Department of Plastic Surgery
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SURGICAL TREATMENT AND LONG-TERM OUTCOMES OF CLEFT LIP AND PALATE

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DOCTORAL DISSERTATION

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To my family.

ABSTRACT

Background. Treatment protocols for orofacial clefts (OFC) have evolved over the years. Modern outcome goals of primary repair have shifted from solely achieving an intact palate repair towards successful long-term outcomes, with focus on speech development, occlusion, hearing, appearance, and maxillary growth. An anatomically and functionally intact palate are vital for development of proper speech; this is among the most important aspects of cleft repair. Unsuccessful primary repair may result in velopharyngeal insufficiency (VPI) due to a structural deficit in the palate or an oronasal fistula (ONF). These complications may be severe enough to have a detrimental impact on the growing child's psychological health and social relationships and to require a secondary surgical (SS) intervention in the form of speech-correcting surgery (SCS), fistula repair, or both. These complications not only create a surgical dilemma (particularly ONFs) but also cause additional pain and suffering for the child and increased medical costs. Although a myriad of surgical treatment protocols and techniques for OFCs has been developed due to the controversies concerning speech and maxillofacial growth, the optimal protocol regarding both timing and repair method remains unclear.

The Cleft and Craniofacial Center, Department of Plastic surgery, Helsinki University Hospital has a history of various surgical protocols and techniques that have been utilized over the past three decades.

Aims. The main aim with this thesis was to retrieve an overview of the long-term incidence for SS, with focus on SCS and fistula repair in different types of cleft palates (CP), including patients with Robin sequence (RS), treated at the Cleft and Craniofacial Center, Department of Plastic surgery, Helsinki University Hospital. The different surgical protocols and techniques utilized since the 1990s at the cleft center were also assessed and compared.

Methods. This thesis consists of four separate studies, thus creating a study series involving the most common types of OFCs classified by the Veau system (isolated cleft palate [ICP], unilateral cleft lip and palate [UCLP], and bilateral cleft lip and palate [BCLP]), including RS. All studies were retrospective single-center follow-up studies. Only non-syndromic (ns-CP) subjects born between 1990 and 2011 were included, and all were treated and followed by the multidisciplinary cleft team as a part of the standard treatment protocol at the time of the cleft center. Only children with frequent follow-up to at least 8 years of age or longer were included in the ICP and RS studies (Studies I-II), whereas results were analyzed at alveolar bone grafting (ABG) and post-ABG in the UCLP and BCLP studies (Studies III-IV).

The primary palatoplasty protocols utilized throughout the years involved four different single-stage techniques and two different two-stage protocols, early soft palate repair combined with short delayed hard palate repair, and early hard palate repair combined with short delayed soft palate repair.

Results. The thesis included altogether 872 patients with ns-CP: ICP 423 (SCP 123 and HSCP 300), RS 78, UCLP 290, and BCLP 81. The long-term incidence for SS was high, and ranged between the Veau hierarchy from 23.6% to 46.9% (mean 34.5%) for SCS and 0.8-53.1% (mean 20.9%) for fistula repair. Extensive clefts, partly or totally detached from the vomer as the HSCP (inclusive RS) and BCLP were more likely to require SCS. Fistula repair followed the severity of the Veau hierarchy.

The outcome differences between the surgical protocols in CLP (UCLP and BCLP) were small, indicating that none of the treatment protocols was clearly superior to another. However, for both SCS and fistula repair, attention was drawn to the somewhat more favorable outcomes of the single-stage protocol. Moreover, no single-stage technique was clearly superior to another.

A substantial number of fistulas were closed at ABG, particularly the single-stage protocol with a high rate of anterior fistulas, especially in connection to a perialveolar fistula.

RS is associated with a high incidence of SCS and fistula formation. Gender, age at primary palatoplasty, surgical technique, surgeon, cleft severity, and airway management at infancy do not appear to be associated with need for SS.

Conclusion. As SS (SCS and fistula repair) are common in patients with OFCs in the long-term, these surgeries are particularly anticipated in extensive clefts and in patients with associated RS. No surgical protocol or technique is superior to another regarding the long-term need for SCS or fistula repair. Proper fistula assessment requires long-term follow-up, as a substantial part of the ONFs is repaired at ABG.

Keywords. Cleft lip and palate, cleft palate, Robin sequence, velopharyngeal insufficiency, fistula, velopharyngeal incompetence, palatoplasty, cleft palate, Veau classification

ABSTRAKT PÅ SVENSKA

Bakgrund. Under årens lopp har vårdprogram för patienter med spaltmissbildning (spalt i läppen, käken och/eller gommen; LKG) utvecklas. Målsättningen med vården har förändrats från att inte enbart reparera defekten till att uppnå långsiktiga och framgångsrika resultat med fokus på tal, bett, utseende och tillväxt av käken. En hel och fungerande gom är nödvändig för produktionen av normalt tal, vilket därför är en av det viktigaste aspekterna kring vård av LKG. Förvärvad velofaryngeal insufficiens (VPI) kännetecknas av ett hypernasalt och oförståeligt tal. Detta fenomen kan uppstå hos individer med korrigerad gomspalt pga. en strukturell defekt i den korrigerade gommen till exempel av oförmåga att stänga den velofaryngeala sfinktern på grund av en kort gom eller genom en förbindelse (t.ex. en oronasal fistel) mellan mun och näshåla som ger upphov till ett luftläckage från munhålan till näshålan vid tal. Dessa komplikationer kan medföra negativa samt ödesdigra konsekvenser för det växande barnet samt kräva återställande sekundära operationer i form av talförbättrande operationer (SCS) eller stängning av oronasala fistlar. Dessa komplikationer utgör inte enbart ett kirurgiskt dilemma – i synnerhet reparationen av oro-nasala fistlar – utan medför även ytterligare smärta och lidande för barnet samt förhöjda kostnader. Trots att det har utvecklats otaliga protokoll och tekniker för primär-kirurgi, för att gynna både tal och tillväxten av käken, förkommer det än så länge ingen konsensus angående vilket protokoll som är lämpligast.

Läpp- och gomspaltscentret Husuke vid Helsingfors universitetssjukhus har en historia med flera olika vårdprotokoll samt operationstekniker över de senaste årtionden.

Målsättning. Målsättningen med denna studie var att retrospektivt erhålla en översikt samt sammanfatta behovet av sekundär kirurgi med fokus på SCS eller fistelkorrektion i olika typer av spalt patienter, inklusive patienter diagnostiserade med Robin sekvens (RS) samt därtill evaluera och jämföra långtidsresultaten beträffande olika kirurgiska protokoll och tekniker som utövats sedan 1990-talet på läpp- och gomspaltscentret.

Metoder. Avhandlingen består av fyra separata studier som därmed skapar en studieserie angående de vanligaste typerna av LKG, klassificerade enligt Veau systemet (isolerad gomspalt [ICP], unilateral (ensidig) läpp- käk- och gomspalt [UCLP] och bilateral (dubbelsidig) läpp- käk- och gomspalt [BCLP]) inklusive RS. Alla studier var retrospektiva singelcenter-studier där enbart icke-syndromatiska patienter (ns-CP) var inkluderade och patienterna var födda mellan 1990 och 2011. Samtliga vårdade patienter var uppföljda av läpp- och gomspaltscentrets multidisciplinära spaltteam enligt rådande standardiserade vårdprotokoll. Enbart barn med regelbunden uppföljning till minst av en ålder på 8 år eller längre var inkluderade i studierna I-II (patienter med ICP eller RS) medan resultaten var analyserade vid bentransplantationen (ABG) i studierna III-IV (patienter med UCLP och BCLP).

Primäroperationerna som tillämpats under åren involverade fyra olika operationstekniker som utförts i en omgång (single-stage) samt två olika protokoll som

utfördes i två omgångar (two-stage); tidig slutning av mjuka gommen i kombination med efterföljande slutning av den hårda gommen samt vice versa.

Resultat. Avhandlingen omfattar total 872 inkluderade patienter med icke-syndromatiska spaltmissbildningar: ICP 423 (SCP 123 och HSCP 300), RS 78, UCLP 290, samt BCLP 81. Långtidsincidensen för sekundära operationer i gommen var hög och varierande mellan spalttyperna; SCS från 23.6% till 46.9% (medelvärde 34.5%) samt 0.8-53.1% (medelvärde 20.9%) för korrektion av fistlar. Omfattande spalter som delvis eller totalt är åtskilda från vomern som HSCP (inklusive PRS) samt BCLP var mer sannolika för att kräva SCS medan behovet för korrektion av fistlar följde Veau spalthierarkin.

Frånsett små skillnader uppkom inga entydiga skiljaktigheter mellan de kirurgiska protokollen som använts för primär-kirurgi av CLP (UCLP och BCLP). Trots detta fästes det uppmärksamhet vid de relativt gynnsamma resultaten av single-stage protokollet, både beträffande behovet av SCS samt för reparation av fistlar. Tillika, visade sig ingen single-stage operationsteknik vara överlägsen i jämförelse med de övriga.

En betydande del av fistlar är reparerade vid ABG. Speciellt single-stage protokollet har ett högt antal med speciellt anteriot lokaliserade fistlar som ofta var associerade med en perialveolara fistlar.

RS är associerad med ett högt behov av både SCS samt fistlar. Varken kön, primäroperationsteknik, kirurg, svårighetsgrad av spalt eller svårighetsgrad av obstruktion framkom som predisponerande faktor för det följaktiga behovet av sekundär kirurgi.

Slutsats. Sekundärkirurgi i form av SCS och reparation av oronasala fistlar är vanliga inom LKG och är speciellt förväntade hos barn med omfattande spaltmissbildningar och i samband med RS. Inget kirurgiskt vårdprotokoll eller teknik visade sig vara bättre än en annan. Långtidsuppföljning är essentiell vid evaluering av oronasala fistlar, då en betydande del av dessa repareras vid ABG.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Gustafsson C, Heliövaara A, Leikola J, Rautio J. Incidence of Speech-Correcting Surgery in Children With Isolated Cleft Palate. Cleft Palate Craniofac J. 2018 Sep;55(8):1115-1121.

II Gustafsson C, Vuola P, Leikola J, Heliövaara A. Pierre Robin Sequence: Incidence of Speech-Correcting Surgeries and Fistula Formation. Cleft Palate Craniofac J. 2020 Mar;57(3):344-351.

III Gustafsson C, Heliövaara A, Leikola J. Long-Term Follow-up of Unilateral Cleft lip and Palate: Incidence of Speech-Correcting Surgeries and Fistula Formation. Cleft Palate Craniofac J. 2021 Dec 6:10556656211055641. Epub ahead of print. PMID: 34866444.

IV Gustafsson C, Heliövaara A, Rautio J, Leikola J. Long-term Follow-up of Bilateral Cleft Lip and Palate: Incidence of Speech-Correcting Surgeries and Fistula Formation. Cleft Palate Craniofac J. 2022 Jun 20:10556656221102816. Epub ahead of print. PMID: 35726173.

ABBREVIATIONS

ABG	Alveolar bone graft
UCLP	Unilateral cleft lip and palate
BCLP	Bilateral cleft lip and palate
CP	Cleft palate
CLP	Cleft lip and palate (UCLP & BCLP)
CL/P	Cleft lip with or without cleft palate
HSCP	Hard and soft cleft palate
Husuke	The Cleft and Craniofacial Center, Department of Plastic surgery at Helsinki University Hospital
ICP	Isolated cleft palate
IVVP	Intravelar veloplasty
MI	Minimal-incision technique
OFC	Orofacial clefts
ONF	Oronasal fistula
SC	Scandcleft trial (Semb et al., 2017)
SCS	Speech-correcting surgeries
SCP	Soft cleft palate
SS	Secondary surgery
Post ABG	Total follow-up time at data collection (After ABG)
RS	Robin sequence
VWS	Van der Woude syndrome
VPF	Velopharyngeal function
VPI	Velopharyngeal insufficiency
VPS	Velopharyngeal sphincter
V-W-K	Veau-Wardill-Kilner technique
VPD	Velopharyngeal dysfunction

1 INTRODUCTION

Orofacial clefts (OFC) are among the most common congenital malformations in the head and neck region (Bicknell et al., 2002). The geographical distribution of orofacial clefts variates greatly in Europe. Finland has the highest incidence of 23.5 per 10 000 live births (National Institute for Health and Welfare) (THL, 2017); the corresponding European mean incidence is 15.2 per 10 000 live births (Calzolary et al. 2004). OFCs are commonly divided into cleft lip with or without cleft palate (CLP) and isolated cleft palate (ICP). These types differ both epidemiologically and etiologically from each other. The etiology is considered to be an outcome of both hereditary and environmental factors (Smarius et al., 2017). As such, ICP is often associated with other malformations or genetic syndromes when compared with CLP (Dixon et al., 2011). In contrast to the rest of the world, where ICP is the rarest type of orofacial cleft (Burg et al., 2016), ICP is the most common cleft type in Finland (THL, 2017).

The cleft type and its severity impact the development of not only growing facial structures (bones, soft tissues, and occlusion) but also speech development and hearing. OFCs impose not only a significant burden of care in terms of treatment, but may also affect the quality of life, health, and social integration of the affected patients and their families (Wehby and Cassell, 2010). Treatment requires often frequent management in a multidisciplinary setting involving plastic surgeons, oral- and maxillofacial surgeons, ENT specialists, specialized nurses, speech pathologists, psychologists, special dentists, orthodontists, and prosthodontists (Rautio et al. 2010). The treatment path is long, often up to adolescence, through standardized protocols of the cleft unit (Shaw et al. 2001). In Finland, cleft care has been centralized to special cleft teams since the 1940s. Approximately 120 children per year are born in Finland with OFCs; of these, approximately 100 are treated at the Cleft and Craniofacial Center, Department of Plastic surgery at Helsinki University Hospital. The remaining patients are treated in Oulu University Hospital (Rautio et al. 2010).

Patients affected by cleft lip and palate are managed by protocols consisting of both non-surgical and surgical interventions. The optimal treatment protocol in terms of method and timing for surgery remains uncertain due to controversies concerning speech and the growth of the maxillary structures and the great diversity of surgical treatment protocols between institutions (Smith and Losee, 2014). However, the numerous treatment protocols all have the same goal with cleft surgery: to close the defect, restore palate function to allow normal feeding and speech, and to improve hearing and occlusion while minimizing impact on the growing craniofacial structures (Haapanen, 1992; Gart and Gosain, 2014). Surgery also seeks to achieve a normal facial appearance to ensure healthy development of the child's self-esteem and to reduce the stigma caused by the cleft.

One of the most important aspects in cleft treatment is the development of normal speech, commonly referred to as velopharyngeal competence (VPC). This is defined as the ability to close the velopharyngeal sphincter (VPS) during speech. If

this is not possible due to a structural deficit, velopharyngeal insufficiency (VPI) will develop, as excessive air will flow into the nasal cavity, producing characteristic hypernasal resonance, nasal emissions, weak pressure consonants, and compensatory articulation (Gart and Gosain, 2014, Kummer, 2014, Samoy et al., 2015). VPI is common in children with a history of an OFC. The cause is believed to be multifactorial (Gart and Gosain, 2014) and not yet fully understood. Left untreated, VPI may have a detrimental impact on the growing child's psychological health and social relationships (Wehby and Cassell, 2010). If VPI is severe or conservative management in form of speech therapy fails to improve the condition, speech-correcting surgery (SCS) is needed (Becker et al., 2004, Andersson et al., 2010, Gart and Gosain, 2014).

Another important complication following cleft repair is wound dehiscence in the form of a palatal fistula. Palatal fistulas result from improper healing of the palate that may be caused by several factors, such as bleeding, infection, excessive tension, or tissue scarring (Alonso and Raposo-Amaral., 2018). Although small fistulas may remain non-symptomatic, larger ones can cause symptoms as nasal regurgitation and have an adverse impact on speech outcome, necessitating surgical intervention (Hardwicke et al., 2014). Surgical management is challenging and reoccurrence is common (Shankar et al., 2018), thus prevention is of paramount importance during the primary palatoplasty.

This thesis consists of a study series involving the most common OFCs in Finland and provides a comprehensive overview of the different surgical protocols and techniques utilized at a single cleft center over the last three decades. Long-term outcomes for secondary surgical burden of care, such as SCS and fistula repair, are assessed and compared.

2 REVIEW OF THE LITERATURE

2.1 EMBRYONIC DEVELOPMENT

Clefts of the lip and palate comprise both clinically and etiologically a broad spectrum of defects, which varies from mild orbicularis oris muscle discontinuity (cleft lip) and submucous cleft palate to more severe phenotypes, such as complete UCLP and BCLP. The etiology behind these malformations is thought to be a combination of both environmental and genetic factors. The most critical period for development of facial structures falls within the first trimester (Alonso and Raposo-Amaral., 2018). To understand the development of a facial cleft, it is important to understand the embryonic development of normal facial structures.

By the fourth gestational week, neural crest cells—unique embryonic cells that give rise to diverse connective and neural tissues—originating from the dorsal neural tube, migrate to form five areas (prominences) that subsequently develop the facial structures **(Figure 1)**. Within these prominences a further process of proliferation, merging, and fusion occurs and conclusively develops the facial structures. These prominences constitute **the frontonasal (central) prominence** that forms the cranial portion of the facial structures as the forehead, nose, philtrum, and the middle portion of the upper lip and the primary palate; the bilateral **maxillary prominence** grows into the maxilla, lateral aspects of the upper lip, and the secondary palate; while the bilateral **mandibular prominence** forms the lower portion of the face, such as the mandibula and lower lip (Bernheim et al., 2006).

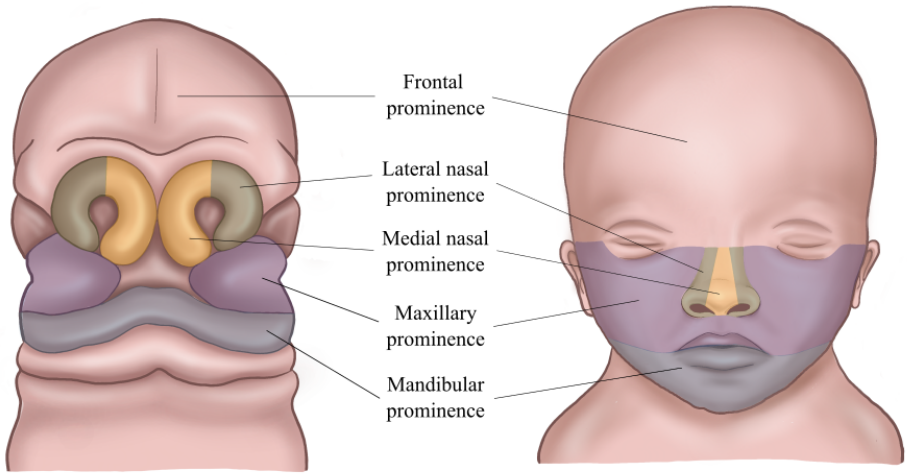

Figure 1. Facial development from the five facial prominences at approximately the fifth gestational week. Copyrights to Charlotta Gustafsson-Silén.

The nasal placodes (ectodermal thickenings) rise from the frontonasal prominence during the fifth gestational week. These structures invaginate into nasal pits, consisting of a nasal ridge divided into two separate medial and lateral prominences. At the same time, the maxillary processes undergo extensive growth, both in a forward direction and towards the middle, pushing the adjacent nasal prominences so that the medial components eventually merge in the middle. This forms the upper jaw, nose, philtrum, and the intermaxillary segment. This is also known as the primary palate, which houses the four incisor teeth and comprises the hard palate anterior to the foramen incisivum (Wang and Milczuk, 2020).

Once the primary palate has formed, the secondary palate (the hard and soft palate), located just posterior to the foramen incisivum, starts to develop between the sixth and eighth gestational weeks. Here, the palatal shelves of the maxillary prominences expand medially and fuse together in the midline, thereby separating the nasal and oral cavities from each other. Together with the primary palate, they form the definitive palate. This palatal fusion occurs from an anterior to posterior direction, beginning at the foramen incisivum at the eighth gestational week, completing the hard palate by the ninth week, and ending at the uvla by the twelfth gestational week (Kosowski et al., 2012).

