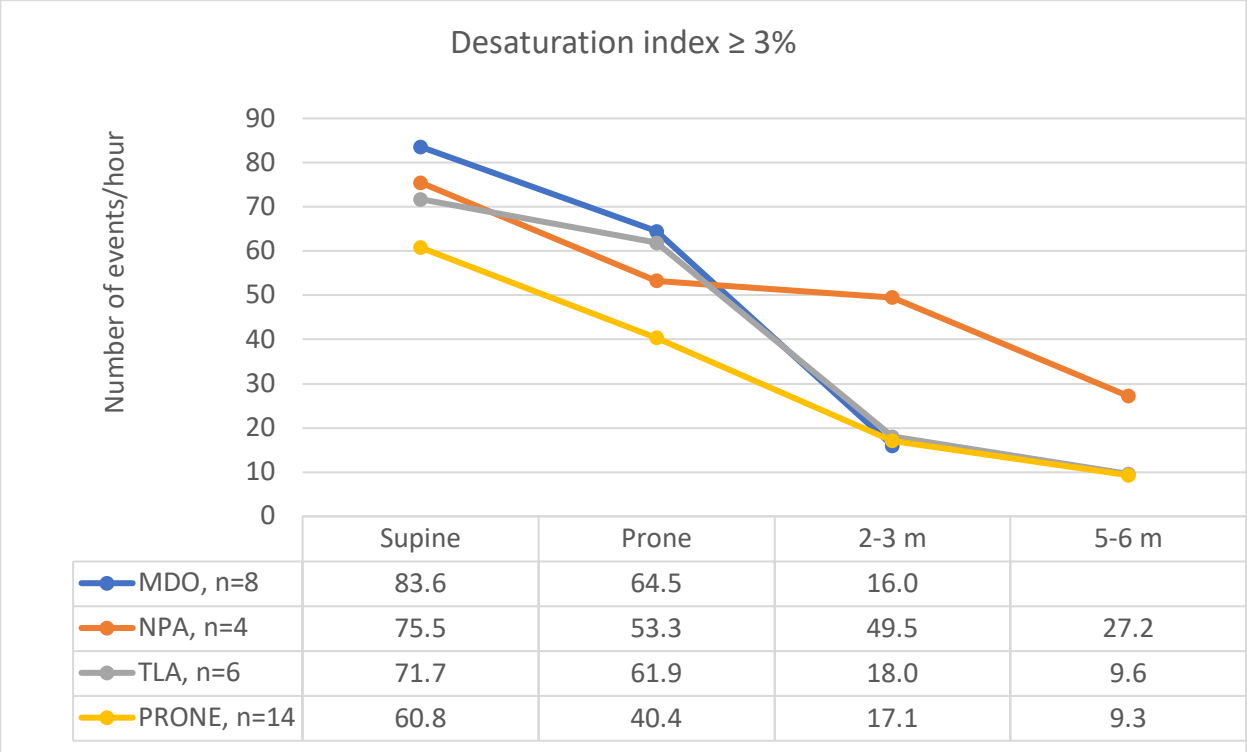
Abbreviations:

MDO: patients treated surgically with mandibular distraction osteogenesis;

NPA: Nasopharyngeal airway;

TLA: patients treated surgically with tongue-lip adhesion;

PRONE: patients for which the prone position was used with no other treatment



	Supine	Prone	2-3 m	5-6 m
MDO, n=8	83.6	64.5	16.0	
NPA, n=4	75.5	53.3	49.5	27.2
TLA, n=6	71.7	61.9	18.0	9.6
PRONE, n=14	60.8	40.4	17.1	9.3

Fig 4.4.3. Evolution of the desaturation index in the first 6 months of life

There was a significant decrease in the desaturation index over time for

TLA

There was a significant difference between groups (analysis of variance, $p < 0.001$)

Abbreviations:

MDO: patients treated surgically with mandibular distraction osteogenesis.

NPA: Nasopharyngeal airway; the desaturation index represent data without the NPA

TLA: patients treated surgically with tongue-lip adhesion;

Prone: patients for which the prone position was used with no other treatment

M: months

Table 4.4.1 Degree of obstruction as assessed by polysomnography at 10-11 months of age

Group	Degree of obstruction (MOAHI)			
	None **< 1 ev/hour**	**Mild** **1-5 ev/hour**	**Moderate** **5-10 ev/hour**	**Severe** **> 10 ev/hour**
PRONE (n = 10)	3	4	3	0
NPA (n = 4)	0	0	3	1
TLA (n = 5)	0	4	1	0
MDO (n = 8)	0	8	0	0
Total group	3	16	7	1

The data is presented as number of patients in each group.