If this growth process is disturbed and some of the facial prominences do not meet and fuse, this will turn into facial clefts, which can occur either unilaterally or bilaterally. Cleft lip is due to a failure to fuse the medial nasal process with the maxillary process. The severity of the defect may vary from mild discontinuity of the orbicularis oris to a complete cleft of the maxillary bone, depending on the timepoint of disruption, since the fusion process occurs from a cranial to caudal direction. Similarly, if the disruption occurs during the secondary palatal fusion from the maxillary prominences, a cleft palate will develop. Since the primary and secondary palate develop from separate prominences, the facial clefts are usually divided into cleft lip with or without CP, and separately ICP (Smarius et al., 2017). In females, the secondary palate is believed to be completely fused 1 week later than in their male counterparts (Kosowski et al., 2012). This may explain why the female sex is predominant in ICP, unlike in other cleft types, where the male sex is more affected (Calzolari et al., 2004; Kosowski et al., 2012).

2.2 CLASSIFICATION OF CLEFTS AND PHENOTYPES

Generally, clefts are roughly classified into unilateral or bilateral; cleft lip (CL), cleft lip with or without cleft palate (CL/P), ICP isolated cleft palate, or submucous cleft palate (SMCP). These malformations can vary in severity from incomplete to complete, and clefts including the primary palate can be either unilateral or bilateral. Moreover, clefting can also be classified as nonsyndromic and syndromic depending on the concomitant presence of other malformations.

Classification of cleft lip and cleft palate has an important role in both diagnosis, treatment, and prognosis and for clinical and epidemiological research. However, due to the ranges of morphologies and severities of different clefts, there is

not unanimous agreement on classification. A myriad of variations has been described in the literature (Davis and Ritchie, 1922, Veau, 1931, Kernahan and Stark, 1958, Kernahan, 1971, Kriens, 1989) both based on morphology and embryological development. However, only a few have found clinical application.

Tessier (Tessier 1976) described one of the most comprehensive although one of the most popular classification systems of rare craniofacial clefts. This classification involves a series of severe craniofacial clefts, more than just the lip and the upper jaw (as in CP). Dividing both soft tissue and hard tissue defects into 14 facial meridians using key landmarks such as the mouth, nose, and eye sockets; Midline clefts (meridians 0 and 14), paramedian clefts (meridians 1, 2, 12, and 13), orbital clefts (meridians 3, 4, 5, 9, 10, and 11), and lateral clefts (meridians 6, 7, and 8).

Davis and Ritchie (1922) were among the first to introduce a classification system that divided the OFCs based on the alvelus into a three-group system. They proposed that the alveolar process has central importance on surgical management, and thus the cleft phenotypes were described according to this structure. However, due to uncertainties in the classification, and overlapping in the categories (CL/P phenotypes may involve multiple structures) this classification received criticism and is no longer in practical use.

In 1931, Victor Veau simplified the classification by dividing the palatal cleft into four types in “Division Palatine”, while using the incisive foramen as an anatomical landmark **(Figure 2)**. He advocated for a clear and concise description and purposefully excluded specific details (such as degree of severity) from the classification system. This simple classification system was greatly appreciated by many surgeons (Allori et al., 2017) and is still widely used today.

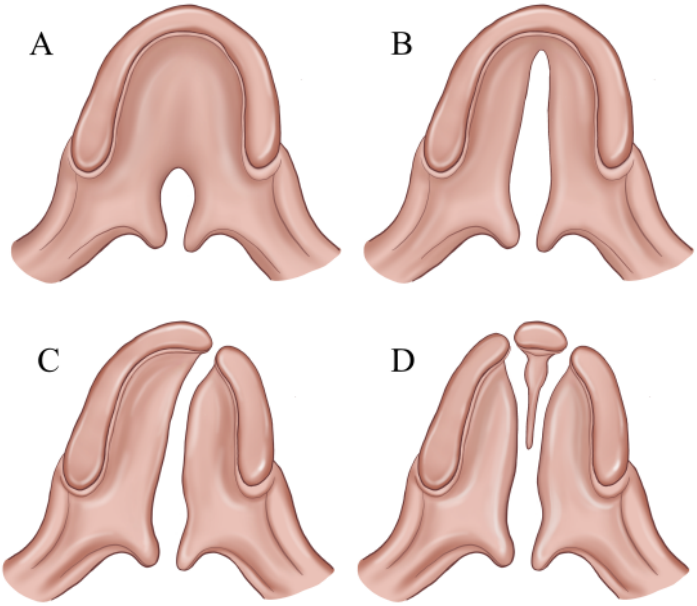

Figure 2. Veau classification of cleft types. A) Soft cleft palate (SCP), B) Hard and soft cleft palate (HSCP), C) Unilateral cleft lip and palate (UCLP), D) Bilateral cleft lip and palate (BCLP). Copyrights to Charlotta Gustafsson-Silén.

Kernahan and Stark (1958) were among the first to define the primary and secondary palate based on its embryological anatomy. They proposed the following three groups: cleft anterior to the incisive foramen, clefts posterior to the incisive foramen, and clefts affecting structures anterior and posterior to the incisive foramen. Later, Kernahan (1971) modified this classification into the symbolic "Y" classification, where the incisive foramen serves as a reference **(Figure 3)**. Here, the "Y" resembles an intra-oral view of the cleft lip and palate, where the affected cleft defect is labeled from 1-9, each representing a specific anatomic location (1, right lip; 2, right alveolus; 3, right premaxilla; 4, left lip; 5, left alveolus; 6, left premaxilla; 7, hard palate; 8, soft palate; 9, submucous cleft).

In 1989 Kriens described the LAHSHAL system **(Figure 3)**, where the anatomy of a bilateral cleft is described from right to left, namely lip (L), alveolus (A), hard (H), and soft palate (S). Capital letters stand for a complete cleft; a small letter indicates an incomplete cleft. Due to its simplicity, this classification system is preferred by many surgeons and is also compatible with the International Classification of Diseases (ICD 10) system (ICD-10, version 2020) (Taub & Silver 2016), where Q35 indicates cleft palate, Q36 cleft lip, and Q37 cleft lip and palate.

Numerous classifications systems have since been proposed, although none are universally adopted.

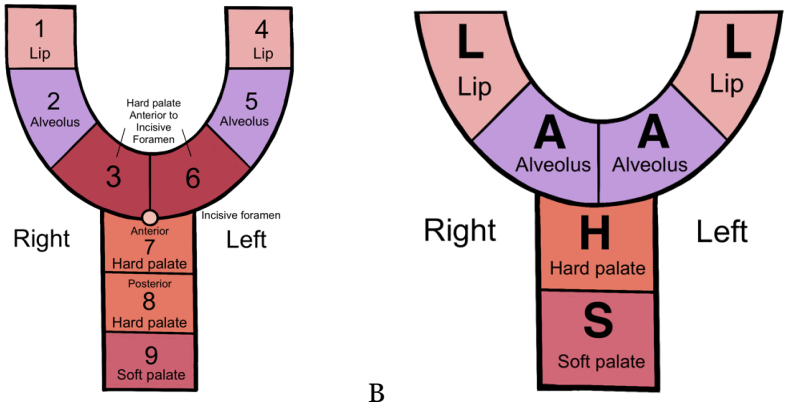

Figure 3. A) The Kernahan´s "Y" classification system, and B) The LAHSHAL system. Copyrights to Charlotta Gustafsson-Silén.

2.3 EPIDEMIOLOGY

The worldwide incidence for orofacial clefts (OFC) is approximately 1 per 700 live births. However, it is important to note that appropriate data are not available from some parts of the world. The corresponding prevalence in Europe is 15.2 per 10 000 (Calzolary et al. 2004); Finland has the highest prevalence of OFC (23.5 per 10 000 live births) (THL).

Both the prevalence and patterns for CP and CLP are distributed heterogeneously between ethnic groups (Mossey et al., 2009). Whereas CL/P is the most common form of OFC worldwide, ICP is more common than CL/P in Finland. Overall, a high prevalence of OFC is observed in Asians whereas the lowest rates are

observed in Africans. A high prevalence of ICP is observed in northern European countries, particularly in Finland but also in Canada, while lower rates are observed in Africa (Burg et al., 2016). One theory behind these ethnic differences may be the size of the facial processes and their interconnection to adjacent processes. Characteristic facial features of Asians are smaller and flatter midface structures in combination with broader upper facial structures and elliptical palate. These features may contribute to OFC. In comparison to Africans, who often have larger and broader noses, implicating larger frontonasal processes and larger palate, these structural features may lead to lower rates of OFC (Burg et al., 2016).

As mentioned, Finland has the highest prevalence of OFC, in particularly ICP, with a frequency of 13.7 per 10 000 live births. Approximately 130 children are born per year in Finland with OFC. Since 1963, these children have been documented in a national register on congenital malformations (National Institute for Health and Welfare [THL]). Regional differences in OFC, particularly ICP, prevalence has also been noted in Finland. The prevalence of ICP seems to increase in the northern and eastern parts on the country, whereas the lowest prevalence is in the southern and western part of the country. Thus, as previously hypothesized, head size is thought to be a contributing factor (Lilius, 1992).

2.4 ETIOLOGY

The etiology behind clefts is thought to be a combination of both environmental and genetic factors. While familial inherence does occur, traditional Mendelian inheritance is rare and multifactorial sporadic inheritance is more common. Therefore, it is difficult to identify predisposing genetic factors (Kosowski et al., 2012). However, emerging evidence suggests that CLP and CP arise from different mechanisms and genetic etiologies (Smarius et al., 2017).

After observing inheritance of clefts in families, Fogh-Anderson (1942) was among the first to describe genetic factors behind orofacial clefts. Since then, several genes throughout the human genome have been identified as linked to the development of the lip and palate. These include transforming growth factor-alpha (TGF-α), which was one of the first identified genes that showed an association with nonsyndromic CLP. Other genes include transforming growth factor beta 2 (TGF-β2), transforming growth factor beta 3 (TGF-β3), MSH homebox 1 (MSX1), MAF BZIP Transcription Factor B (MAF B), fibroblast growth factor receptor 1 (FGFR1), among others (Dixon et al., 2011). Interferon regulatory factor-6 (IRF6) has previously been shown to have an association with development of OFCs. A recent study identified a functional variant of an IRF6 enhancer (rs570516915) that is specifically expressed in the Finnish and Estonian population and has a strong association with the development of OFCs, particularly ICP. This may explain the high prevalence and distribution of ICP in the Finnish population (Rahimov et al., 2022).

Epidemiological studies have proposed several environmental factors and teratogens that are implicated in cleft development. While some have a consistently stronger association, such as alcohol consumption and cigarette smoking,

other suggested factors, such as folate and zinc deficiency, among others, have more inconsistent evidence for involvement (Rahimov et al., 2012). Overall, the studies are controversial and the results from these studies should be interpreted with caution, as confounding variables and recall bias are possible (Dixon et al., 2011).

The increasing knowledge of possible etiological factors and identification of how different factors and specific genes contribute to the formation of ns-CL/P plays an important role in genetic counseling, family planning, prevention, treatment planning, and education. The recurrence rate for clefts is high in families with ns-CL/P. Compared with individuals without a history of clefts, the risk for cleft is estimated to be 32 times higher in first-degree relatives (Sivertsen et al., 2008). Moreover, unaffected parents that have a child with a cleft have a 4.4% risk of conceiving another child with CLP and a 2.5% risk with ICP. The risk for conceiving a child with CLP and ICP is 3.2% and 6.8% if one of the parents is affected with a cleft. The risk further increases to 15.8% for CLP and 14.9% for ICP if one of the parents and a sibling have a cleft (Wang and Milczuk, 2020).

2.5 ASSOCIATED SYNDROMES AND ANOMALIES

Patients with orofacial clefts have a higher incidence of associated syndromes or anomalies compared to non-cleft individuals. Today, over 500 syndromes have been identified as associated with clefts (Dixon et al., 2011). Therefore, clefts are often divided into non-syndromic and syndromic clefting. ICP is more frequently associated with additional syndromes (s-ICP) or anomalies than CL/P (s-CL/P). Approximately 50% of the ICP population has an associated anomaly or syndrome; the corresponding proportion is 30% in the CL/P population (Dixon et al., 2011). Among these, Van der Woude syndrome (VWS) is the most common type of syndromic clefting, with a 2% prevalence rate in Finnish cleft children (Lilius, 1992). VWS is characterized by pits in the lower lip, and this autosomal-dominant inherited disorder is caused by mutations in the IRF6 gene (Rahimov et al., 2012, Rahimov et al., 2022). Other well-known cleft-associated syndromes are Robin sequence (RS), DiGeorge (22q11.2 deletion) or velocardiofacial syndrome, Apert syndrome, Crouzon syndrome, Sticklers syndrome, and Treacher Collins syndrome, among others (Leslie and Marazita, 2018).

2.5.1 ROBIN SEQUENCE

Robin sequence (RS) is a condition characterized by a clinical triad involving micrognathia, a retroposed tongue (glossoptosis), and upper airway obstruction (Breugem et al., 2016) **(Figure 4)**. This condition is commonly associated with a wide U-shaped cleft palate (Hanson and Smith, 1975) and may be part of a syndrome or appear in isolation (Smith, 1975). Although the sequence was originally described in the nineteenth century, the first case report was published by the French physician Pierre Robin in 1923. RS is a rare condition with a prevalence of 1 per 8000 to 14 000 live births (Bush and Williams, 1983; Printzlau and Andersen, 2004; Vatlach et al., 2014). This condition is named as a sequence as the separate anomalies are believed

to arise from one underlying malformation. There are some uncertainties on the underling pathogenesis and many theories exists. Among these, one theory suggests that mandibular hypoplasia is the first abnormality that then leads to glossoptosis, which in turn causes airway obstruction and development of a cleft palate, due to a mechanical hinderance that ultimately prevents the palatal shelfs from fusing during gestation (Giudice et al., 2018). Clinically, these infants present with an underdeveloped mandible and a retroposed tongue and suffer from mild-to-severe obstruction and breathing problems, malnutrition, and feeding difficulties (Benjamin and Walker, 1991). Conservative management with positioning combined with bottle feeding techniques or by nasogastric tubes is sufficient for most of these patients for breathing and feeding difficulties. Within first few months of life, most outgrow these concerns, although the "catch-up growth" theory of the mandibula is disputed (Mackey 2011). However, the cleft palate requires surgical management as for any other cleft palate patient, although management is often postponed until the breathing difficulties resolve. The palatal morphology of the RS cleft has been described as wider (Rintala et al., 1984; Godbout et al., 2014) and even longer (Godbout et al., 2014) than ICP. Differences in speech outcomes have also been reported between ICP and RS, with poorer results in RS (Stransky et al., 2013, Hardwicke et al., 2016).

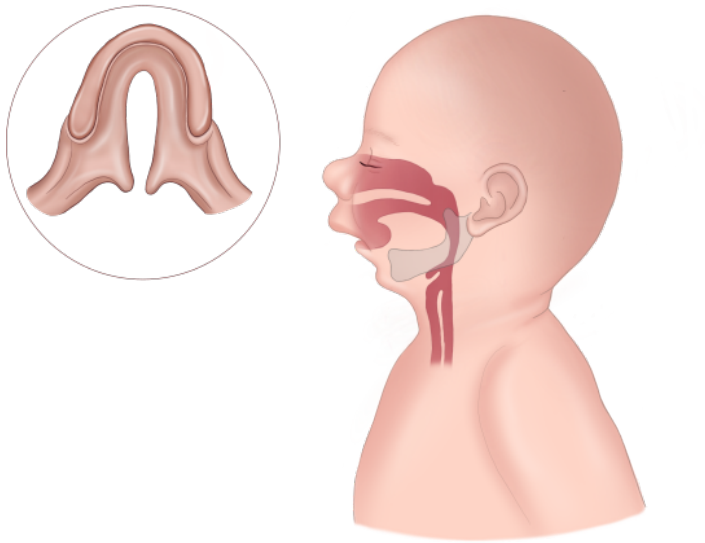

Figure 4 Robin sequence is characterized by micrognathia, a retroposed tongue (glossoptosis), upper airway obstruction, and a "U-shaped" CP. Copyrights to Charlotta Gustafsson-Silén.

2.6 ANATOMY

It is essential to understand the normal anatomy of the lip and palate to understand cleft lip and palate.

In addition to the multiple important motor functions that the lips provide, they also provide vital sensory information, such as touch, pain, and

temperature perception. The lip consists of mucosa, muscle, and skin. The red, mucous membrane part of the lip is surrounded by a white cutaneous structure known as the vermilion border. This anatomical border is an important landmark in cleft lip reconstruction when aiming for a proper cosmetic and natural-looking result (Baker, 2007). The orbicularis oris muscle encircles the mouth, where it forms a complete sphincter that controls the movements of the mouth and lips, such as closing the mouth and protruding the lips. However, it also serves as an insertion site for other muscles in the facial and oral region. These muscles control the facial expressions and originate bilaterally in a radial formation around the mouth, providing an indirect connection to the facial skeleton. Whereas the levator muscles (levator labi superioris and levator labii superioris alaeque nasi) are responsible for elevating the upper lip, the zygomaticus muscles (zygomaticus major and minor) pull the labial commissure superolaterally. In the lower lip, the depressors (depressor anguli oris, depressor labii inferioris, and mentalis) are responsible for protrusion and moving the lip inferolaterally.

The philtrum is the central skin between the lip and nose, a vertical groove outlined by two parallel raised ridges. The philtrum has no functional importance but is of aesthetic significance (Baker, 2007). However, this is also the area where the uni-or bilateral cleft is formed. The tip of the nose and the nostrils are formed by the nasal alae cartilage. The nasal septum and columella divide the nostrils from each other.

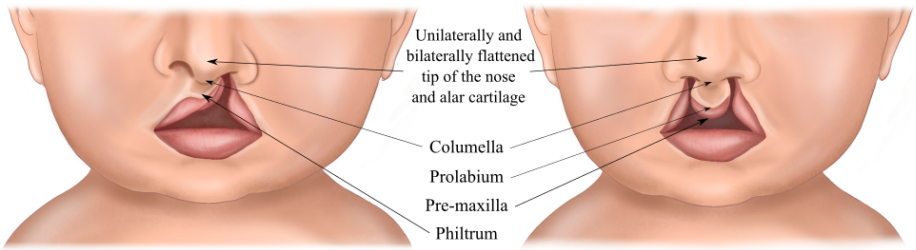

Figure 5. Illustrative drawing of complete UCLP and BCLP. Copyrights to Charlotta Gustafsson-Silén

In patients with orofacial clefts, the abnormal appearance and function of the lip and mouth is related to the degree of deformity. In cleft lip, the continuity of the muscle ring and sphincter is broken **(Figure 5)**. The muscle fibers run in an inferior-to-superior direction attaching to the margins of the cleft edges, such as in unilateral clefts, medially inserting into the columella and laterally to the nasal alae. However, in bilateral cleft lips, these muscle fibers insert along the lateral aspect of the cleft while the muscle in the prolabial segment of the premaxilla is often deficit. Moreover, the bony deformity of the premaxilla may be severely protruded, pushing the lip far anteriorly and resulting in a short columella (Wang and Milczuk, 2020).

In addition to the maxillary bone deficiency and absence of the nasal floor on the cleft side, typical anatomical characteristics of the nasal deformity in total UCLP include lowering and flattening of the lateral cartilage on the cleft side, from its normal curved position, and deflection of the nasal tip toward the noncleft side

(Figure 5). The columella is often shorter on the cleft side, and the septum lies on the noncleft side due to the muscle tension from the opposite side.

On the other hand, in total BCLP the nasal deformity is associated with the severity of the cleft lip deformity and with the degree of premaxillary protrusion. A severely protruded premaxilla is often associated with a short or nearly absent columella and the alar cartilages are subluxed from the normal position while lowering and flattening the nasal tip, creating the characteristic horizontally oriented and wide nostrils (Wang and Milczuk, 2020).

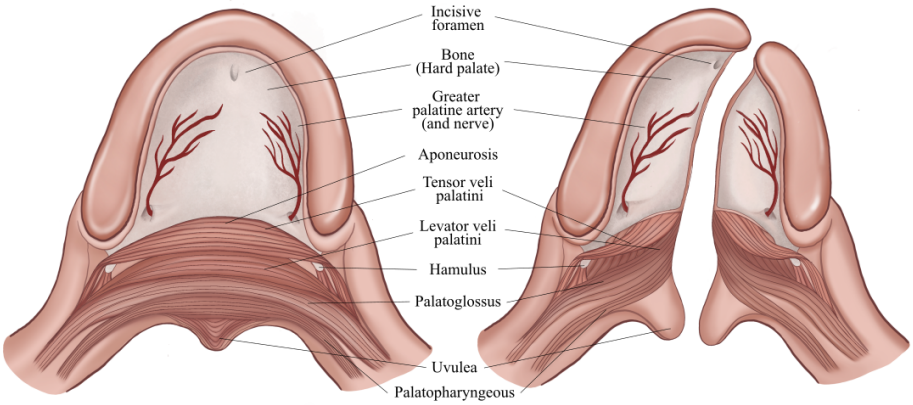

Figure 6 The anatomy of the palate and cleft palate. Copyrights to Charlotta Gustafsson-Silén.

While the palate is generally subdivided into the hard and soft palate, the most important aspect of the palate is to separate the oral cavity from the nasal cavity. The hard palate consist of the anterior and bony aspect of the palate, covered by a thick mucosal layer, and is cranially attached to the vomer, which serves the most caudal aspect of the nasal septum. The soft palate (also known as the velum), in turn, serves the posterior aspect of the palate, which consists of five muscles covered with a thin mucosal layer. These five muscles are levator veli palatin, tensor veli palatini, palatoglossus, palatopharyngeus, and musculus uvulae **(Figure 6)**. Together, these muscles are important for the closure of the nasopharyngeal sphincter (VPS), which in turn is important for both swallowing and speech (Alonso and Raposo-Amaral., 2018).

The levator veli palatini muscle originates from the petrous portion of the temporal bone and to some extent from the medial rim of the cartilaginous auditory tube. The fibers course anterio-medially inserting in the middle of the soft palate, creating a horizontal muscle sling (aponeurosis). This muscle is critical for closure of the VPS as it provides the superior and posterior movement of the soft palate against the posterior pharyngeal wall. The tensor veli palatini muscle originates from the cranial base and lateral side of the cartilaginous part of the auditory tube. Before inserting at the dorsal edge of the hard palate, the muscle becomes a tendon that travels around the hamulus in an almost 90° turn entering the soft palate. Together with the adjacent levator veli palatini, it aids the opening of the auditory tube during

swallowing and yawning, thus permitting drainage and pressure equalization between the middle ear and pharynx (Sweeney et al., 2015). The abnormal insertion and function of the tensor veli palatini is believed to influence the development of middle-ear problems and otitis media in patients with a history of CP (Heidsieck et al., 2016). The uvular muscle is an intrinsic muscle of the velum, which originates from the palatal aponeurosis and provides increased muscle tissue in the middle and dorsal part of the velum that in turn facilitates VPS closure.

Whereas the levator veli palatini provides the elevating function of the palate, the palatoglossus and palatopharyngeus provides opposite movements. The palatoglossus originates from the lateral aspect of the velum and inserts in the lateral aspect of the tongue. Contracting this muscle lowers the velum and elevates the posterior tongue, which is important for swallowing. Moreover, the palatopharyngeus originates from the anterior part of the velum and courses in a posterior direction inserting in the lateral walls of the pharynx. This muscle tenses the velum by pulling it downwards in a posterior direction as well as pulling the lateral pharyngeal walls medially, narrowing the nasopharynx, which is important during VPS closure (Alonso and Raposo-Amaral., 2018).

The muscles of the velopharyngeal sphincter described above receives its innervation primarily by the pharyngeal plexus that originates mainly from the vagus nerve and by the mandibular branch of the trigeminal nerve. While the vagus nerve innervates almost the whole velum, the tensor veli palatini receives its innervation from the mandibular branch of the trigeminal nerve and the uvular muscle from the minor palatine nerve (Sweeney et al., 2015).

In CP, insertion of the velar musculature is abnormal and is directed in an anterior orientation towards the side of the cleft and the posterior aspect of the hard palate, without attachment to the contralateral side **(Figure 6)**. This discontinuous structure is unable to create the physiological muscular sling that is vital for the proper function of the palate and VPS (Alonso and Raposo-Amaral., 2018).

2.7 CLINICAL OUTCOME MEASURES AND CHALLENGES IN CLEFT CARE

2.7.1 SPEECH AND VELOPHARYNGEAL DYSFUNCTION

The production of normal speech requires not only a mobile and intact palate that separates the oral and nasal cavities but also a properly functioning velum that can close the velopharyngeal sphincter back in the nasopharynx. Hence, by pushing the muscles of the soft palate against the posterior pharyngeal wall, airflow through the nose during speech is prevented and food and liquids do not escape to the nasal cavity during swallowing. If the velum fails to close the velopharyngeal sphincter (due to a variety of reasons), excessive air will flow to the nasal cavity hinders production of proper speech. This phenomenon is known as velopharyngeal dysfunction (VPD). VPD may be due to several reasons, such as an anatomical deficit in cleft palate

patients or functional changes after adenoidectomy (often temporary, rarely long-term) or orthognathic surgery. These anatomical conditions and structural deficits that prevent velopharyngeal closure are commonly known as velopharyngeal insufficiency (VPI). However, neurological disorders (muscle weakness or difficulty with muscle coordination of the palate), syndromes, and unknown causes may also drive VPD (Glade and Deal, 2016).

VPI is characteristic by hypernasal speech and audible nasal emission due to excess airflow through the nose **(Figure 7)**. Weak oral-pressure consonants (/p/, /t/, /k/, /s/) are also present due to the decreased oral pressure that leads to development of compensatory articulation. This speech may be difficult to understand and may have a detrimental impact on a child's psychological health and social relationships (Barr et al., 2017).

VPI is not uncommon in children with repaired clefts. Although the reasons behind development of VPI in CP patients are not fully understood, structural changes are of major importance, such as palatal shortening, scar contracture, fistulas, and insufficient levator function following primary repair. However, neurological deficits and associated muscle hypotonia may also play an important role, particularly in syndromic clefting.

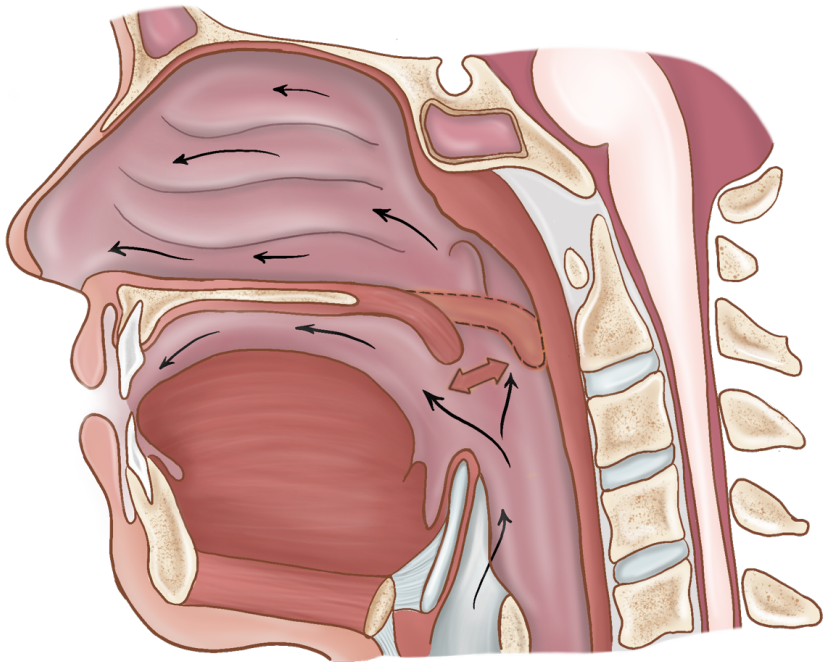

Figure 7. Velopharyngeal insufficiency (VPI). If the velum is too short, the velum does not close the velopharyngeal sphincter (VPS) in the back of the nasopharynx, causing excessive airflow into the nasal cavity during speech. Copyrights to Charlotta Gustafsson-Silén.

Speech and development of VPI in cleft patients are carefully assessed and documented, already from an early age, by trained speech pathologists. Although perceptual assessment of speech is the gold standard in evaluation of cleft speech, instrumental analysis is used to complement it (Rizzo et al., 2022). Procedures such as nasoendoscopy, nasometry, videofluoroscopy, or dynamic magnetic resonance imaging (MRI) provide objective and numeric measurements. While nasoendoscopy with a flexible fiberoptic nasoendoscope provides direct information on the function of VPS during speech, videofluoroscopy provides objective information on the movement of velum towards the posterior pharyngeal wall, which aids visualization of structural deficits. However, results should be assessed with interpretation of the speech characteristics (Kummer, 2014). In contrast to nasoendoscopy assessment, videofluoroscopy provides precise outcome measurement variables, such as the velopharyngeal gap size and velum length, which are important for research.

Perceptual assessment of VPI (particularly hypernasality, nasal air emission, and weak oral pressure buildup) is evaluated by assessing resonance, airflow control, and articulation. The severity of VPI is commonly documented on a scale measurement (Glade and Deal, 2016). However, no universal standardized classification protocol exists, which confounds comparisons between cross-center studies.

The management of VPI in children with repaired CP involves both surgical and non-surgical interventions. With conservative management, such as speech therapy, compensatory speech patterns can be corrected. However, in cases of inadequate closure of the VPS due to an anatomic deficiency, speech therapy cannot replace the importance of surgery. Therefore, speech-correcting surgeries (SCS), also commonly known as VPI surgery, should be considered in children with moderate-to-severe VPI (Kummer 2014, Glade and Deal, 2016).

2.7.2 PALATAL FISTULA

Breakdown of the repaired palate leads to a connection between the oral and the nasal cavity. This is a well-known complication following primary repair and also indicates the surgical outcome of the primary repair. Fistulas may develop anywhere (most commonly in the midline) in the palate **(Figure 8)** as a result of unsuccessful wound healing. This may be due to excessive tension, infection, or hematoma. Particularly extensive and wide clefts are more prone to develop fistulas due to the inevitable tension occurring at repair (Alonso and Raposo-Amaral., 2018).

Palatal fistulas vary greatly, from small asymptomatic pinhole fistulas to larger defects that may entail hygiene issues (such as dental decay) and also cause unpleasant symptoms such as nasal regurgitation of food and fluids. Palatal fistulas may also impact speech due to nasal air emission through these defects (Hardwicke et al., 2014). This excessive air escape through a fistula may mimic VPI caused by the inability to close the velopharyngeal sphincter, causing articulation difficulties due to weak oral pressure buildup and potential hypernasal resonance. It is therefore important to distinguish the etiology behind VPI. However, an experienced speech

pathologist can often differentiate between these two. As nasal air emission secondary to an oronasal fistula is dependent on the location and size of the palatal fistula, it is important to identify the pattern of air emission (Kummer, 2014) or temporarily occlude the fistula (such as with chewing gum) during speech assessment (Murthy, 2011). Moreover, instrumental assessment, such as nasoendoscopy, is also essential to characterize VPS function.

The reported incidence of fistula is highly variable in the literature (0 to 76%) (Smith, 2007), most likely due to the lack of a universal standardized protocol of documentation and classification of these structural defects. To address this, standardized classification systems, such as the Pittsburgh classification (Smith et al., 2007) (**Figure 8 and 20**) have been proposed to standardize the classifications according to fistula location, particularly in terms of intentional perialveolar fistula and unintentional fistula in the secondary palate. This is because anterior fistula in the primary palate in Veau III-IV clefts (UCLP and BCLP), also known as perialveolar fistulas, are often intentionally left open at primary palate repair (Smith et al., 2007). Fistulas may develop immediately as a complication after palatal repair. These early fistulas are especially difficult to treat and have high recurrency rates. However, fistulas may also develop later, prior to, and during orthodontic treatment that may lead to potential palatal expansion and may thereby remain undiagnosed until several years after the primary palatal repair (Shankars et al., 2018).

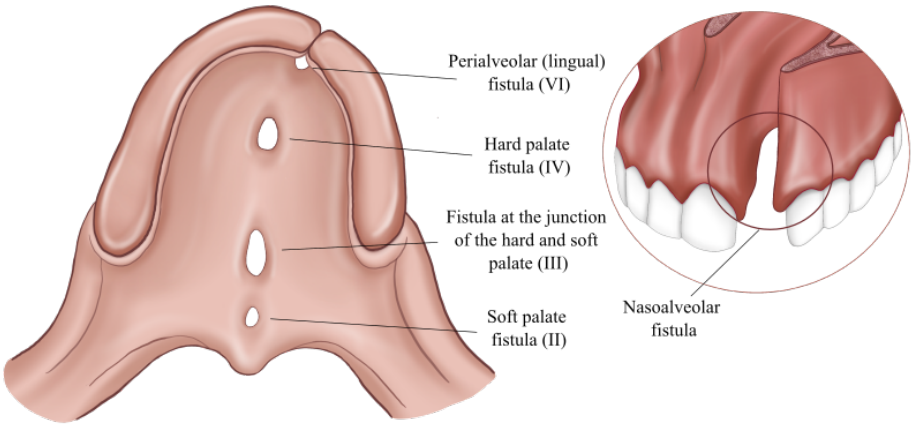

Figure 8 Possible fistula locations in the palate and perialveolar fistula (The Pittsburgh location is referred to by their Roman numerals). Copyrights to Charlotta Gustafsson-Silén.

While some smaller fistulas may heal by secondary attention (Tache, 2019), management of symptomatic fistulas often requires surgical closure (Hardwicke et al., 2014). If surgery is not an option, oral occluding appliances may be considered. However, palatal fistulas are not only a technical surgical dilemma but also lead to an additional surgical procedure associated with high recurrence risk and increased medical costs, not to mention the additional pain and suffering for the child

(Thompson et al., 2017). Therefore, prevention is paramount during the primary repair. Different methods and strategies have been developed to address this unfortunate complication, such as relaxing lateral incisions and acellular dermal matrix (Steele and Seagle, 2006, Losee et al., 2008, Agir et al., 2015, Simpson et al., 2019). More recently, buccal fat pads have become more common to fill dead space (Thurston et al., 2020).

2.7.3 MAXILLOFACIAL GROWTH

The maxillary growth in cleft children is affected by several factors, such as intrinsic growth disturbances and iatrogenic growth restrictions from both surgery and non-surgical maneuvers. The growth differences are smallest in the cleft of the primary palate and greatest in combined clefts of lip and palate. In operated UCLP, regardless of method, these patients show crossbite and retrusion of the maxillary profile relative to the cranial base (Semb, 1996, Shi and Losee, 2015, Heliövaara et al., 2021, Küseler et al., 2021). This maxillary hypoplasia does not only impact occlusion and appearance but can also impact speech and the patient's self-esteem. While agenesis has an unfavorable impact on craniofacial growth and on dental arch relationship (Rizell et al., 2021), some evidence suggests that the severity of the cleft palate is related to the maxillary growth. The larger the initial cleft is, the greater risk for development of some degree of maxillary retrusion (Chiu et al., 2011, Corcoran et al., 2021). However, the evidence for this is not yet conclusive.

Each surgical intervention inevitably leads to growth restriction to some degree, due to scar contracture in growth-sensitive areas (Ross, 1970). Lip repair is associated with growth restriction in the sagittal plane, whereas cleft palate inhibits growth in all dimensions of the maxilla, since the structures around the operated area seem to grow more rapidly. The growth restriction leads to malocclusion, particularly anterior and lateral crossbites, which require orthodontic treatment and orthognathic surgery (Le Fort 1 osteotomy) at an older age (Heliövaara and Leikola et al., 2021). Therefore, some cleft centers prefer to delay the palatoplasty to allow growth of the maxillary structures. However, this in turn interferes with speech development, given that early structural integrity of a repaired palate is vital to enable proper speech development. Others prioritize speech, since this is often more challenging to correct than malocclusion (Leow and Lo, 2008). This ongoing debate regarding optimal timing of primary palatoplasty has led to a myriad of different surgical protocols, involving single-staged and staged methods; however, no definitive protocol exists. On the contrary, maxillary advancement for maxillary hypoplasia and malocclusion also has a risk of negatively impacting VPS leading to VPI, although articulation may paradoxically improve due to the improved occlusal relationship of the jaws (Alaluusua et al., 2020).

2.7.4 HEARING

Hearing plays a critical role in a child's speech and communication development. Impaired hearing can lead to delayed speech, language, and social development.

Middle-ear problems and associated hearing loss is a well-recognized problem in children with CP (Gani et al. 2012). This emphasizes the importance of proper follow-up of these patients already from an early age (Lehtonen et al., 2016). More than 90% of children with CP have otitis media with middle-ear effusion (OME), commonly known as "glue ear", during the time of cleft palate repair. After repair, the prevalence reduces, although most children still suffer from middle-ear disease throughout childhood (Heidsieck et al., 2016). Treatment of OME and Eustachian tube dysfunction in CP is controversial (Ponduri et al., 2009). The treatment may be initially conservative and usually requires insertion of ventilation tubes (VT), as this condition may lead to conductive hearing impairment (Gani et al. 2012). Children with CP have a particularly high incidence for VT insertion when compared with their non-CP counterparts, and repeated VT insertion is often needed (Lehtonen et al., 2016). The reason behind this condition is believed to originate in the dysfunction of the Eustachian tube and tensor veli palatini muscle due to the anatomical abnormalities of these structures that are normally responsible for opening of the Eustachian tubes, permitting ventilation and drainage of the middle ear. Therefore, it is important to preserve the integrity of the tensor veli palatini muscle at primary palatoplasty (Heidsieck et al., 2016).

2.8 TREATMENT OF PATIENTS WITH OROFACIAL CLEFTS

Children born with cleft lip and or palate require long-term treatment and follow-up, spanning from birth to adulthood, by a multidisciplinary team specialized in cleft care. A cleft team consists of various healthcare professionals, such as plastic surgeons, maxillofacial surgeons, orthodontists, speech pathologists, ear, nose, and throat (ENT) specialists, geneticists, and specially trained nurses (Rautio et al., 2010).

Due to both aesthetic and functional implications that follow with OFCs, surgical treatment is essential. However, the surgical management often depends on the severity and nature of the cleft. Severe clefts, as UCLP and BCLP, require multiple surgical interventions. Combined with the rehabilitation that follows, this adds to the substantial and costly burden of care (Wehby and Cassell, 2009). Modern treatment protocols tend to focus on speech development and maxillary growth and not just on closing the defect. Therefore, there is general uncertainty whether one treatment protocol is superior to another, and various variations in protocols exist between institutions (Leow and Lo, 2008). These tailored management protocols, corrective surgeries (also known as secondary surgery), and multidisciplinary rehabilitation are often inevitable and reflect the several challenges that the child faces growing up. These include scarring, fistula, VPI, speech delay, dental issues, hearing impairment, maxillary hypoplasia, appearance, psychological concerns, and low quality of life (Marcusson et al., 2001, Tache and Mommaerts, 2009). Today's society has a generally increased demand for improving physical appearance, and patients with OFCs are not exempt from this. However, the rate and need for secondary surgeries may also be interpreted as a measure regarding the success of the primary surgery.

Surgical outcomes are associated with the experience and skill of the surgeon and not only on the particular surgical method (Shaw et al., 1992). Centralization and standardization with high-volume surgeons are associated with superior surgical outcomes compared with non-standardized low-volume surgeons (Ness et al., 2018). Not only does the quality of cleft care improve by centralization, this also allows development of research expertise on a sufficiently large patient population and follow-up that will improve and evolve patient care (Rautio et al., 2010, Ness et al., 2018). Therefore, to ensure the quality of cleft care, centralization is essential. Centralization was already implemented in Finland in 1948 (Rautio et al., 2010).

2.8.1 BASIC PRINCIPLES OF PRIMARY SURGERY

The primary surgeries of CP are often performed within the first year of life, where the surgical protocol and timing diverge based on the cleft type and severity. If the child develops VPI needing SCS, surgery is usually performed before school age (between 4 to 7 years of age), while fistula repair is performed according to the severity of symptoms, either alone or in combination with another procedure. Alveolar bone grafting (ABG) is performed in patients with total CLP before the eruption of the permanent canines (between 9 to 12 years of age). Due to the development of crossbite and maxillary hypoplasia, orthognathic surgery is usually performed at the end of the growth phase (after 16 to 18 years of age). The surgical timing at Husuke is shown in **Figure 9**.