Abbreviations:

ev/hour: number of events/hour (obstructive events)

MOAHI: mixed obstructive apnea/hypopnea index

MDO: patients treated surgically with mandibular distraction osteogenesis

NPA: Nasopharyngeal airway

TLA: patients treated surgically with tongue-lip adhesion

PRONE: patients for which the prone position was used with no other treatment

Chapter 5

Comprehensive scholarly discussion of all the findings

5.1 DESCRIPTION OF THE COHORT

We have a small cohort of patients with Robin sequence (as compare to cohorts from large centres in the USA or Europe) due to the demographics of the province and the presence of two pediatric hospitals in the city receiving referred cases. It was therefore extremely important to carefully evaluate the hospital database with the medical record archivist in order to retrieve all the cases with a good search strategy. It was also important to describe thoroughly the cohort in order to compare to larger cohorts in other published series; then, our results obtained with data on oximetry and polysomnography could be applicable to other centers.

Our cohort can be compared adequately to other published cohorts and data summarized in review papers (Abel, Bajaj et al. 2012, Cote, Fanous et al. 2015, Butow, Morkel et al. 2016, Hsieh and Woo 2019). Indeed, the subdivision in non-syndromic and syndromic is similar; the degree of severity also can be compared to that of others, considering that we are a referral center as well; the investigation and management strategies are also very similar in accordance with the most recent published guidelines (Evans, Sie et al. 2011, Fan, Mandelbaum et al. 2018, Gomez, Baron et al. 2018). Finally, the treatment used is similar to that of others. Indeed, in a review of literature published in 2015, (Cote, Fanous et al. 2015) collected data on 1425 cases in 14 cohorts with 68% of the infants treated non-invasively, which is close to our data of 67%. Our reported rate of tracheostomy was lower than in most studies possibly because mandibular distraction osteogenesis is now used to avoid tracheostomy, a surgical technique that was not available in prior studies. Our use of nasopharyngeal airway and CPAP is lower than that reported in the few series published, where this was predominantly used (Marques, de Sousa et al. 2001, Abel, Bajaj et al. 2012, Daniel, Bailey et al. 2013, Amaddeo, Abadie et al. 2016). Our institutional protocol moved away from nasopharyngeal airway in favor of surgery several years ago, as mandibular distraction became available.

The outcome of our patients in terms of detailed evolution in the first year of life brings interesting data, not available in the literature. Most studies have focused on the neonatal

outcome post intervention (Almajed, Viezel-Mathieu et al. 2017). With our data, we were able to report on more long-term success/failure of the treatment. We saw in this cohort that patients undergoing tongue-lip adhesion had the lowest success rate at 22%; most infants needed additional measures to normalize the airway obstruction, being the prone position, further surgery (MDO) or the use of CPAP. Our data shows a lower success rate than that of a recent publication showing a success rate with TLA of 47% (Resnick, Dentino et al. 2016)(Resnick, Calabrese et al. 2018). Our results might be lower because in the early years at our institution, TLA was used in syndromic patients with Robin sequence and severe obstruction. A recent study has shown worse outcome of surgery in syndromic Robin sequence(Resnick and Calabrese 2019).

Our results and that of others emphasize the idea that, patients who fail non-invasive measures have the most severe degree of obstruction and should be followed closely in the months and years after that. This is because a persistence or recurrence of obstruction can happen even after surgery. This will be explored more in detail in the next sections.

5.2 USE OF TIMELY POLYSOMNOGRAPHY TO MONITOR EVOLUTION IN ROBIN SEQUENCE

Despite the small size of our cohort due to difficulties obtaining polysomnography, the review of polysomnography data was informative on many aspects.

Obstructive apnea

Close follow-up for the presence of obstructive apnea either in the first few months, pre-palatal closure or post-palatal closure is important for detecting suboptimal outcome. We identified with polysomnography moderate or severe obstructive sleep apnea in 45 % of infants in the first few months of life, in 32% pre-palatal closure and 41% post-palatal closure. There is a paucity of publications on the long-term evolution of infants with Robin sequence, and most publications did not use polysomnography (Costa, Tu et al. 2014, van Lieshout, Voshol et al. 2016, Opdenakker, Swennen et al. 2017, Resnick, Calabrese et al. 2018).