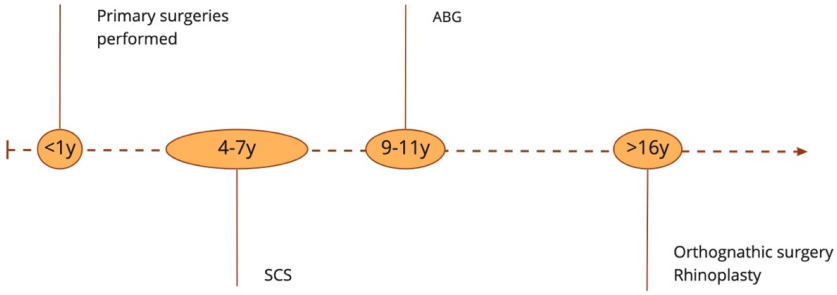

Figure 9. Surgical timing at Husuke. SCS, Speech-correcting surgeries; ABG, alveolar bone graft.

A myriad of primary surgical treatment protocols for CP repair have been described both in terms of timing and surgical techniques. Many of these principles are centuries old but are still used today, although large variations exist between regions, institutions, and surgeons (Naidu et al., 2022). Despite the variety of surgical treatment protocols, the goals and principles of primary surgery remain the same; to repair and restore the integrity of the structural defect with the aim of normal appearance, hearing, and velopharyngeal function that allows normal production of speech without restricting growth of the facial structures. The optimal protocol is a subject of debate. Randomized controlled studies are limited (Shaw et al., 2000, Mossey and Castilla, 2002) and the final treatment outcomes can only be evaluated at

the end of the growth period, several years after primary surgery (Rautio et al., 2010), which complicates the assessment of particular surgical methods. However, with good primary repair, the need for additional secondary procedures decreases in addition to the surgical burden for the child and the economic burden for society, which are both currently important aspects of cleft care.

2.8.2 PRINCIPLES OF PRIMARY LIP AND NOSE REPAIR

Primary lip repair in UCLP and BCLP is usually performed as the first surgical procedure together with primary nose repair. This procedure is commonly performed at 3 to 6 months of age (Marcus et al., 2017). However, the child's weight and health status may affect the timing (Nahai et al., 2005). Following labial repair, the tension in the lip will steer the maxilla to its correct position over the following months and make the cleft narrower (Shi and Losee, 2015), which supports the following palatoplasty.

Presurgical nasoalveolar molding (NAM) or infant orthopedics are an approach that manipulates the alveolar segments and reduces the gap between them with the aim of facilitating the surgical repair. Although this is a popular treatment approach at many centers, controversial results exist regarding its necessity (Grayson and Cutting, 2001, Bongaarts et al. 2004, Prahl et al. 2006, Heijden et al., 2013, Pontes et al., 2021). Since the level of beneficial evidence is conflicting and due to the geographical distances in Finland and practical considerations, NAMs are not utilized at Husuke.

Various techniques have been described throughout the years for both primary lip and nasal reconstruction, where commonly old-fashioned staged protocols have been replaced by single-staged approaches. As mentioned, repair was initially commonly staged (to prevent major impact on maxillary growth) with focus on lip repair, due to a misconception that early manipulation of nasal cartilage was thought to prevent its growth and was therefore postponed (Salyer, 1986). Lip repair in total CLP (UCLP and BCLP) was initially commonly performed by a temporary closure without reconstruction of the pathologic anatomy, creating a restraining force that causes a narrowing effect on the alveolar segments, which in turn helps the final repair. This procedure is more commonly known as "lip adhesion" (Marcus et al., 2017). However, this procedure was later considered unnecessary and contributed to scarring that made the final cheiloplasty difficult and ultimately fell out of use (Mulliken, 2001). Furthermore, the nasolabial reconstruction was later synchronized at the same time.

Until the 1930s, cleft lip repair mainly focused on paring the cleft margins and approximating the incised edges in the middle. However, the difficulties with this approach were the uneven vertical height of the lip on the normal and cleft side. Decades of innovative geometric designs slowly solved this height-deficiency issue, although this was often at the expense of visible scars and a disrupted philtrum column (Marcus et al., 2017). In 1955, Millard introduced a rotation-advancement technique that has since served as a framework for lip reconstruction. This technique offers a balance of the Cupid's bow, where the continuity of the philtrum's column is

not disrupted and the scar resembles a philtrum column (Marcus et al., 2017). Since then, not only has Millard himself introduced refinements to this method (Millard 1964 and 1970), but a myriad of modifications has been presented (Roussel et al., 2015). Among these, Fisher (2005) introduced his "an anatomical subunit approximation technique" for lip repair of UCLP. With this technique, scars are avoided both on and under the columella and the inclusion of a cutaneous triangle immediately above the white roll both balances the vertical length and breaks up the philtral scar.

One of the most important aspects of the labial repair is to dissect and release the muscles from their pathologic insertions and return them to their normal positions in both the lip and at the nasal floor by repositioning the alar cartilage in its more anatomical position (Pujol and Riera March 2021). Therefore, synchronous correction of the nasal deformity with labial repair is essential, with the aim to achieve an ideal outcome. The goal is to achieve a good foundation of the lower third of the nasal structures that will allow future proper growth and postpone the definitive rhinoplasty into young adulthood (Marcus et al., 2017).

Nasolabial reconstruction is commonly described as more challenging in wide cleft particularly in BCLP when compared with UCLP, where esthetically impeccable results are difficult to achieve (especially regarding the nose) due to the tension in the muscles and the abnormal position of the bony structures, such as the protruded premaxilla (Pujol and Riera March 2021). In these cases, the nose often appears short and flat. Particularly in BCLP, attention is drawn towards lengthening the columella. As in UCLP, several techniques for labial repair have been described in BCLP. In the past, staged approaches were common, where one side was first repaired followed by the other side, due to the protruded premaxilla and tension at repair. These procedures involved both lip adhesion and other approaches often utilized in UCLP lip repair (Marcus et al., 2017). Today, a single-stage "straight-line" bilateral lip-repair is common, which facilitates a symmetrical outcome and is performed along with nasal repair. However, the approach is often case-specific due to the severity and asymmetry of the clefts. One popular approach is Mulliken's (2001) described technique for bilateral naso-labial repair. Similarly, nasal-repair approaches differ between surgeons. However, a common approach for nasal repair is McComb's (1975) described technique.

2.8.3 PRINCIPLES OF PRIMARY PALATOPLASTY PROTOCOLS

Unfortunately, maxillary growth and speech do not develop simultaneously, which has led to disagreements on the timing of cleft repair. However, since emerging evidence suggests that the development of speech is substantially disturbed if hard palate repair is delayed by years (Rohrich et al., 1996, Lohmander-Agerskov, 1998, Holland et al., 2007, Kappen et al., 2017, Willadsen et al., 2017), early palate repair by the first year of age has become a more standard approach (Willadsen, 2012, Klintö and Lohmander, 2017). Nevertheless, some are concerned about a possible growth-restricting impact on the maxillary structures and prefer delayed closure of the hard palate (Friede at al., 2001).

While there is increasing agreement on the timing of cleft palate repair, with beneficial speech outcomes of early repair, the surgical protocols and techniques remain controversial (Naidu et al., 2022). Initially, various single-stage repair methods were widely used until two-staged palatoplasty protocols were introduced a century ago (Gillies and Fry, 1921) to circumvent the controversial debate regarding speech and midfacial growth. This two-stage approach proposed initial repair of the soft palate, thereby obturating the hard palate by several years until the delayed hard palate repair. Later, a converse protocol of initial hard palate closure with vomerine flaps with delayed soft palate closure were developed and has since increased in popularity among surgeons. Although all these protocols are practiced today in different units, there is no consensus regarding the superiority of one protocol over another. There is great variability between regions and cleft centers (Naidu et al., 2022).

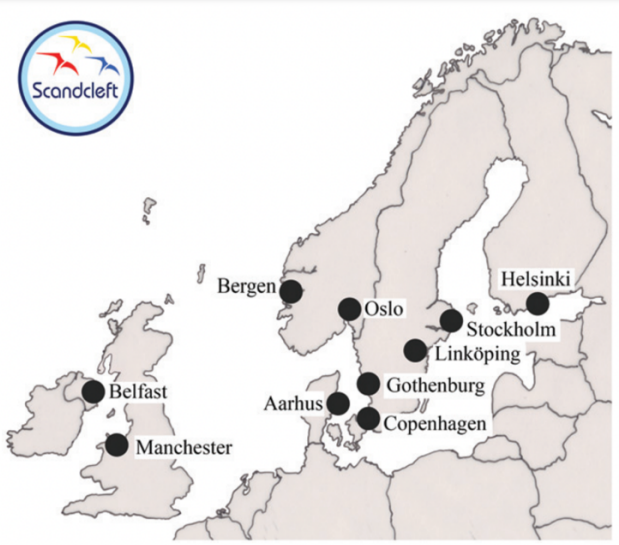

Figure 10. Cleft units participating in the Scandcleft study (Semb et al., 2017). Reproduced with the permission from the Taylor and Francis group (https://tandfonland.com).

The Cleft and Craniofacial Center, Department of Plastic surgery at Helsinki University Hospital (Husuke) also has a history of various protocols and single-stage techniques used over the past decades. The main reason behind the different protocols is explained by participation in the Scandcleft study (SC) (1997-2006) (Rautio et al., 2017). In this prospective intercenter study, four surgical protocols for treatment of children with complete UCLP were compared to assess outcomes with a focus on speech and dentofacial growth. The study was conducted by 10 North European cleft teams **(Figure 10)**, where three concurrent randomized trials compared a traditional method of the cleft center (Arm B-D) **(Figure 11)** against the common method of the trial, which was early soft palate closure and lip repair at 4 months of age and a short delay of hard palate closure at 12 months of age (Arm A). The Helsinki cleft team participated in Trial 2, where the traditional method at the time, single-stage closure at 12 months of age, was compared to the new method described above (Arm A). No surgical protocol was superior regarding speech or

dentofacial growth, although a small difference was noted. A key finding in this study was the long learning curves and adoption for a new surgical method, as the surgeons achieved the best results with a familiar technique, which questioned the importance of surgical protocols compared to the experience of the surgeon performing a familiar technique (Rautio et al., 2017).

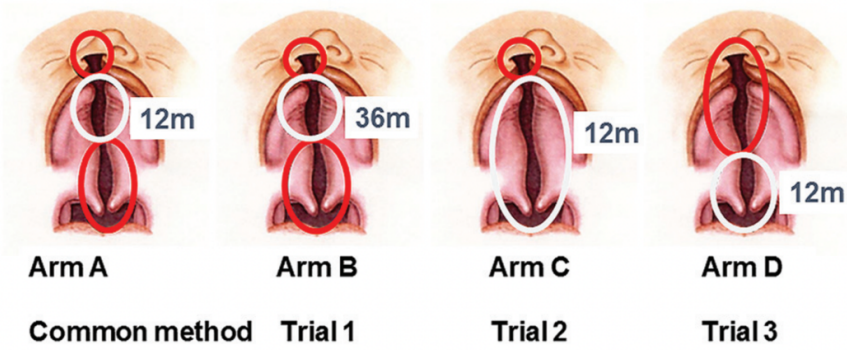

Figure 11. Scandcleft surgical protocols. Common method of the study (Arm A); lip and soft palate repair at 3-4 months of age followed by hard palate repair at 12 months of age were compared against the traditional method of the cleft units (Arm B-D) in separate trials. Arm B; lip and soft palate repair at 3-4 months of age followed by delayed hard palate repair at 36 months of age. Arm C; lip repair at 3-4 months followed by total cleft palate repair at 12 months of age. Arm D; lip and hard palate repair at 3-4 months of age followed by soft palate repair at 12 months of age. (Semb et al., 2017). Reproduced with the permission from the Taylor and Francis group (https://tandfonland.com).

Numerous surgical approaches have been described in the literature, many having both advantages and shortcomings. These techniques are continuously evolving with various modifications. In this context, this review will provide a more detailed description of the techniques and protocols that have been utilized at Husuke during the past three decades.

2.8.3.1 PRINCIPLES OF SINGLE-STAGE PALATOPLASTY

Early in the twentieth century, Victor Veau described the importance of re-approximation of the levator palatini muscle in the midline to restore the anatomic structures of the cleft muscles. This objective of preserving the anatomy by repairing the pathological-oriented muscles, also known as *intravelar veloplasty* (IVVP), was further improved by Kriens (1969) and has since been adopted in combination with several techniques to improve the velopharyngeal competence. Sommerlad (1994) introduced a modification of this technique involving radical and extensive dissection of the muscles from both the oral and nasal mucosa together with the dividing of the tensor palatini tendon and repositioning the muscle at the hamulus level. This method has resulted in good speech outcomes. Sommerlad later introduced the operating

microscope to permit precise levator muscle reconstruction with improved speech results (Sommerlad, 2003).

In 1926, Pichler introduced *vomer flaps* **(Figure 12)** as an option for hard palate repair. However, this inferior-based vomer flap as originally described was later reported to associate with high fistula rates and maxillary retrusion (Friede and Johanson, 1977; Mølsted et al., 1987). However, this was later avoided by modifying the technique with a more superior-based vomer flap, and by restricting the dissection of the flap near the cleft margin (away from the vomeropremaxillary suture), just sufficient enough to close the nasal mucosa on the opposite side (Dealaire and Precious, 1985, Leow and Lo, 2008). The foundation behind the vomer flaps is the reduced area of denuded palatal bone that results in scarring and may interfere with maxillary growth. Not only have previous reports shown improved craniofacial morphology (Brattsöm et al., 2005, Kulewicz and Dudkiewicz, 2010), but also acceptable results of hard palate morphology were observed compared with other procedures for early hard palate repair (Rochrich et al., 1996, Holland et al., 2007). However, some are concerned that the denuded surface of the vomer may result in scar tissue that may restrict maxillary growth (Friede, 1978, Delaire and Precious, 1985, Friede and Enemark, 2001, Emami A and Hashemzadeh, 2020). The well-vascularized vomerine mucoperiosteal tissue has been described as very versatile and can be used in several different ways, although they are most often used in the repair of the anterior portions of the cleft, such as the hard palate (Agrawal and Panda, 2006, Agrawal, 2009). While some adopt the flap for a single-layer closure, the flap is widely used for closure of the nasal layer to provide a two-layer closure in the hard palate region to achieve lower fistula rates (Smith and Losee, 2014).

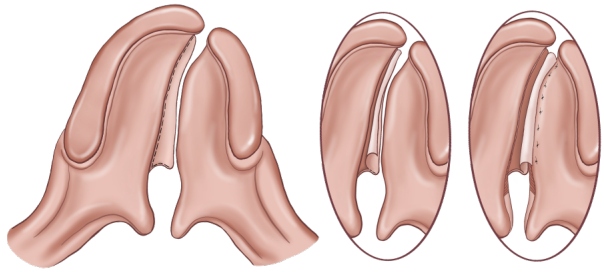

Figure 12. Illustration of the vomer flap. Copyrights to Charlotta Gustafsson-Silén.

Langenbeck's technique **(Figure 13)** is among the oldest and still widely used technique today (Naidu et al., 2022), also at Husuke. This technique was originally described in 1862 (von Langenbeck 1862) and involves the raising of two bipedicled mucoperiosteal flaps that are anteriorly attached to the alveolar margin, without lengthening the palate. The lateral release, along the alveolar margins, allows the medial advancement and midline closure of the flaps, while lateral sutures are performed if tension allows. This method was a fundamental breakthrough in cleft surgery, as prior to this, mucosal flaps were raised with high breakdown tendency. Later, a modification involving muscle dissection and reconstruction of the muscular sling with IVVP became more common to improve VPI. Although there is the advantage of closing wide clefts, the drawbacks described with this technique are the

inadequate retropositioning and lengthening of the palate, resulting in suboptimal speech outcomes.

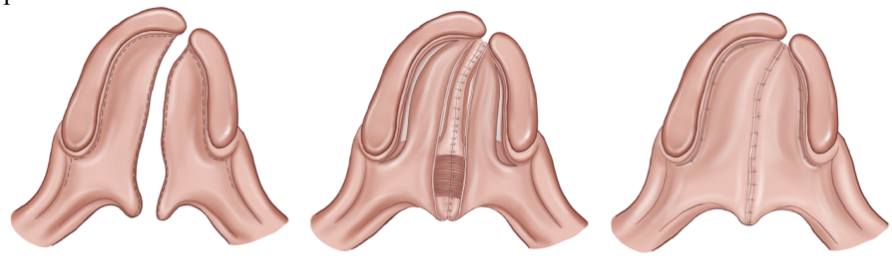

Figure 13. Langenbeck technique. Copyrights to Charlotta Gustafsson.

The *Veau-Wardill-Kilner* (V-W-K) technique **(Figure 14)**, described by Dorrance and Bransfield, 1946, was initially developed as a modification to the Langenbeck technique with the aim of increasing the retropositioning of the soft palate. In this technique, the design of the flaps resembles the Langenbeck technique. However, by raising two mucoperiosteal flaps based on the greater palatine pedicle posteriorly, particular attention was given to force the flaps of the hard palate in a V-Y retroposition ("pushback"). In addition, a horizontal back cut in the nasal lining at the border of the hard and soft palate was performed, which attempted to achieve more length to the soft palate. This maneuver enabled palatal retroposition with improved speech results, although the disadvantage with this technique is leaving extensive raw areas anteriorly and laterally along the alveolar margin that heals with secondary intention. These areas were later described to paradoxically shorten the palate by scar contractures, affecting the long-term VPI and causing alveolar arch deformity and dental malalignment. The singe-layered closure at the back-cut area was also prone for fistulas. Due to these drawbacks, the popularity of this technique was reduced (Leow and Lo, 2008).

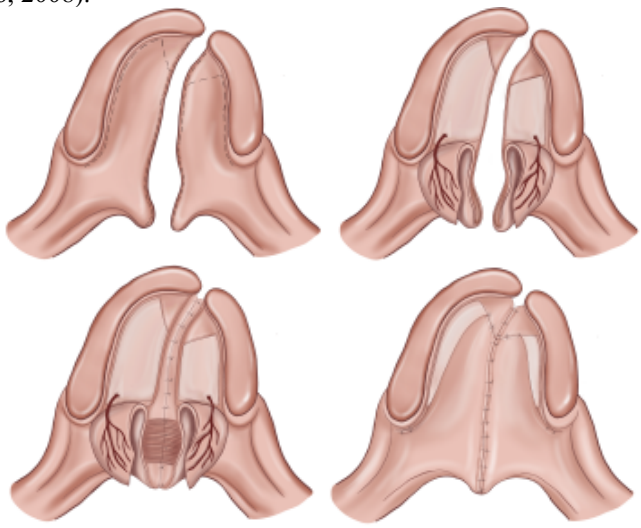

Figure 14. Veau-Wardill-Kilner (V-W-K) technique. Copyrights to Charlotta Gustafsson-Silén.

The *two-flap technique* **(Figure 15)** was originally described by the Polish surgeon Bardach in 1967 (Bardach., 1995). Initially, only narrow clefts could be repaired due to limited release of the mucoperiosteal flaps, yet some modifications involving lengthening the relaxing incision along the alveolar margins and extensive dissection enabled repair of wider clefts (Leow and Lo, 2008). This technique is similar to the V-W-K technique. However, the mucoperiosteal flaps, based on the greater palatine vessels, are returned to the donor areas and thereby avoid areas of secondary healing over exposed bone. As common in cleft repair, the retroposition of the soft palate is often inadequate and therefore attention is given particularly to the dissection and retroposition of the muscles, followed by reconstructing the muscle sling with IVVP. Some combine a Furlow double-opposing Z-palatoplasty to achieve this effect.

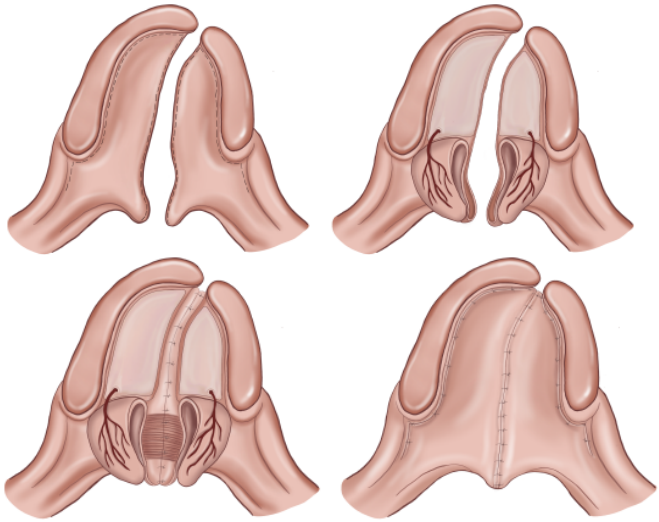

Figure 15. Two-flap technique. Bardach method. Copyrights to Charlotta Gustafsson-Silén.

In 1995, Mendoza et al. described a technique using minimal incisions (MI) **(Figure 16)**, using only incisions along the midline of the cleft in combination with IVVP, reconstructing the muscular sling. No relaxing incisions are performed. The advantage described with this technique is the decreased scar tissue in the palate, although the drawbacks include limited use in narrow clefts and inadequate retropositioning, as described with Langenbeck's procedure (Pan et al., 2014).

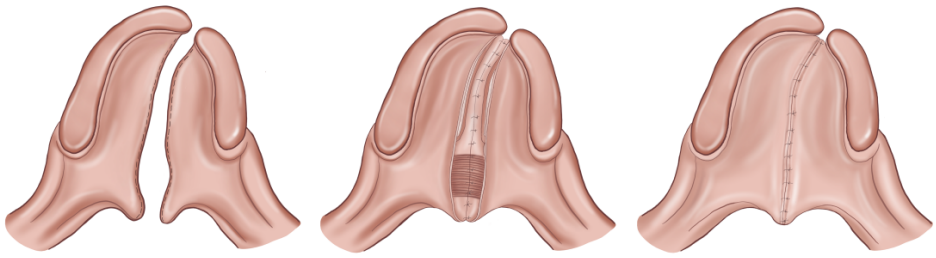

Figure 16. Minimal incision technique (MI). Copyrights to Charlotta Gustafsson-Silén.

Furlow double opposing Z-palatoplasty **(Figure 17)** was originally described by Furlow in 1986. The non-anatomical repair of the palate with this technique had the advantage of a lengthening effect of the soft palate while simultaneously repositioning the levator sling within the posteriorly mobilized flaps. Since introduced, this technique has undergone several modifications. This technique involves Z-plasty designed flaps of both the oral and nasal mucosa in combination with the velar muscle without dissecting the levator free from both the oral and nasal mucosa on both sides. When transpositioned, from the sagittal to the horizontal plane, the muscles are partly overlapped, with the flaps laying in a reversed configuration to one another, hindering the suture lines to lie on another. Although technically challenging, this technique has become more popular among surgeons, particularly for its favorable speech outcome. Accordingly, this technique is also utilized as a SCS method (VPI surgery) (Leow and Lo, 2008). While this technique is effective in repairing submucous and narrow clefts, some problems may be encountered when trying to repair wider clefts due to the lack of soft palate tissue (Losken et al., 2011). Some have tried to circumvent this tissue deficiency by incorporating tissue from the surrounding anatomy, such as buccal flaps (Mann and Fisher, 1997).

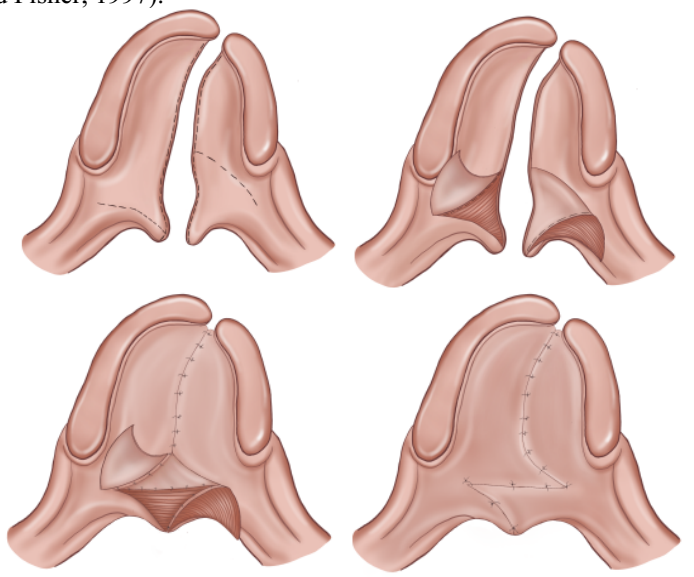

Figure 17. Furlow double opposing Z-palatoplasty technique. Copyrights to Charlotta Gustafsson-Silén.

2.8.3.2 PRINCIPLES OF TWO-STAGE PALATOPLASTY

Delayed hard palate closure. Two-staged protocols have been adopted due to the controversies surrounding potential maxillary growth disturbances and speech. Some advocate early repair of the lip and soft palate while the hard palate repair is delayed. This procedure of reconstruction of the anterior and posterior palatal arch have been described to give a molding effect by narrowing the anterior palate and facilitating the

delayed repair with a more tension-free repair without extensive mucoperiosteal elevation (Rohrich and Gosman, 2004).

This procedure was initially introduced by Gillies and Fry (1921), who proposed initial soft-palate repair, whereas the hard palate was obturated for several years until the delayed hard palate repair. This protocol rapidly gained interest especially after reporting excellent growth results of the maxillary structures. This protocol was implemented and popularized, with the age of hard palate repair ranging from 7 to 14 years at different units (Schweckendiek and Doz. 1978 [Marburg, Germany]; Hotz et al., 1978; Hotz and Gnoinski, 1979 [Zürich, Switzerland]; Friede and Enemark, 2001, Lilja et al., 2006 [Gothenburg, Sweden]). Later, after being criticized for poor speech development (Cosman and Falk, 1980; Witzel et al., 1984) due to the delayed hard palate repair, interest was lost in this protocol. However, the Gothenburg cleft team in particular has long experience with this protocol (Lohmander et al., 2017) and today still utilizes this method, although hard palate repair has been preponed with years in favor of speech development. This method also served as the "common arm A" method in the SC study (Semb et al., 2017) as modification of the original Gotenburg method (Friede et al., 1980). Here, the soft palate repair is performed in a zic-zac fashion along the border of the soft and hard palate, whereby a triangular shaped mucoperiosteal flap is raised in the medial part of the hard palate. The defect in the nasal mucosa was covered by a posteriorly based raised vomer flap. In contrast to the original method in Gothenburg, instead of the transverse incision of the nasal mucosa that allows retroposition of the muscle, IVVP with muscle mobilization along the nasal mucosa were performed in the SC study. Here, at the second stage a vomer flap was raised to close the hard palate and sutured under the mucoperiosteum of the hard palate on the cleft side (Rautio et al. 2017).

Thus, the evidence of superiority of this approach for beneficial maxillary outgrowth remains controversial (Rohrich et al., 2004, Holland et al., 2007, Kappen et al. 2017, Kappen et al. 2018).

Early hard palate closure. After introduction of vomerine flaps in 1926 (Pichler) as an option for single-layered closure of the hard palate, this method has been widely incorporated with other methods for a more secure two-layer closure. However, since the Oslo cleft team incorporated this method in a two-stage protocol involving early hard palate closure with a vomer flap with delayed soft palate closure, this method has gained popularity among surgeons in recent decades. This protocol also served as a method (Arm D) in the SC study (Semb et al., 2017), although it was not part of the Helsinki's cleft unit. Here, a vomer flap is turned and tucked under the mucoperiosteum of the cleft side of the hard palate and is fixed with mattress sutures. While the second stage of palate repair were performed without relaxing incision - if possible, as the muscle repair were performed with IVVP (Rautio et al. 2017). The early vomer flap narrows the cleft width (de Jong and Breugem, 2014), offering a more favorable condition with less tension at soft palate repair, which prevents complications such as fistulas. The impact of these methods on maxillary growth is unclear, although some have reported favorable results (Brattsöm et al., 2005, Mølsted et al., 2005, Daskalogiannakis et al., 2011, Hathaway et al., 2011) while others are

concerned (Delaire and Precious, 1985, Friede and Enemark, 2001, Emami A and Hashemzadeh, 2020, Heliövaara et al., 2021). The impact on speech outcomes divides opinions, presumably due to the reported short palates that is thought to be caused by scar contracture in the palate (Ganesh et al., 2015, Rossell-Perry, 2018).

2.8.4 SECONDARY SURGERY

2.8.4.1 SPEECH-CORRECTING SURGERY

The need for SCS (VPI surgery) to correct VPI following primary surgery of the palate varies considerably in the literature (5-56%) (Sullivan, 2009, Lithovius et al., 2014, Kappen et al., 2017, Rautio et al., 2017, Sell et al., 2017, Smyth and Wu, 2019). As the reason behind VPI is a structural deficit due to insufficient closure of the VPS during speech, the treatment goal is to narrow and obturate the VPS by surgical means while avoiding obstruction. Since 1865 (Gart and Gosain, 2014), these types of surgical interventions have been performed, initially by trying to attach the soft palate to the posterior pharyngeal wall. Numerous methods have been used over the years. Similar to primary repair, the ideal management method (Collins et al., 2012; Gart and Gosain, 2014) and the timing of the procedure are disputed. Conservative management cannot replace the necessity of SCS in the management of VPI, where SCS is recommended for children with severe or moderate VPI with insufficient improvement after speech therapy. Many factors impact the frequency of these procedures, including VPI severity, the threshold for the surgeon, concomitant syndromes or anomalies, and the child's and family's desires (Hosseinabad et al., 2015). These factors explain the wide range of incidences between centers.

Although SCS can be performed at any age, these procedures are traditionally performed before school age to avoid negative social and psychological consequences of poor speech intelligibility (Becker et al., 2004; de Buys Roessingh et al., 2008). Moreover, early diagnosis and treatment lead to more successful results, presumably due to the belief that early management yields faster resolution of mislearning and compensatory speech patterns (Riski, 2013). Therefore, the decision for VPI surgery at Husuke has been made earlier in recent years (as early as 3 years of age) if the child displays severe VPI at a young age (Pitkänen, 2022). However, although speech has usually developed enough by the age of 3 years and the child is sufficiently cooperative for speech evaluation, cooperation for instrumental assessment is often not sufficient. Accordingly, SCS at this age should only be performed if the speech assessment is reliable. Although most of the secondary SCSs are performed in childhood, a considerable number are performed at a later stage, due to growing structures (Riski, 2013) or after orthognathic surgery (Alaluusua et al., 2019).

Generally, SCS methods are either static or functional in their design. Today, the most common procedures are the pharyngeal flap **(Figure 18)**, usually superiorly located, various sphincter pharyngoplasties, and repair of the soft palate either by the Furlow double-opposing Z-plasty technique or "palate re-repair"

(Pearson and Kirschner, 2011; Collins et al., 2012; Gart and Gosain, 2014). Although not currently in widespread use, posterior wall augmentation, by means of either injectable or implantable materials, have been described (Gart and Gosein, 2014). Increased attention has been given to advances in autologous fat grafting and its potential applications (Gart and Gosein, 2014).

Pharyngeal flap methods are the traditional and currently the most used methods for management of VPI. Although variations in designs have been described (Hynes, 1950, Honig, 1967, Shprintzen et al., 1979, Jackson, 1985), the main feature is raising a superiorly based flap **(Figure 18)**, consisting of mucosa and muscle from the posterior pharyngeal wall, that is then sutured into the soft palate (de Blacam, et al., 2018). The width of the flap is individually tailored to the extent of lateral pharyngeal wall movement, thus providing a static bridge that obturates the airflow to the nasal cavity during speech. Although the method is effective for treating VPI (Sullivan et al. 2010, de Blacam, et al., 2018) it paradoxically may cause upper airway obstruction and obstructive sleep apnea (OSA), which is a serious complication and the common drawback with this method (Gart and Gosein, 2014). Therefore, alternative techniques have become popular, such as "palate re-repair" techniques that involve radical palatal muscle retropositioning that Sommerlad initially described for primary CP repair, although these principles are commonly also used in treatment for VPI (Sommerlad et al., 2003). Moreover, Furlow double-opposing Z-plasty, a technique also initially described for primary CP repair, was later shown to be a successful secondary procedure to correct VPI (Randall et al 1978). This technique has since gained popularity among surgeons particularly due to the advantages of fewer complications (in the form of respiratory obstruction) and OSA when compared with traditional pharyngeal flaps (Liao et al., 2004, Abdel-Aziz et al., 2018).

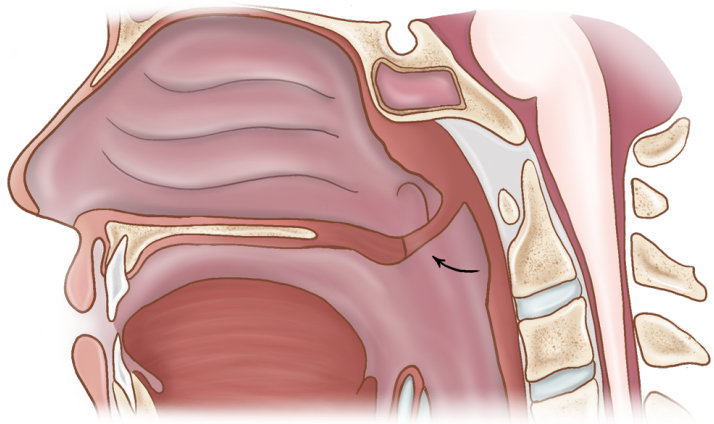

Figure 18. Superiorly based pharyngeal flap. Copyrights to Charlotta Gustafsson-Silén.

Tailored approaches are common (Gart and Gosein, 2014, Nam, 2018), where the technique is chosen according to the velopharyngeal closing pattern as observed by videofluoroscopy and nasopharyngoscopy, or perhaps even by dynamic MRI. The Furlow Z-plasty method has been particularly successful in correction of

marginal to moderate VPI (Chen et al., 1994, Hudson et al., 1995, Dailey et al., 2006), and many recommend this method if the velopharyngeal gap is small (<9 mm) (Gart and Gosein, 2014, Reddy et al., 2016, Chim et al., 2015). Larger gaps are usually corrected by pharyngeal flaps. In the past 20 years at the Cleft and Craniofacial Center, Department of Plastic surgery at Helsinki University Hospital (Husuke), a staged approach that usually uses Furlow double-opposing Z-plasty as the primary SCS procedure, regardless of the VPI severity or the velopharyngeal gap size, has been chosen. At Husuke, this method is a good treatment option for correction of even severe VPI (Ahti et al. 2020, Ahti et al. 2021). This method is considered to be more suitable than pharyngeal flaps concerning postsurgical recovery and has less tendency for airway obstruction, particularly in small children.

2.8.4.2 FISTULA REPAIR

Surgery for palatal fistula following palatal primary repair depends on size, location, and symptomatology. Therefore, management is based on a multidisciplinary approach that involves proper assessment of both speech and the dental arch and condition of local tissues. In particular, the functional and symptomatic aspects should be given appropriate attention prior to the repair decision, as not every visible fistula requires surgical repair. Moreover, the appropriate timing for fistula repair depends on symptom severity. Fistulas that impact speech or cause significant regurgitation of food or fluids into the nose often require earlier repair, whereas fistulas that cause occasional regurgitation of fluid or food can be delayed and repaired in combination with other procedures (Murthy, 2011).

These palatal fistulas are a surgical challenge due to inevitable scarring, altered vascularity, and persistent tension in the corrected palate, which explains why the recurrence rate is often high after fistula repair (Diah et al., 2007, Landheer et al., 2010). When deciding on repair technique, it is essential to consider the condition of the local tissues. Scarring from previous surgical procedures, inflammation, oral hygiene, or concomitant planned procedures may impact the type of procedure that is feasible (Murthy, 2011). While various methods for fistula repair have been proposed (Othieno and Tatum, 2021), the conventional management for a palatal fistula comprises a two-layer closure of the nasal and oral mucosa (Nicole et al., 2019) by mobilizing the mucosal layers and occasionally applying turnover flaps or relaxing incisions. Multilayer closure, vital for fistula repair, is challenging to perform due to the paucity of local tissue. Therefore, some have addressed this problem by utilizing the buccal fatpad for additional tissue; this method has recently gained popularity in both primary and secondary palate repairs (Saralaya et al., 2020). Other described methods are cancellus bone grafts (Parwal et al. 2017) or acellular or synthetic collagen matrix. On the other hand, larger defects may require repair by local or distant tissue flaps, such as buccal musculomucosal flaps, which have recently attracted interest particularly in VPI surgery (Mann et al., 2011) and in fistula repair (Ashtiani et al., 2005). Fortunately, these large, complicated defects are rather rare. If surgery is avoided, a prosthetic occluding appliance can be applied to cover the fistula. However, oral hygiene and dental health issues are common (Murthy, 2011).

2.8.4.3 ALVEOLAR BONE GRAFT

Total CLP that transverses the alveolar ridge produces separate palatal segments. The repair of this alveolar defect with bone graft is important, not only to stabilize the dental maxillary arch, facilitate eruption of canines, and support the teeth adjacent to the cleft (Desai et al., 2021). But also, to improve oral hygiene, facial morphology, and speech-related problems (as articulation errors) through elimination of an anterior oronasal fistula (Lilja, 2009). In addition to the functional aspects, ABG also provides aesthetic benefits. Since the 1950s and 1960s, primary bone grafting during the early months of life has fallen out of favor due to concerns regarding midface growth disturbances (Lilja, 2009). Today, secondary bone grafting performed during the period of mixed dentition (between 9 to 12 years of age in Finland) and ideally prior to eruption of the permanent canines is advocated at most institutions (Murthy and Lehman, 2005, Weissler et al., 2016). Presurgical orthodontics are almost always performed. In bilateral clefts, the bone graft is performed either in a one-stage or two-stage procedure, depending on the anatomy of the patient. There are several different donor sites. Iliac crest, particularly with minimally invasive harvest, is one of the most popular alveolar bone graft sources, providing cancellous bone, although some concerns on morbidity exist (Weissler et al., 2016). Sometimes the procedure is performed together with a resorbable collagen membrane to prevent fibrous and epithelial ingrowth (Aly and Hammouda, 2016).

3 AIMS OF THE STUDY

This thesis and study series is focused on the following aims:

I. To determine the long-term secondary surgical burden of care in terms of speech-correcting surgeries (SCS) and fistula repair in patients with non-syndromic OFC treated in Finland.

II. To assess the impact of Robin sequences on the long-term secondary surgical burden of care and to assess potential implicating factors.

III. To assess the cleft type and impact of severity on the need for SCS and fistula repair and the repaired fistula's location in the palate.

IV. To compare the long-term outcomes of different surgical treatment protocols utilized in UCLP and BCLP and the different single-stage techniques used over the past decades at the Cleft and Craniofacial Center, Department of Plastic surgery, Helsinki University Hospital.

4 MATERIALS AND METHODS

4.1 PATIENTS

Each study of this thesis was a retrospective single-center follow-up study. All patients included were treated at the Cleft and Craniofacial Center, Department of Plastic surgery at Helsinki University Hospital, Finland and born between 1990 and 2011. Data were retrospectively collected and originated from electronic patient records and medical charts in the hospital's archive. The study protocol was approved by the Helsinki University Hospital and principles outlined in the Declaration of Helsinki were followed.

The subjects were followed regularly as a part of the standard treatment protocol of the cleft center by a multidisciplinary cleft team consisting of a plastic/maxillofacial surgeon, ENT specialist, a speech pathologist, a phoniatrist, an orthodontist, and specialist nurses.

Due to the high variation in anatomy and degree of cleft severity and the various surgical protocols, each study assessed a particular anatomical cleft type that was divided according to the Veau classification system, the International Classification of Diseases (ICD 10) system, or both; Q35 was cleft palate (Q35.3 SCP and Q35.5 HSCP) and Q37 was cleft lip and palate (Q37.4 BCLP and Q37.5 UCLP). Only non-syndromic patients were included in the study. Patients with incomplete cleft or other comorbidities, such as other craniofacial anomalies in the head or neck region, were excluded.