In addition, the follow-up period has often been limited to the immediate post-operative period in the case of palatal closure (up the 7 days) (van Lieshout, Voshol et al. 2016, Opdenakker,

Swennen et al. 2017). Of importance in our cohort, the percentage of severe obstructive apnea post-palatal closure (months after surgery) represents very important data as intervention might improve the infant rapidly. Indeed, five of the six infants with severe obstruction post-palatal closure had important growth of oropharyngeal lymphoid tissues and the polysomnography normalized after surgery. This has not been reported so far in the literature.

One study (Lee, Thottam et al. 2015) looked at the evolution of polysomnography over time, but the period of observation was shorter than ours (up to 6 months) and found no improvement of indices of obstructive apnea in their population; except for infants who had MDO. A very recent study provides more comprehensive data over a period up to 15 months of age in infants treated conservatively. Indeed, Ehsan et al. provided polysomnography data at different points over the first 15 months of age and showed resolution of obstructive events by 15 months (Ehsan, Kurian et al. 2019). In these infants treated conservatively, a significant proportion had moderate to severe obstruction still at the age of 6-12 months. For infants undergoing surgery, Resnick et al. also provided data for months to years after surgery (Resnick, Calabrese et al. 2018). This group, however, did not provide details of the timing of polysomnography during follow-up and the number of studies done.

It is evident from our data, and from scarce results of the literature, that follow-up for possible persistence or recurrence of obstructive sleep apnea in infants with Robin sequence is important and should be on-going for months. Mainly in the first few years of life and post palatal closure for those with associated cleft palate and during the time of maximal oropharyngeal growth of lymphoid tissue secondary to recurrent viral infections.

Central apnea

We found that although many infants had increased central apnea index on the PSG, only 25% of the infants had a moderate or severe degree (index of central apnea (>5 events/hour). Most of the events were not associated with significant drop in SpO2 and only one infant needed treatment with oxygen (syndromic RS with central nervous system anomalies). Central apnea has

been described in infants with Robin sequence (MacLean, Fitzsimons et al. 2012, Lee, Thottam et al. 2015). In the study of Lee et al., although they report a high proportion of central apnea, the examination of their individual data shows that most infants had an index below 5 events/hour, a finding similar to ours. These authors did not correlate with oxygenation parameters. Maclean et al. did not present separately the central apnea events from the other parameters of polysomnography, but we can see from their detailed results that these events were present (difference between total events and obstructive events). We do not know the proportion of infants with moderate or severe central apnea. Their cohort included only 8 infants with Robin sequence. In a very recent study, Ehsan et al. (Ehsan, Kurian et al. 2019) have studied a larger cohort and showed the presence of increased central apnea index in the first few months of life in infants with RS, an index that decreased significantly with time and reached normal value in the older group (> 12 months); the proportion of infants with increased central apnea was not provided in that study. Finally, it is possible that the low proportion of infants in our cohort with significant central apnea was due to many of them sleeping still in the prone position at the time of polysomnography. Indeed, Hong et al. have shown that the central events were much less frequent in that position (Hong, Wee et al. 2019).

The identification of significant central apnea, although not frequent, is important, as treatment might be needed.

5.3 CORRELATION OXIMETRY AND POLYSOMNOGRAPHY

The most important finding was that the desaturation index ≥ 3% on oximetry correlated well with indices of obstruction on polysomnography; this could enable physicians to predict which infants would not need a polysomnography. A high positive predicted value was not an important parameter for us as we knew that some infants with predominance of central apnea will have a high desaturation index but a low index of obstruction on the polysomnography. It was important, however, that all infants with a low desaturation index (cut off chosen) were those with no significant obstruction on the polysomnography (100% negative predictive value); in addition, infants with moderate or severe obstruction on polysomnography should all have a desaturation index above the cut-off chosen (100% sensitivity). For our group, in the age range

studied, a desaturation index ≥3% of <7 events/hour would have meant that 28% of the infants did not needed a polysomnography. With a desaturation index ≥3% of <10 events/hour, it would have been 47%. These results are novel as there is no similar data in the literature for infants with Robin sequence.