4.2 HUSUKE'S HISTORY OF PRIMARY SURGERY PROTOCOLS AND TECHNIQUES

The Cleft and Craniofacial Center, Department of Plastic surgery at Helsinki University Hospital (Husuke) has a history of various protocols and techniques for primary surgery. As previously described in section 2.83, participation in the SC study (1997-2006) (Semb et al., 2017) had a major impact on the variations in surgical protocols. The surgical protocols and techniques utilized at Husuke are described in more detail in section 2.8. The timing of the surgical protocols is shown in **Figure 19**.

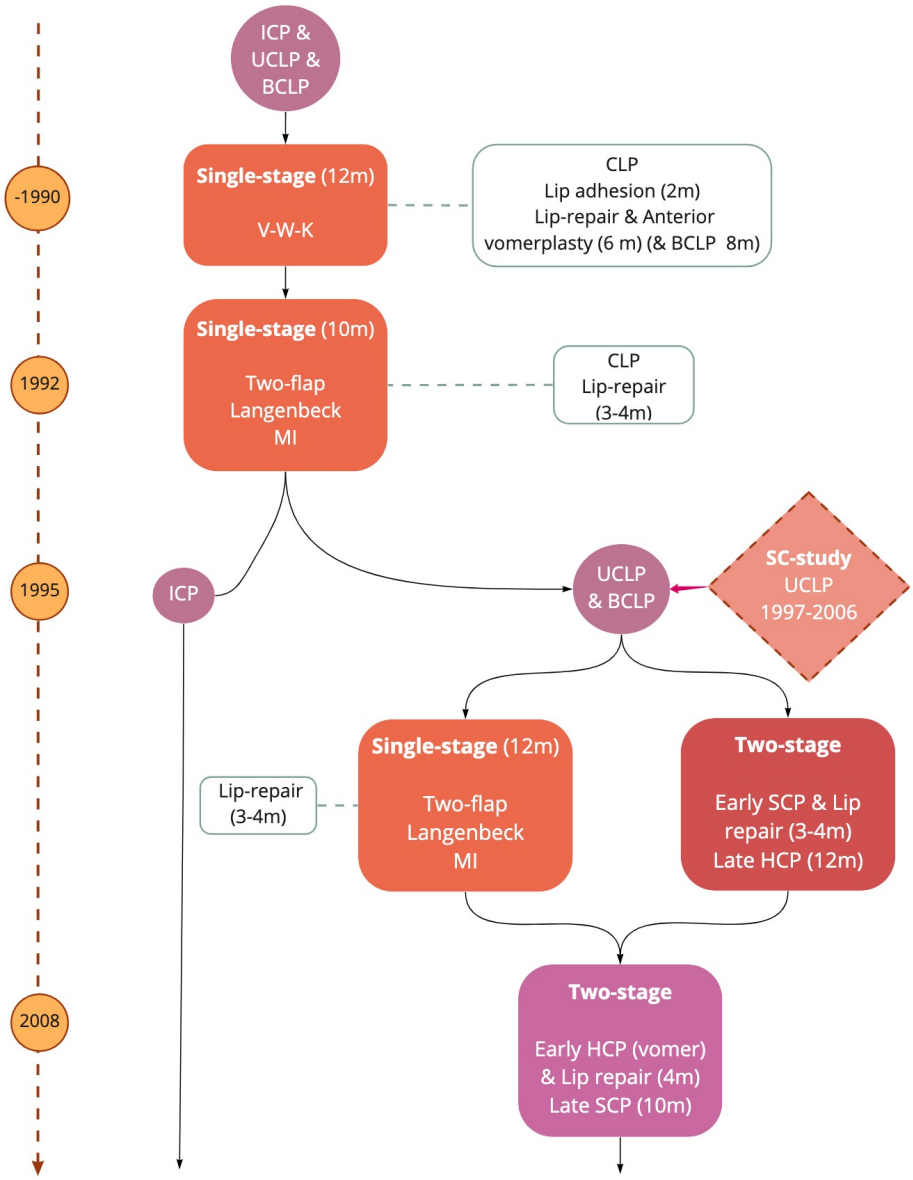

Figure 19. Primary surgery protocols at the Cleft and Craniofacial Center, Department of Plastic surgery at Helsinki University Hospital (Husuke) since the 1990s. ICP, isolated cleft palate; UCLP, unilateral cleft lip and palate; BCLP, bilateral cleft lip and palate; HCP, hard cleft palate; SCP, soft cleft palate; CLP, cleft lip and palate (UCLP & BCLP); m, months, SC-study, Scandcleft study (Semb et al., 2017).

The surgical protocol for ICP has remained as a single-staged procedure throughout the years. The surgical procedure for CLP has changed, although the same principles in both UCLP and BCLP were followed with a few exceptions. Initially, lip

repair was staged without presurgical orthopedics, with lip adhesion at 2 months of age followed by lip repair according to Millard's (1970) method in combination with anterior vomerplasty and nose repair at 6 months (in separate operations in BCLP at 6 and 8 months of age). Here, nose repair involved limited mobilization of the alar cartilage with the aim of fixing them with bolster sutures that were removed a few days later. Along with the aforementioned protocol for nasolabial repair for patients with CLP, cleft repair for all CP patients was performed by a single-stage procedure at the age of 12 months according to the V-W-K technique (Dorrance and Bransfield, 1946), which has been the standard technique since the 1940s.

Since 1992, primary lip repair was performed in combination with nasal repair at the age of 3-4 months. Lip adhesion and anterior vomerplasty were no longer performed, as the adhesion caused excessive scarring and was therefore considered unnecessary, and the anterior hard palate was often so narrow that closure with a vomer flap at the second lip repair was not feasible. As lip repair for UCLP continued to follow the unilateral lip repair principles described by Millard (1970), the bilateral repair was further changed to a single-stage bilateral "straight-line" repair. The method was a modified technique described by Garcia-Velasco and Nahás (1988), where the muscle was sutured in the midline (tension was occasionally unavoidable) by intentionally discarding the prolabium vermilion, while the lateral mucosal flaps served as the new reconstructed vermilion. Whereas the primary nose repair in UCLP has remained alongside lip repair via McComb-"like" (1975) principles, nose repair in BCLP was performed by releasing the alar cartilage, which attempts to achieve more length to the columella and rotating the cartilage medially and anteriorly into a more anatomical position while fixing them with buried resorbable mattress sutures. Simultaneously, due to the commonly reported drawbacks and concerns of the V-W-K technique, the common palate repair protocol was further changed to a similar two-flap technique described by Bardach (1995) in combination with a vomer flap. This creates a double-layer closure in region of the hard palate, which is important for fistula prevention. Soft palate muscles were re-organized by the principles described by Sommerlad (1994). Timing of palate repair was changed to the age of 10-12 months. However, the minimal incision technique (MI) (Mendoza et al., 1994) was applied for less extensive clefts, and lateral relaxing incisions were applied when required if tension occurred (Langenbeck, 1861). These both techniques (MI and Langenbeck) in combination with a vomer flap to close the nasal layer of the hard palate and Sommerlad's IVVP for velar lengthening were used.

The two-stage repair protocol, where lip and soft palate repair occurred at 4 months and delayed hard palate closure at 12 months, was introduced at Husuke slightly before the recruitment of patients into the SC study (1997-2006) (Semb et al., 2017). Although the protocol was initially employed in the UCLP population according to the SC study, the two-stage approach was also partly employed in the BCLP population, although the nasolabial repair followed the principles described above. However, although part of the UCLP and BCLP population received repair by the previously described protocol, the single-stage protocol was still used at the center at 12 months of age, as in the isolated cleft population (ICP).

Another two-stage protocol was introduced at Husuke after the SC study **(Figure 19)**. This consisted of early vomer flap of the hard palate in combination with lip repair at 4 months followed by short delayed soft palate closure 6 months later. Although labial repair for UCLP has for decades followed Millard's (Millard 1970) principles, Fisher's (Fisher 2005) technique is also currently used. Moreover, the naso-labial repair for BCLP is nowadays repaired via a modified technique of Mulliken's method (1958). This protocol has since remained the standard protocol at the cleft unit for both UCLP and BCLP, although soft palate repair has been performed using Furlow's double opposing Z-palatoplasty technique in recent years. Prior to the recent implementation of the Furlow method in CP repair, this technique was utilized in submucous cleft repair for years at Husuke.

The surgeries were mainly performed by plastic surgeons with special training and several years of experience in cleft surgery.

4.3 SPEECH ASSESSMENT AND SPEECH-CORRECTING SURGERY

All subjects were followed according to the standard treatment protocol at the cleft center. These follow-up visits occurred at 3, 5 to 6, 8, and 10 years and up to the age of 18 years or beyond, if necessary. However, children with ICP who were born in the early 1990s had a shorter follow-up time of 10 years, as was the practice at that time. Speech assessment was evaluated with both perceptual and instrumental (nasometer, videofluoroscopy, and sometimes nasopharyngoscopy) techniques and was performed by an experienced speech pathologist. Some small differences in speech assessment have occurred over the years. The following cleft speech characteristics related to VPI were routinely evaluated: hypernasality, audible nasal air leakage, weakness in pressure consonants (/p/, /t/, /k/, /s/), oral stops, and compensatory articulation. Nasometry assessment for detection of hypernasality was used in children >5 years of age if cooperation was sufficient. In contrast to nasometry, videofluoroscopy and nasopharyngoscopy was not routinely performed during speech assessment. However, these were performed if needed during planning of SCS.

A 5-point (0 to 4) numeric scale has been adopted at Husuke to rate the degree of VPI symptoms. A scale value ≥2 was considered a symptom of VPI.

(0) **Normal velopharyngeal competence.**

(1) **Mild and occasional VPI. Borderline competent VPF.**
Nasal emissions only temporarily detected. Overall speech sound was nearly normal and pressure consonants were not affected. No further speech correction treatment was required.

(2) **Mild and consistent VPI.**
Mild nasal emissions and speech nasality were present at all times. However, pressure consonants were not affected.

(3) **Moderate and consistent VPI.**

Speech featured moderate nasality at all times in combination with weakness in pressure consonants.

(4) Severe and consistent VPI.
Severe nasal emission with highly nasal speech. The pressure consonants were either weak or replaced by glottal stops.

SCS (VPI surgery) was recommended for children with moderate-to-severe VPI or who presented insufficient improvement after speech therapy. However, the final decision was made by the surgeon, child, and the family. Both primary surgery techniques and surgical techniques utilized for SCS have changed over time. Velopharyngeal flaps were for years the standard technique for SCS. However, since 2005 a staged approach has been utilized at Husuke. Furlow double-opposing Z-plasty is the primary SCS of choice. In case of insufficient improvement of velopharyngeal function, a secondary SCS procedure may be performed, either by re-Furlow palatoplasty or by using the superiorly based pharyngeal flap. However, it is important to emphasize that several SCS options are available and individualized treatment planning is essential (section 2.841, speech-correcting surgery).

4.4 FISTULA DEFINITION AND REPAIR

The subject's medical and operative records were retrospectively reviewed, and the location of the palatal fistula was recorded and localized accordingly. In each study, a palatal fistula was considered an unintended defect in the palate that resulted from improper healing. Due to the general lack of consistent methodologies and reporting standards for fistulas and the limitations of the retrospective nature of the studies, only fistulas that required surgical closure were included. However, postsurgical fistulas after the primary palatoplasty were included in study III, where patients with Robin sequence were investigated. Surgical repair was recommended for symptomatic fistulas that affected speech or caused nasal regurgitation of food and liquids. Fistula repair was mainly performed by suturing the oral and nasal mucosa in separate layers. Lateral incisions were applied if tension occurred. Fistulas were occasionally repaired by local flaps, re-palatoplasty, or in combination with collagen membrane for additional support.

In the studies that included patients with clefts of the palate (ICP, study I and RS, study II), the fistula location was classified as follows: HCP (1), the junction of hard and soft palate (2), and SCP (3). However, for total UCLP (study III) and BCLP (study IV), fistula were localized according to the Pittsburgh classification system (Smith et al., 2007) **(Figure 20)**. If several defects were identified in the palate,

they were counted as separate fistulas; hence, if they crossed several positions in the palate they were only counted as one fistula according to the most anterior location.

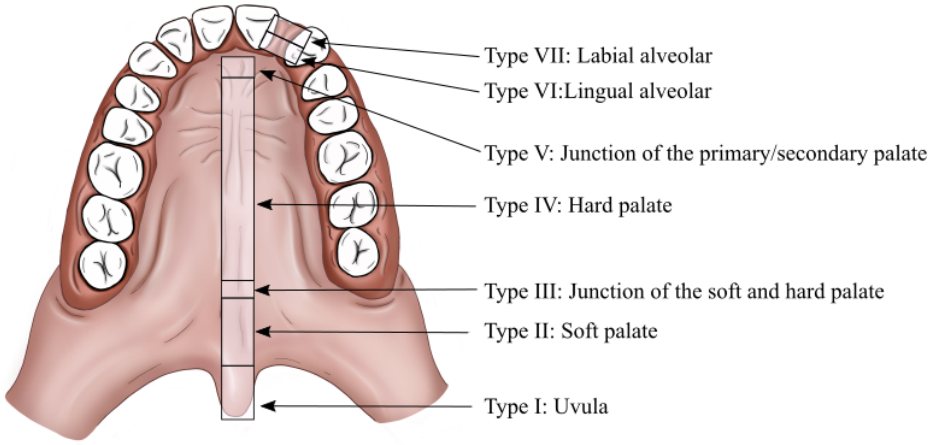

Figure 20. "Pittsburgh fistula classification system" by Gustafsson et al. (2021) is licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Colored and edited by Charlotta Gustafsson-Silén.

4.5 DESCRIPTION OF THE STUDIES

4.5.1 STUDY I. LONG-TERM OUTCOMES OF SECONDARY SURGERY RATES AND COMPARISONS OF SURGICAL TECHNIQUES IN ISOLATED CLEFT PALATE

In this study, the long-term outcomes regarding SS rates for both fistula repair and SCS were assessed in patients with isolated cleft palates. The subjects were born between 1990-2000 and the severity of the cleft was further divided according to extent in the palate as total clefts of the hard and soft palate (HSCP) and soft palate clefts alone (SCP). In addition, influence of factors such as cleft severity and primary technique were assessed. Syndromic clefts, except VWS, were excluded as well as incomplete clefts as submucous clefts. Patients with less than 8 years of follow-up were excluded.

4.5.2 STUDY II. LONG-TERM FOLLOW-UP OF RS: INCIDENCE OF FISTULA FORMATION AND SECONDARY SURGERIES AND ASSESSMENT OF CAUSAL FACTORS.

In this study, the aim was to assess the incidence for fistula formation and need for SS in terms of fistula repair and SCS in a population diagnosed with RS. In addition, possible causal factors such as gender, surgeon, age at primary palatoplasty, surgical technique, degree of airway obstruction in infancy, and cleft severity were assessed. Outcomes were evaluated at 8 years of age and at data retrieval.

The patients were born between 1990 and 2009. Each RS diagnosis was set by the cleft team, a geneticist, or both to identify syndromic children. The RS diagnosis was made for patients who presented with micrognathia, U-shaped cleft, respiratory obstruction during infancy, and glossoptosis. Follow up and speech evaluation were performed as previously described. Postoperative fistulas and their location were visually diagnosed by the surgeons. Symptomatic fistulas were surgically repaired.

Cleft severity was assessed in terms of cleft extent and width. The cleft extent was categorized according to Jensen et al. (1988) as follows: cleft of only the soft palate (1), cleft extending to 1/3 of the hard palate or less (2), cleft extending to over 1/3 of the hard palate into the subtotal palate (3), and total cleft, extending to the foramen incisivum (4). Cleft width was categorized as follows: ≤9 mm (1), 10 to 12 mm (2), and ≥13 mm (3), where the border of the soft and hard palate served as the measurement point. Management of airway obstruction was applied as a severity measurement for the degree of obstruction at infancy and was further categorized as follows: bottle feeding combined with prone positioning due to mild obstruction (1), nasogastric feeding due to obstruction difficulties during feeding (2), and severe respiratory difficulties requiring noninvasive mechanical ventilation or even invasive support in the form of nasopharyngeal tubes, endotracheal intubation, or tracheostomy (3). All subjects received single-stage primary palatoplasty by the previously described surgical techniques according to the cleft center's protocols for ICP. The timing of primary palatoplasty was divided as follows: ≤9 months (1), 10 to 12 months (2), and ≥13 months (3).

4.5.3 STUDY III AND IV. LONG-TERM OUTCOMES OF SECONDARY SURGERY RATES AND COMPARISON OF SURGICAL PROTOCOLS IN UCLP AND BCLP.

Consistent with the general aim of this study series, the objectives of the respective studies were to determine the incidence of SCS and repair rates for postalveolar fistulas in UCLP and BCLP from a long-term perspective. Additionally, the different study protocols utilized over the years were compared. The studies were divided into separate articles due to the high variation in anatomy and degree of cleft severity between UCLP and BCLP. Subjects were born between 1990 and 2011 in the UCLP study and between 1990 and 2010 in the BCLP study. Subjects were followed and evaluated for speech and fistulas as previously described. The outcomes were analyzed at Husuke at the time of secondary ABG between 9 and 11 years of age, before eruption of the upper canines. This procedure is usually performed with cancellous bone graft from the iliac crest. Moreover, the outcomes were also analyzed at data retrieval to obtain a broader long-term perspective.

The surgical protocols for primary cleft repair followed the either single-stage or two-stage approach as previously described. Repaired fistulas were localized according to the Pittsburgh classification system (Smith et al., 2007) **(Figure 20),** where only postalveolar fistulas were included (Pittsburgh I-V) as unintended defects in the palate.

4.6 STATISTICAL ANALYSIS

Statistical analyses were performed with SPSS Statistics for Macintosh, version 21.0-25.0 (IBM Corp, Armonk, NY, USA). Categorical comparisons were performed with χ^2 and Fisher's exact test. Results are mainly presented as proportions (%). Comparison of continuous data and nonparametric values was performed with Mann-Whitney *U* and Kruskal-Wallis tests, as variables were mainly skewed due to small groups. The results are presented as medians with interquartile ranges (IQR). Throughout the study, differences were considered significant when $P < .05$.

5 RESULTS

5.1 PATIENT DEMOGRAPHIC CHARACTERISTICS (STUDIES I–IV)

Table 1. Patient characteristics (Studies I-II).

	ICP (Study I)			**RS** (Study II)
	SCP	**HSCP**	*P*	
No. of patients	123	300		78
No. of excluded patients	74	189		25
Gender (male)	49 (39.8)	108 (36.0)	.458	44 (74.6%)
Birth weight, grams	N/A	N/A		N/A
Gestational age, weeks	N/A	N/A		39 (30.0-42.0)
Age at first palatoplasty, months	9.4 (8.8-11.5)	9.5 (9.0-11.1)	.303	10.0 (6.0-16.0)
Age at SCS, years	5.2 (4.4-8.5)	6.4 (4.5-8.6)	.499	6.00 (4.7-7.8)
Age at first fisula repair, years	3.7	3.2 (1.9-5.5)		4.6 (3.4-12.7)
Total follow-up time, years	13.0 (10.0-16.0)	14.0 (10.0-16.0)	.211	14.0 (8.0-27.0)

Categorical data presented as n (%), continuous data as median (interquartile range, IQR). HSCP, hard and soft cleft palate; ICP, isolated cleft palate; N/A, not applicable; RS, Robin sequence; SCP, soft cleft palate.

Table 2. Patient characteristics (studies III-IV).

	UCLP (Study III)				**BCLP** (Study IV)		
	Single-stage	**Delayed HCP repair**	**Early HCP repair**	*P*	**Single-stage**	**Delayed HCP repair**	*P*
No. of patients	186	63	41		59	22	
Gender (male)	105 (56.8)	40 (63.5)	26 (63.4)	.538	44 (74.6%)	17 (77.3%)	.804
Cleft side (left)	107 (57.5)	41 (65.1)	26 (63.4)	.509	N/A	N/A	
Birth weight, grams	3480 (3102.5-3995.0)	3625 (3315.0-3995.0)	3570 (3147.5-3977.5)	.160	3460 (2840.0-3935.0)	3935 (2945.0-3750.0)	.889
Gestational age, weeks	40 (39.0-40.3)	40 (39.0-41.0)	40 (39.0-41.0)	.208	39 (38.5-40.5)	39 (38.0-40.0)	.642
Age at lip repair, months	3.9 (3.4-4.7)	3.9 (3.7-4.2)	4.0 (3.6–4.3)	.821	4.1 (3.4-5.2)	4.1 (3.6-4.6)	.975
Age at first palatoplasty, months	10.9 (9.6-12.2)	3.9 (3.7-4.2)	4.0 (3.6–4.3)	**<.001**	10.6 (9.0-11.9)	4.1 (3.7-5.5)	**<.001**
Age at second palatoplasty, months	N/A	12.1 (11.6-12.6)	10.1 (9.3-11.4)	**<.001**	N/A	19.1 (15.5-25.9)	
Age at ABG, years	9.6 (9.1-10.4)	9.9 (9.5-10.5)	10.1 (9.6-10.8)	**.008**	9.9 (9.4-10.8)	9.9 (9.2-10.6)	.441
Post ABG, total follow-up time, years	17.4 (13.1-20.4)	17.0 (14.3-18.4)	10.5 (10.0-11.6)	**<.001**	18.0 (15.0-21.4)	16.6 (13.2-19.1)	.470

Categorical data presented as n (%), continuous data as median (interquartile range, IQR). ABG, alveolar bone graft; HCP, hard cleft palate; N/A, not applicable; Post ABG, total follow-up time at data collection.

5.2 STUDY I

A total of 423 patients (266 females, 62.3%) were included in the study after excluding 263 patients. Three hundred patients (70.9%) had HSCP and the remainder (n = 123, 29.1%) had SCP. Four experienced cleft surgeons performed 90% of the primary repairs. Patient characteristics are presented in **Table 1**.

5.2.1 SECONDARY SURGERY

The overall incidence of SCS in the study population was 33.3% (n = 141). Of these, 19.9% (n = 28) had re-SCS performed; the incidence in HSCP was 37.3% (n = 112) and in SCP 23.6% (n = 29). This difference between cleft severity was statistically significant (χ^2 = 7.428, *P* = .006, df = 1). The first SCS method utilized was either Furlow's Z-palatoplasty (45.4%) or pharyngeal flap (51.5%).

There were correspondingly statistically higher fistula repair rates in HSCP (10.7%, n = 32) than SCP (0.8%, n = 1) (χ^2 = 11.776, *P* = .001, df = 1). Of the 33 patients that required fistula repair, a quarter developed a recurrent fistula (n = 8, 24.2%) and a fifth required fistula re-repair (n = 6, 18.2%). Almost 1 in 5 patients (n = 28, 19.9%) that received SCS also required fistula repair, either in a single procedure (n = 10) or in combination with SCS (n = 18). Secondary surgeries are presented in **Table 3**.

While most fistula repairs occurred in the hard palate (n = 18, 54.5%), there was no significant difference between location of the repaired fistulas or fistula re-repair (**Table 4**).

Table 3 Rates of Speech-Correcting Surgeries and Fistula Repair After Primary Palatoplasty in ICP (SCP and HSCP).

	No. of patients (%)	SCS		Fistula repair	
		Tot. Follow-up	*P*	Tot. Follow-up	*P*
ICP	423	141 (33.3)		8 (10.3)	
Gender		.	.569		0.399
Male	266	55 (35.0)		10 (6.4)	
Female	157	86 (32.3)		23 (8.6)	
SCP	123	29 (23.6)	**.006**[a]	1 (0.8)	**.001**[a]
Technique			.306		1.00
Two-flap	25	7 (28.0)		0 (0.0)	
Langebeck	5	2 (40.0)		0 (0.0)	
MI	68	18 (26.5)		1 (1.5)	
V-W-K	22	2 (9.1)		0 (0.0)	
HSCP	300	112 (37.3)		32 (10.7)	
Technique			.363		<.**001**
Two-flap	138	53 (38.4)		12 (8.7)	
Langebeck	32	12(37.5)		2 (6.3)	
MI	82	25(30.5)		4 (4.9)	
V-W-K	48	22 (45.9)		14 (29.2)	

Categorical data presented as n (%), continuous data as median (interquartile range, IQR). ISCP, isolated cleft palate; SCP, soft cleft palate hard cleft palate; HSCP, hard and soft palate; SCS, speech-correcting surgery; MI, minimal incision technique, V-W-K, Veau-Wardill-Kilner technique.

[a] Comparison between HSCP and SCP.

5.2.2 COMPARISONS BETWEEN SURCICAL TECHNIQUE

For all subjects that had primary palatoplasty in a single-stage procedure, Bardach's 2-flap technique (n = 163) and Mendoza's minimal incision technique (MI) (n = 150) were the most common surgical procedures. More specifically, MI was the most common procedure in SCP (55.3%), while the two-flap technique was commonly required in HSCP (46.0%). No differences were observed between the techniques (χ^2 = 2.703, *P* = .440, df = 3) regarding the long-term need for SCS. However, for fistula repair rates, the V-W-K technique had the most frequent need for repair 20.0% (χ^2 = 18.859, *P* = <.001, df = 3) in ICP **(Table 3)**; particularly in HSCP.

Table 4 Fistula location in ICP and RS.

Location	ICP	RS	
	Fistula repair	Identified fistula	Fistula repair
Hard palate	18 (54.5)	6 (31.6)	3 (37.5)
H/S palate	6 (18.2)	9 (47.4)	1 (11.1)
Soft palate	9 (27.3)	4 (21.1)	4 (50.0)

Categorical data presented as n (%). ICP, isolated cleft palate; RS, Robin sequence; H/S, the border of the hard and soft palate.

5.3 STUDY II

Of the initial 103 patients diagnosed with RS, 78 met the inclusion criteria. All subjects had undergone single-staged palatoplasty. Patient characteristics are shown in **Table 1**.

Most patients had clefts encompassing >1/3 of the hard palate extending into the subtotal cleft (50.0%, n = 48). No cleft limited to the soft palate alone was identified. Correspondingly, most patients (51.9%, n = 27) had a cleft width of 10-12 mm at the border of the soft and hard palate. An association was found of increasing cleft width with increasing age at primary repair (P = .025).

5.3.1 SECONDARY SURGERY

The incidence for SCS was 43.6% (n = 34) at 8 years of follow-up, which was the shortest follow-up criterium according to earlier practice in the 1990s. However, the overall incidence was 47.4% (n = 37) (**Table 5**). The median age at first SCS was 6 years, and 13.9% (n = 5) required re-SCS during the overall follow-up.

A total of 24.4% (n = 19) developed a postsurgical fistula. By 8 years of age, fistula repair was performed in 7.7% (n = 6) and in 10.3% (n = 8) by total follow-up.

Although postoperative fistulas commonly occurred at the border of the hard and soft palate (47.4%), fistulas located in the hard or soft palate more often required SCS and fistula repair. However, this finding was not statistically significant.

5.3.2 IMPLICATING FACTORS

When possible impacting factors for SS rates were assessed, no significant association was observed for gender, surgeon, age at primary palatoplasty, surgical technique, cleft severity (extent and width), or degree of airway obstruction in infancy regarding incidence of SCS, fistulas, or repaired fistulas. A significant difference between surgeon and fistula repair rate by the total follow-up was observed (P = .029) **(Table 5).**

Table 5 Incidence of Speech-Correcting Surgeries, Fistulas, and Operated Fistulas in RS.

	No. of patients (%)	SCS			Fistula		Fistula repair		
		8 years	*P*	Tot. Follow-up	*P*		8 years	*P*	Tot. Follow-up	*P*
RS	78	34 (43.6)		37 (47.4)		19 (24.4)	6 (7.7)		8 (10.3)	
Gender			.971		.720	.868		1.00[c]		1.00[c]
Male	30	13 (43.3)		15 (50.0)		7 (23.3)	2 (6.7)		3 (10.0)	
Female	48	21 (43.8)		22 (45.8)		12 (25.0)	4 (8.3)		5 (10.4)	
Cleft extent			.341		.282	.593[c]		.848[c]		.563[c]
≤1/3	10	3 (30.0)		3 (30.0)		1 (10.0)	0 (0.0)		0 (0.0)	
>1/3-subt.	48	24 (50.0)		26 (54.2)		12 (25.0)	4 (8.3)		5 (10.4)	
Total	20	7 (35.0)		8 (40.0)		6 (30.0)	2 (10.0)		3 (15.0)	
Cleft width[a]			.446		.802	.248[c]		.277[c]		.277[c]
≤ 9mm	19	7 (36.8)		8 (42.1)		3 (15.8)	2 (10.5)		2 (10.5)	
10-12mm	27	14 (51.9)		14 (51.9)		5 (18.5)	1 (3.7)		1 (3.7)	
≥ 13mm	12	4 (33.3)		7 (50.0)		5 (41.7)	2 (16.7)		2 (16.7)	
Age at palatoplasty[b]			.437		.264	.719[c]		.634[c]		.537[c]
≤ 9	35	17 (48.6)		19 (54.3)		7 (20.0)	4 (11.4)		4 (11.4)	
10-12	29	13 (44.8)		14 (48.3)		8 (27.6)	2 (6.9)		4 (13.8)	
≥ 13	14	4 (28.6)		4 (28.6)		4 (28.6)	0 (0.0)		0 (0.0)	
Technique			.856[c]		.916[c]	.586[c]		.289[c]		.110[c]
Two-flap	45	20 (44.4)		22 (48.9)		13 (28.9)	6 (13.3)		8 (17.8)	
Langebeck	21	8 (38.1)		9 (42.9)		4 (19.0)	0 (0.0)		0 (0.0)	
MI	9	4 (44.4)		4 (44.4)		1 (11.1)	0 (0.0)		0 (0.0)	
V-W-K	3	2 (66.7)		2 (66.7)		1 (33.3)	0 (0.0)		0 (0.0)	
Surgeon			.463		.284	.716[c]		.087[c]		**.029[c]**
A	31	11 (35.5)		12 (38.7)		6 (19.4)	0 (0.0)		0 (0.0)	
B	28	14 (50.0)		15 (60.7)		9 (32.1)	5 (17.9)		6 (21.4)	
C	10	6 (60.0)		7 (70.0)		3 (30.0)	1 (10.0)		2 (20.0)	
D	7	3 (42.9)		3 (42.9)		1 (14.3)	0 (0.0)		0 (0.0)	
E	2	0 (0.0)		0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	
Obstruction			.308		.452	.756[c]		.231[c]		.647[c]
Positioning	30	13 (43.3)		15 (50.0)		8 (26.7)	4 (13.3)		4 (13.3)	
NG	26	13 (53.8)		14 (53.8)		5 (19.2)	2 (7.7)		3 (11.5)	
AI	22	8 (36.4)		8 (36.4)		6 (27.3)	0 (0.0)		1 (4.5)	

AI, airway intervention; HSCP, hard and soft cleft palate; NG, nasogastric tube; SCS, speech-correcting surgery; V-W-K, Veau-Wardill-Kilner.
Categorical data are presented as n (%). Continuous variables are presented as median (IQR, interquartile range).
[a] Data of 58 patients
[b] Months.
[c] Fisher exact's test.

5.4 STUDY III

Altogether, 290 patients (male n = 171; 58.9%) with total ULCP were included; 92 patients did not meet the inclusion criteria and were excluded. Sixty participants (20.7%) presented with Simonart's bands. Three different surgical protocols were compared; one single-staged and two staged. Detailed information regarding the patients and surgical protocols are shown in **Table 2.**

Of the patients in the single-stage protocol, 48 were originally included within Arm C in the SC study (Rautio et al., 2017). Thirty-nine patients were originally

included in common Arm A, which consisted of two-staged palatoplasty with early soft palate repair in combination with lip repair followed by short delayed hard palate repair. Early hard palate and lip repair followed by short delayed soft palate repair was the most recently introduced protocol at the center and thereby the patients had a significantly shorter follow-up time than the older protocols (P = .008). Two experienced cleft surgeons performed 82.8% (n = 240) of the primary repairs.

5.4.1 SECONDARY SURGERY

The respective incidence for SS (SCS and/or fistula repair) by ABG and at the end of follow-up were 37.9% (n = 110) and 42.1% (n = 122), while 23.6% (n = 26) of those receiving SS underwent multiple secondary procedures by the end of follow-up.

More precisely, 25.9% (n = 75) underwent SCS by the time of ABG while 17.2% (n = 50) underwent fistula repair, of whom 24 patients underwent repair prior to ABG **(Table 6 and 7)**. The corresponding incidences by the end of follow-up were 30.3% (n = 88) (at a median age of 5.7 [3.1-23.9] years), of whom 9 patients underwent SCS after osteotomy, and 18.9% (n = 55) underwent fistula repair. Moreover, 26.2% (n = 73) underwent orthognathic surgery (LeFort 1 osteotomy, n = 49 and bimaxillary osteotomy, n = 24) at a median age of 17.1 years (range 11.5-24.1).

Furlow re-palatoplasty was the most common first SCS technique. Among patients receiving SCS, 16.0% (n =12) underwent multiple procedures by the time of ABG, and 22.7% (n = 20) during the total follow-up.

The SCS rates between the two surgeons performing most (81.7%) of the primary repairs differed significantly (37.9% versus 14.4%) (χ^2 = 15.504, df = 1, P = < .001). The surgeon with higher SCS rates performed almost all SCS procedures (90.7%). No differences emerged regarding fistula repair rates (χ^2 = .097, df = 1, P = .756).

5.4.2 COMPARISON BETWEEN THE THREE SURGICAL PROTOCOLS

No significant differences emerged between the three surgical protocols or between the different single-stage techniques regarding the need for SCS by the time of ABG or post ABG. The single-staged two-flap technique had lower SCS rates prior to ABG than the two-stage protocols (14.9% versus 31.7%, χ^2 = 6.314, df = 1, P = .012; and 31.7%, χ^2 = 5.406, df = 1, P = .020), although no difference was observed at post ABG.

The single-stage protocol had lower fistula repair rates prior to ABG compared with early soft palate closure (5.9% versus 14.3%, P = .035). No other significant difference in fistula repair rates was noted between the three surgical protocols or between the single-stage techniques, regardless of the follow-up.

Repaired fistulas were commonly located in the anterior part of the palate (Pittsburgh V, 49.1%, n = 26 and Pittsburgh IV, 28.3%, n = 15), particularly in the single-stage protocol. Anteriorly located fistulas (IV-V fistulas) were more commonly repaired at ABG (92.3%, n = 24/26) compared with pre-ABG (70.8%, n = 17/24) (P = .002). Fistulas with a connection to a perialveolar fistula were solely

repaired in the single-stage protocol ($P = .006$) **(Table 8)**; of whom the majority ($P < .001$) were corrected at ABG compared to repair prior to ABG**.**

Table 6 Incidence for SCS at ABG and post ABG in UCLP and BCLP

Protocol	No. of patients	**SCS** (No. of patients (%))			
		ABG	*P*	Post ABG	*P*
UCLP	290	75 (25.9)		88 (30.3)	
Single-stage	**186**	**42 (22.5)**	.233[a]	**54 (29.0)**	.797[a]
Two-flap	94	14 (14.9)	.064[b]	20 (21.3)	.086[b]
Langenbeck	52	17 (32.7)		21 (40.4)	
MI	16	5 (31.3)		5 (31.3)	
V-W-K	24	6 (25.0)		8 (33.3)	
Arm (C)[e]	48	14 (29.2)		16 (33.3)	
Delayed HCP repair	**63**	**20 (31.7)**	.997[c]	**21 (33.3)**	.863[c]
Arm (A)[e]	39	15 (38.5)		15 (38.5)	
Early HCP repair	**41**	**13 (31.7)**		**13 (31.7)**	
BCLP	81	31 (38.3)		38 (46.9)	
Single-stage	**59**	**19 (32.2)**	.066[d]	**24 (40.7)**	.066[d]
Two-flap	30	9 (30.0)	.730[b]	11 (36.7)	.433[b]
Langenbeck	13	6 (46.2)		6 (46.2)	
MI	8	2 (25.0)		5 (62.5)	
V-W-K	8	2 (25.5)		2 (25.0)	
Delayed HCP repair	**22**	**12 (54.5)**		**14 (63.6)**	

ABG, by time of alveolar bone grafting; Pre-ABG, fistula repair performed before ABG; Post ABG, first SCS performed after ABG.
[a]comparison of the three surgical protocols.
[b]comparison of the single-stage techniques.
[c]comparison of the two two-stage protocols.
[d]comparison of the two protocols.
[e]patients included in Scandcleft randomized study Trial 2 (Rautio et al. 2017).

Table 7 Incidence of fistula repair at ABG and post ABG in UCLP and BCLP

Protocol	No. of patients	**Fistula repair** (No. of patients (%))					
		Pre ABG	*P*	ABG	*P*	Post ABG	*P*
UCLP	290	24 (8.3)		50 (17.2)		55 (18.9)	
Single-stage	**186**	**11 (5.9)**	.106[a]	**35 (18.8)**	.268[a]	**38 (20.4)**	.380[a]
Two-flap	94	4 (4.3)	.311[b]	17 (18.1)	.256[b]	18 (19.1)	.166[b]
Langenbeck	52	4 (7.7)		8 (15.4)		8 (15.4)	
MI	16	0 (0)		2 (12.5)		3 (18.8)	
V-W-K	24	3 (12.5)		8 (33.3)		9 (37.5)	
Arm (C)[e]	48	2 (4.2)		8 (16.7)		9 (18.8)	
Delayed HCP repair	**63**	**9 (14.3)**	.495[c]	**11 (17.5)**	.274[c]	**13 (20.6)**	.143[c]
Arm (A)[e]	39	7 (17.9)		9 (23.1)		11 (28.2)	
Early HCP repair	**41**	**4 (9.8)**		**4 (9.8)**		**4 (9.8)**	
BCLP	81	24 (29.6)		40 (49.4)		43 (53.1)	
Single-stage	**59**	**12 (20.3)**	**.003[d]**	**27 (45.8)**	.286[d]	**28 (47.5)**	.195[d]
Two-flap	30	5 (16.7)	.347[b]	14 (46.7)	.543[b]	14 (46.7)	.292[b]
Langenbeck	13	5 (38.5)		6 (46.2)		6 (46.2)	
MI	8	0 (0.0)		2 (25.0)		2 (25.0)	
V-W-K	8	1 (12.5)		5 (62.5)		6 (75.0)	
Delayed HCP repair	**22**	**12 (54.5)**		**13 (59.1)**		**15 (68.2)**	

ABG, by time of alveolar bone grafting; Pre ABG, fistula repair performed before ABG; Post ABG, first SCS performed after ABG.
[a]comparison of the three surgical protocols.
[b]comparison of the single-stage techniques.
[c]comparison of the two two-stage protocols
[d]comparison of the two protocols.
[e]patients included in Scandcleft randomized study Trial 2 (Rautio et al. 2017).

5.5 STUDY IV

Overall, 81 patients (male n = 61; 75.3%) with total BCLP were included in the study; 67 patients that did not meet the inclusion criteria were excluded. Twenty-seven (33.3%) presented with Simonart's bands. The primary repairs were performed by two different protocols. These were either a single-stage approach (72.8%, n = 59) by four different techniques or a staged approach (27.2%, n = 22) with early soft palate and lip repair followed by delayed hard palate repair **(Table 2)**.

Most had ABG performed bilaterally in a single procedure (71.6%; n = 58) at a mean age of 9.9 (9.4-10.8) years. The remainder had ABG in two separate procedures. Mean total follow-up (post ABG) was 17.7 years (14.2-20.8 years). Two experienced cleft surgeons performed 82.7% (50.6%, n = 41 and 32.1%, n = 26) of the primary palatoplasties at a similar ratio (χ^2 = .386, df = 1, *P* = .535).

Table 8 Location of repaired fistulas by time of ABG in UCLP and BCLP.