In the management of infants with obstructive sleep apnea, the use of results of oximetry parameters has been reported in the literature and is gaining acceptance (Kaditis, Alonso Alvarez et al. 2017). Recommendations, mostly with the use of the McGill oxygen score, have been made for infants with Trisomy 21 and those with mucopolysaccharidosis, two conditions associated with a high prevalence of obstructive sleep apnea (Coverstone, Bird et al. 2014, Pal, Langereis et al. 2015). As for infants with Robin sequence in the neonatal period, Abel et al. used a McGill oximetry score >2 (≥ 3 clusters of desaturation events ≥4% and ≥3 desaturations to ≤90%) to determine indications for nasopharyngeal airway insertion (Abel, Bajaj et al. 2012).

We found only one study exploring the correlation between desaturation index and indices on polysomnography to identify infants with or without obstructions. Indeed, Khayat et al. (Khayat, Bin-Hassan et al. 2017) compared the desaturation index ≥3% and obstructive apnea-hypopnea index (latest AASM guidelines for scoring, as in our study) in 46 patients younger than 2 years of age. They also found a good correlation between both parameters ($r=0.64$, $p<0.0001$). They however did not provide a cut-off value of desaturation index to predict airway obstruction, and they did not do performance analysis.

In older age groups, the use of oximetry and desaturation index is gaining acceptance. Molero-Ramirez et al. (Molero-Ramirez, Maximiliano et al. 2019) found that the desaturation index was a better predictor of adverse events than other parameters of polysomnography in children with obstructive sleep apnea. In two recent reviews, Kaditis et al. suggests the utilisation of oximetry (with the desaturation index ≥ 3% or ≥ 4%) when polysomnography is not available (Kaditis, Kheirandish-Gozal et al. 2012, Kaditis, Kheirandish-Gozal et al. 2016).

The recommendations of Kaditis et al. are derived from studies having looked at oximetry parameters in comparison to indices of airway obstruction in polysomnography, in the age group

of adenotonsillar hypertrophy. Unfortunately, there are many variations in the parameters of comparison used in the studies. Some studies were done while the scoring for events of polysomnography was with the previous recommendations of the AASM, some were done after implementation of the new recommendations. These studies used either the desaturation index ≥ 3% or ≥ 4% in comparison to either the total apnea-hypopnea index or the mixed obstructive apnea-hypopnea index. The first study was by Brouillette et al. (Brouillette, Morielli et al. 2000). They analysed data on 349 children referred for obstructive apnea. They observed a high correlation between MOAHI and Desaturation Index ≥ 4% (r2 = 0.78; P <0.001) with a positive predictive value of 97%. They did not attempt to provide a cut-off value of desaturation index to predict absence of significant obstructive sleep apnea on polysomnography. Then, in a prospective cohort study involving 57 children aged between 4 and 12 years, Kirk et al. (Kirk, Bohn et al. 2003), showed poor agreement between AHI and desaturation index ≥4% by the Bland and Altman analysis. Assessment of sensitivity and specificity using the ROC curve for desaturation index ≥ 4% of >5 events/hour to predict AHI >5 was 66.7% and 60%, respectively. Later, Tsai et al. (Tsai, Kang et al. 2013) studied 148 patients between 3 to 12 years old and found a good correlation between the desaturation index ≥4% and AHI (r=0.886, p<0.001). By ROC curve analysis, they identified an optimal cut-off value of 3.5 events/hour (sensitivity: 83.8%; specificity: 86.5%) for identifying moderate obstructive sleep apnea and a cut-off value of 4.15 events/hour (sensitivity: 89.1%; specificity: 86.0%) for identifying severe obstructive sleep apnea. Finally, Liu et al. (Liu, Tsai et al. 2017) studied 66 children aged between 3 and 12 years with obstructive sleep apnea. They used the cut-off values identified by Tsai et al. (Tsai, Kang et al. 2013) and correlated the desaturation index ≥4% with the apnea-hypopnea index. They found that the NPV and PPV for predicting residual moderate or severe OSAS were, respectively, 85.2% and 60.0 % for moderate OSAS, and 89.7% and 61.5 % for severe OSAS.

The data in the literature for children older than those of our cohort of Robin sequence does not identify a cut off value that could identify children not needing further investigation. Our data, although in a small cohort, was able to identify a cut off value of desaturation index with 100% sensitivity and 100% negative predictive value, for infants not needing polysomnography. The difference with older children is certainly due to the fact that infants are

more prone to have decrease in oxygenation with every respiratory events than older children (Horemuzova, Katz-Salamon et al. 2000) (Marcus 2001). Older children might arouse before any drops in oxygenation; as seen previously, the scoring of obstructive hypopnea depends on a decrease in airflow associated either with drops in oxygenation or arousal.

We are well aware that our findings will have to be validated in other centres and with a larger group of patients. Nevertheless, they are very promising. Serial oximetries during the first year of life will prove to be much more feasible than polysomnography and can be done at home at timely intervals.

5.4 EVOLUTION OF OXIMETRY IN THE FIRST 6 MONTHS OF LIFE

The most important finding on the evolution of oximetry data was that the parameters of airway obstruction improved in all groups over the first six months of life. There was then a further improvement up to 12 to 18 months by criteria of polysomnography. Only the small group treated with a nasopharyngeal airway had less good outcome with needs of further intervention in all patients.

The first improvement occurred in the neonatal period once the appropriate treatment was identified, stepwise: prone position, nasopharyngeal airway or surgery (tongue-lip adhesion or mandibular distraction). We found that the group with nasopharyngeal airway was the slowest to improve and by one year of age, 2 infants had needed surgery and the other two still needed the nasopharyngeal airway.

Data on longitudinal evolution of obstruction in Robin sequence is very scarce in the literature. Ehsan et al. have reported their experience with 142 infants with RS over the first 15 months of age (Ehsan, Kurian et al. 2019)**.** All those infants were treated conservatively and had serial polysomnography. These authors found that the indices of obstruction improved over time. It would appear though, that many of the infants treated conservatively in that cohort had more severe obstructions that those in our cohort. Indeed, the proportion of infants with moderate or severe obstruction between 6 and 12 months and after 12 months was 40% as compared to 30%

in our cohort. We do not know what their conservative management was and if strict prone position was used or nasopharyngeal airways.

There has been longitudinal data published for infants treated with nasopharyngeal airway especially from centres that used preferentially that technique. Our data does not differ from data of those publications as it is reported that infants needed the nasopharyngeal airway for months (Marques, Sousa et al. 2001, Abel, Bajaj et al. 2012) (Marques, Sousa et al. 2001, Wagener, Rayatt et al. 2003).

Our study provides additional important data. The infants who had moderate to severe obstruction at 10-12 months of age (polysomnography data) almost all had elevated desaturation index (≥3%) at 5-6 months of age. Although we could not do correlation studies because of the small number of infants with polysomnography using the same criteria (change in AASM criteria after 2015) this could be an important avenue to explore in future studies as it is likely that polysomnography will continue to be a test not freely available.

Chapter 6

Summary and conclusion

Meeting the objectives

Our first objective was to describe a cohort of infants afflicted with Robin sequence and followed at the Montreal Children's Hospital in recent years and compare to that of other publications. We knew that the size of the cohort would likely be small. It was therefore important to do a thorough review of all information available. We were able to show that our cohort compares very well to other larger cohorts.

Our second objective was to report on the usefulness of timely polysomnography to identify suboptimal outcome in infants with Robin sequence in the first 18 months of life. Longitudinal outcome is an area with a real paucity of data in the literature and detailed results of polysomnography over time is just starting to appear in the past 5 years in the literature. Our data is very important as we identified infants with moderate or severe obstruction for which intervention was needed. This was not available in the literature, even in the most recent studies of the past year.

Our third and most important objective was to correlate the results of polysomnography with oximetry data and determine if we could identify parameters on oximetry that would identify infants not needing polysomnography. This is important, as polysomnography is difficult to obtain in a timely manner in many centers throughout North America and Europe. We were able to identify cut off values for desaturation index on the oximetry that identified all infants with no or mild obstruction on polysomnography (100% negative predictive value); we also showed that all infants with moderate or severe obstruction on polysomnography had a desaturation index below the chosen cut-off value (100% sensitivity).

Our fourth objective was to report on the evolution of oximetry over time in the first 6 months of life and determine if we could identify suboptimal outcome. Interestingly, almost all infants with moderate to severe obstruction at age 10-12 months had had an increased desaturation index at age 5-6 months.

Implications of findings

There is no question that polysomnography should be used to follow infants with Robin sequence in the first several months of life and even beyond one year as resolution of airway obstruction could take longer and even recur after initial improvement. What our study brings, albeit in a small cohort, is the new information that parameters on a simpler test, oximetry, could be used to monitor evolution. Because of the difficulties in obtaining the gold standard test, our findings bring exciting and useful information.

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