Protocol	No. of repaired fistulas	**Pittsburgh location** (No. of fistulas (%))						
		II	**III**	**IV**	**V**	*P*	Connection to perialveolar fistula	*P*
UCLP	54	2 (3.8)	11 (20.4)	15 (28.3)	26 (49.1)		17 (32.1)	
Single-stage	**36**	**2 (5.6)**	**3 (8.3)**	**6 (16.7)**	**25 (69.4)**	<.001[a]	**17 (43.6)**	.006[a]
Two-flap	17	1 (5.9)	2 (11.8)	3 (17.6)	11 (64.7)	1.000[b]	6 (35.3)	.229[b]
Langenbeck	8	0	1 (12.5)	1 (12.5)	6 (75.0)		3 (37.5)	
MI	2	0	0	0	2 (100.0)		2 (100.0)	
V-W-K	9	1 (11.1)	0	2 (22.2)	6 (66.7)		6 (66.7)	
(Arm (C))	8	0	0	1 (12.5)	7 (87.5)		4 (50.0)	
Delayed HCP repair	**13**	**0**	**6 (46.2)**	**6 (46.2)**	**1 (7.7)**	**.682[c]**	**N/A**	
(Arm (A))	10	0	6 (60.0)	4 (40.0)	0		N/A	
Early HCP repair	**5**	**0**	**2 (40.0)**	**3 (60.0)**	**0**		**N/A**	
BCLP	47	3 (6.4)	4 (8.5)	14 (29.8)	26 (55.3)		16 (34.0)	
Single-stage	**30**	**2 (6.7)**	**0 (0.0)**	**9 (30.0)**	**19 (63.3)**	.041[c]	**13 (43.3)**	.074[c]
Two-flap	15	2 (13.3)	N/A	1 (6.7)	12 (80.0)	.010[b]	7 (46.7)	.004[b]
Langenbeck	6	N/A	N/A	5 (83.3)	1 (16.7)		N/A	
MI	4	N/A	N/A	2 (50.0)	2 (50.0)		1 (25.0)	
V-W-K	5	N/A	N/A	1 (20.0)	4 (80.0)		5 (100.0)	
Delayed HCP repair	**17**	**1 (5.9)**	**4 (23.5)**	**5 (29.4)**	**7 (41.2)**		**3 (17.6)**	

Six patients in BCLP and four patients in UCLP had two fistulas repaired at different locations in the palate. No fistula occurred in Pittsburgh location I. Categorical data presented as n (%).
ABG, alveolar bone grafting; SCS, speech-correcting surgery; MI, Minimal incision; Two-flap, Bardach's technique; V-W-K, Veau-Wardill-Kilner technique; N/A, not applicable.
[a]comparison of the three surgical protocols.
[b]comparison of the single-stage techniques.
[c]comparison of the two surgical protocols.

5.5.1 SECONDARY SURGERY

By the time of bilateral ABG 66.7% (n = 54) of the patients underwent SS (SCS and/or fistula repair); 35.8% (n = 29) underwent several procedures. More specifically, 38.3% (n = 31) underwent SCS while 49.4% (n = 40) had fistula repair, although 29.6% (n = 24) were repaired prior to ABG.

At end of follow-up (post-ABG) 74.1% (n = 60) underwent SS, of which 41.9% (n = 34) underwent several secondary procedures. Moreover, 46.9% (n = 38) underwent SCS (at a median age of 5.9 [5.2-8.4] years), of whom 4 patients had their first SCS after orthognathic surgery, and 53.1% (n = 43) underwent repair of fistula. Orthognathic surgery was performed in 33.3% of the patients (n = 27) (LeFort 1 osteotomy, n = 25, bimaxillary osteotomy, n = 1, segmental osteotomy, n = 1) at a

median age of 17.6 (16.3-19.2) years. Furlow re-palatoplasty was the most employed first SCS technique (65.8%).

While no significant difference in fistula repair rates were observed between the surgeons (48.8 % versus 53.8%), a significant difference in SCS rates prior to ABG was noted (51.2% versus 14.4%) ($\chi^2 = 8.735$, df = 1, $P = .033$). The surgeon with a higher SCS rate performed almost all SCS procedures (93.5%).

5.5.2 COMPARISON BETWEEN THE TWO SURGICAL PROTOCOLS

No significant differences ($\chi^2 = 2.375$, df = 1, $P = .123$) were observed between the two surgical protocols on SCS and fistula repair rates during total follow-up, although the single-stage protocol had an overall lower rate of SS (69.5% versus 86.4%). Likewise, by the time of ABG, no significant differences were observed between the single-stage techniques that had the lowest SCS rates (MI, V-W-K, and two-flap technique) (25.0% - 30.0%) and the two-stage protocol (54.5%).

Prior to ABG, the single-stage protocol (particularly the two-flap technique) was associated with lower fistula repair rates than the two-stage protocol (20.3% versus 54.5%) ($\chi^2 = 8.993$, df = 1, $P = .003$) (16.7% versus 54.5%) ($\chi^2 = 8.276$, df = 1, $P = .004$). However, by the time of ABG, the fistula repair rates almost doubled in the single-stage protocol.

The single-stage protocol was associated with repaired fistulas in the anterior part of the palate compared with the two-stage protocol and had a more distributed pattern ($P = .041$). Among the single-stage techniques, the two-flap and the V-W-K technique were especially associated with a connection to a perialveolar fistula ($P = .004$) (**Table 8**).

5.6 COMPARISONS BETWEEN CLEFT TYPES (STUDIES I-IV)

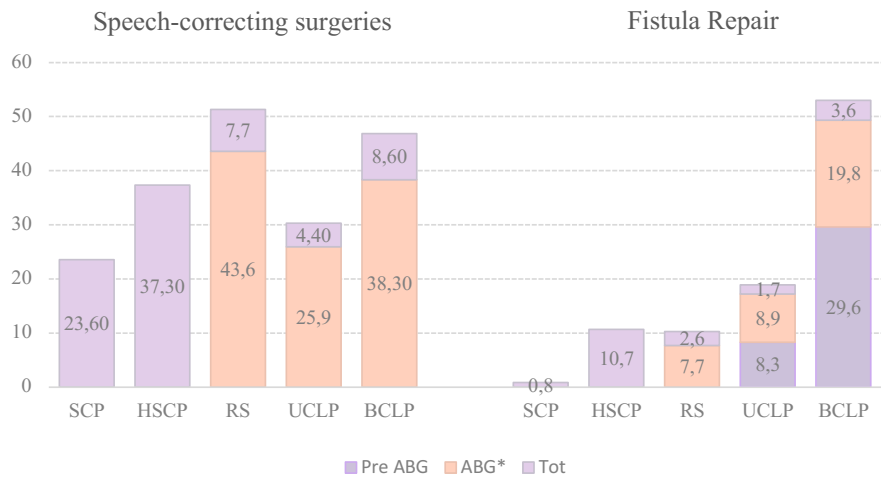

Figure 21. Outcome comparisons (SCS and fistula repair %) between the Veau cleft types and Robin sequence (Studies I-IV). ABG*, by time of alveolar bone grafting (by the age of 8 years in RS); Pre ABG, SCS/fistula repair (%) performed before ABG; Tot, total SCS/fistula repair (%) performed during the total follow-up.

By combining the results of the separate studies (I-IV), the most frequent need for SCS was observed in RS (47.4%, HSCP cleft; 46.9%, BCLP; and 37.3%, HSCP) **(Figure 21)**. Fistula repair was considerably high in BCLP (53.1%) when compared with the other cleft types. The differences in the total SCS rates between the four Veau cleft types ($\chi^2 = 15.219$, df = 3, $P = .002$) and in total fistula repair rates ($\chi^2 = 109.361$, df = 3, $P = <.001$) were statistically significant. A significant difference was observed between all Veau subtypes compared against each other except HSCP and UCLP in terms of total SCS ($\chi^2 = 3.214$, df = 1, $P = .073$). Moreover, BCLP had a significantly higher need for both SCS and fistula repair both prior to ABG and by the time of ABG. No significant difference regarding SCS was observed between the RS and HSCP ($\chi^2 = 2.646$, df = 1, $P = .104$).

6 DISCUSSION

6.1 GENERAL CONSIDERATIONS

Since VPI and dehiscence as fistulas have detrimental effects on the child, these complications are often described to associate with the severity of cleft type and should be avoided by successful primary palatoplasty. While the literature often tends to focus more on cleft speech related outcomes and post-operative fistula prevalence, the occurrence of secondary surgical intervention for complications, particularly from a long-term perspective, is commonly under-reported. Although there are many ways to assess success of primary palatal repair, some may find SS rates to be a coarse indicator. However, this is a clear and easily understood variable and more importantly reflects the worst outcomes of repair, namely the child's surgical burden (Rautio et al. 2017) and additional medical costs.

While the ideal surgical protocol for primary cleft repair is debated, various surgical approaches in terms of both single and staged protocols with considerable differences in timing of repair have been described in the literature (Shaw et al., 2001, Rautio et al., 2017). While many centers have well-defined standard protocols, the effectiveness and success of these have been challenged throughout the years, leading to new modified techniques and principles. This evolution in treatment protocols reflects modern cleft surgery, where controversies concerning speech, fistulas, and craniofacial growth have impacted the various techniques that are in practice today.

As a reflection of the general evolution in cleft care, the Cleft and Craniofacial Center of Helsinki University Hospital (Husuke) has a broad history of various surgical protocols and techniques for primary palatal repair during the past decades. Apart from small variations in timing and techniques, the primary palatoplasty procedures for ICP have not substantially changed and are still today performed in a single-staged procedure. On the other hand, the protocols for CLP (UCLP and BCLP) have changed over the years. However, even today these protocols and techniques have not been assessed and compared from a long-term perspective regarding secondary surgery in the palate.

Therefore, the main purpose of this thesis was to perform a comprehensive review of the secondary surgical burden of care (in the form of SS as SCS and fistula repair) from a long-term perspective in children with CP treated at Husuke. The different primary surgical approaches utilized throughout the years were also assessed and compared. Due to the great variation in anatomy of different cleft types, the conditions were evaluated in separate studies to facilitate interpretation of outcomes.

6.2 INCIDENCE OF SPEECH-CORRECTING SUREGERY

Surgical outcomes of both speech and wound dehiscence as fistulas have been described to relate to cleft severity. While the findings of this thesis (Study I, III, and IV) are somewhat consistent with the common belief that speech outcome is consistent with the Veau hierarchy, extensive clefts have poorer outcomes and are more likely to need corrective surgery. Moreover, the present study's results support the theory of Marrinan et al. (1998) and others (Bicknell et al., 2002, Sullivan et al., 2009), highlighting the importance and involvement of the vomer and its attachment to the palatal shelves. With an attached vomer (SCP and UCLP), the palate shelves presumably generate more palatal length after repair, which is beneficial for speech. Clefts with an unattached and separate vomer (BCLP, HSCP) result in shortened palatal shelves; a short palate following repair is reflected in inferior speech outcomes and VPI. Consistent with previous studies, we observed the greatest need for SCS in the BCLP population (Study IV) (Bicknell et al. 2002, Marrinan et al., Sullivan et al., 2009, Smyth and Wu, 2019, Bailie and Sell, 2020), where as many as 46.9% received SCS (38.3% before ABG). This is in contrast with 37.3% in HSCP, 30.3% (25.9% before ABG) in UCLP, and 23.6% (the lowest) in SCP. Particularly in ICP (Study I), the incidence of SS was strongly influenced by the cleft extent. It is therefore important to distinguish SCP from HSCP when reporting surgical results of ICP, as it is not uncommon that these are often reported as one group. The present results confirm the common belief of substantial speech deficits within the RS population, as almost half of the subjects (47.4%) requiring SCS at some point.

Although many reports have focused on speech-related outcomes, SS for VPI remain commonly under-reported (Bailie and Sell, 2020, Rossell-Perry, 2018, Reddy et al., 2018, Stein et al. 2019), which challenges the comparisons of the literature. However, while reported, studies generally show somewhat lower rates for VPI surgery compared to the present study series (Sullivan et al., 2009, Marrinan et al. 1998, Klintö et al., 2018, Smyth and Wu, 2019). Although, some have reported comparable results (Kappen et al., 2017, Rautio et al., 2017, Sell et al., 2017). There may be several explanations for this, such as variations in treatment protocols, socioeconomic status, and healthcare access. One important difference is that centers differ in their thresholds for SS to further improve the outcomes of primary repair. Pharyngeal flaps are the most common type of VPI surgery, followed by sphincter pharyngoplasty. Re-palatoplasty, including Furlow Z-plasty, are not yet well established and represent only 8% of VPI surgeries (de Blacam et al., 2018). Knowing the associated obstruction risk with pharyngeal flaps (Gart and Gosein, 2014), the threshold for surgery is most likely higher with this technique compared to the Furlow Z-plasty method, which is not only a reliable and safe procedure but also an effective method to treat VPI (Ahti et al. 2020, Ahti et al. 2021). In recent decades, this method has been the primary technique of choice for SCS at Husuke. Another a central factor behind the large variations may be that many studies have considerably shorter follow-up times (Marrinan et al., 1998, Sullivan 2009, Landheer et al., 2010, Smyth and Wu, 2019, Bailie and Sell, 2020), often including subjects with only 4-5 years of follow-up. Shorter follow-up times may exclude children who receive surgical intervention

at an older age; since SCSs are commonly performed just prior to school age. In contrast, results from reports with sufficient follow-up are comparable with the present study (Bicknell et al. 2002, David et al., 2011). Moreover, the present study revealed that some procedures are performed at the end of the growth phase (post ABG), whereas 3.2-4.9% of the CLP patients received their first SCS after orthognathic surgery.

6.3 INCIDENCE OF FISTULA REPAIR

Unintentional palatal fistulas are due to wound breakdown following primary cleft repair. These defects can be clinically significant or functional depending on its size and location. When large enough, these defects can affect speech due to excessive nasal air emission and decreased intraoral pressure leading to hypernasal resonance and VPI and result in regurgitation of fluid and food into the nasal cavity (Losee et al, 2008). The indication for surgical repair is related to the associated symptoms. A symptomatic fistula is not only troublesome for the patient but also for the surgeon, as reoccurrence rates are high after surgical repair (Smith, 2007, Landheer et al. 2010, Hardwicke et al. 2014). Numerous techniques have been described to prevent or repair these defects with both local and distant flaps but also with synthetic materials (Ha et al. 2020). In Husuke, the technique for fistula repair may differ somewhat among surgeons. However, two-layered repair is primarily achieved by suturing the oral and nasal mucosa in separate layers and with the possible use of resorbable collagen membrane and lateral incisions.

The success of primary surgery is often measured with fistula occurrence following repair (Landheer et al., 2010, Reddy et al., 2018, Rossell-Perry, 2018, Stein et al., 2019). The incidence for fistulas varies widely (0 to 76%) (Smith, 2007) in the literature. However, the definite operative burden for symptomatic fistulas generally remains unclear. Despite this rather common problem in cleft care, there is a lack of consensus regarding fistula terminology, classification, and clinical relevance (Shankar et al., 2018). This leads to misleading interpretations of the literature and limits cross-study comparisons. Accordingly, the Pittsburgh classification system (2007) was developed to clarify and standardize classification of fistulas. Due to its simplicity of fistula identification based on anatomic location, the Pittsburgh classification system has since 2007 gained popularity among surgeons. Despite standardization based on anatomical location, standardized criteria for fistula reporting (Tache et al., 2019) are lacking and standardized protocols are thus warranted. Consistent with the lack of prior standardized reporting practices for fistulas at Husuke, only symptomatic defects that were identified in the operating records and that required surgical intervention were included, such as in the SC study (Rautio et al., 2017). Moreover, defects repaired during ABG were also identified and reported.

Both adequate follow-up and the reporting of timepoints are important when assessing fistula occurrence (Shankars et al. 2018). Distinguishing the timing of fistula repair additionally describes fistula evolution in the palate. For instance, early

fistula repair following primary palatoplasty often represents significant fistulas that arise as an immediate complication. In contrast, late fistula repair, for example at ABG, may represent fistulas that may develop or are previous defects that enlarge during orthodontic treatment and palatal widening. While some smaller, less symptomatic fistulas heal by secondary intention (Tache, 2019), some symptomatic fistulas are intentionally deferred to ABG. However, it is important to note that minor fistulas may be repaired at this point, representing less symptomatic fistulas, which in turn may lead to interpretation errors when assessing symptomatic fistulas. Moreover, the intraoperative examination at ABG offers a precise evaluation of the palate, as a substantial proportion of pinhole or small fistulas may remain unidentified during normal examination. Shankars et al. (2018) reported that 26% of fistulas are undiagnosed before the intraoperative examination during ABG, which additionally can result in an unexpected increase in operative time. As most studies assessing fistulas report short-term outcomes (Tache, 2019, Park et al., 2022) that are identified predominantly in a non-surgical setting (Marrinan et al., 1998, Sullivan 2009, Landheer et al., 2010, Smyth and Wu, 2019, Bailie and Sell, 2020), this may lead to underreporting of defects in the palate as well as neglecting fistulas that have not yet enlarged to be identified. Therefore, in contrast to the literature, to meaningfully evaluate and report the long-term outcome for SS rates, the outcomes were assessed prior to ABG, at ABG, and post ABG in the CLP population. Consistent with Shankars et al. (2018) a large number of fistulas were repaired during ABG in CLP; more specifically, the repair rates almost doubled at ABG in the present study.

Recently, a systematic review (Tache, 2019) reported fistula incidence of 2%, 7.3%, 8.3%, and 12.5% in the Veau classification (I, II, III, and IV, respectively), with a mean value of 9.94%. The definitive repair rates were not reported, although such rates were likely lower as not all fistulas are symptomatic and therefor do not require surgery. On the contrary, a recent cross-sectional study from the United Kingdom reported a 31.3% prevalence for nonperialveolar palatal fistulas in UCLP, with a repair rate of 10.4% by age 5 (Yang et al. 2020). This repair rate is comparative with the 8.3% incidence (pre ABG) observed in UCLP (Study III). From the systematic review (Tache, 2019), a trend following the Veau hierarchy and fistula occurrence were observed. The reported incidences for ICP were quite similar to the present study's total follow-up fistula repair rates (Study I; 10.7% in HSCP and 0.8% in SCP). Moreover, this significant difference, such as the SCS occurrence, highlights the need to distinguish HSCP from SCP while addressing ICP outcome parameters. However, much higher incidences in the CLP population was observed during the total follow-up period (Study III; 18.9% UCLP and Study IV; 53.1% BCLP) in the present study. While there may be several explanations for this, as described above, a central explanation is the variable follow-up times. The systematic review included studies with a post-surgical follow-up period as short as 6 months, thereby questioning the validity of the results.

Similarly, fistula incidence also appears to increase when adequate long-term follow-up outcomes are reported. Moreover, David et al. (2011) reported a fistula rate as high as 79% in BCLP. While Shankar et al. (2018) reported late fistula rates (fistulas or recurrence of previously repaired fistulas) at ABG of 51% in UCLP and

76% in BCLP. Shankar and colleagues described that instead of new defects developing in the palate, the late fistulas represent small, already existing defects that enlarge during palatal expansion. These observations of David et al. (2011) and Shankar et al. (2018) are comparable with the observations of Study III and IV.

6.4 LOCATION OF REPAIRED FISTULAS

The border of the hard and soft palate has often been described as particularly problematic and a common location for unintentional fistulas, as it represents the widest part of the palate with the greatest tension at closure for both the nasal and oral layers (Amaratunga 1988). In contrast, patients with CLP are commonly described to have a high representation of fistulas in the hard palate (Pittsburgh IV) (Smith et al., 2007, Passos et al., 2014, Shankar et al., 2018, San Basilio et al., 2020, Yang et al., 2020). Similarly, repair was most often performed in fistulas located in the hard palate in all CP types in the present study series. Almost half of the operated fistulas in CLP (Study III-IV) by the time of ABG are repaired during ABG. Nearly all (>90%) of these were Pittsburgh IV-V fistulas, of which almost one-third in the respective CLP populations were associated with a perialveolar fistula (Pittsburgh VI-VII). Similarly, David et al. (2011) observed a high representation of anterior postalveolar fistulas in BCLP, which most were surgically closed at ABG. Correspondingly, Shankar et al. (2018) noticed a high increase in fistula rates at ABG (55%) in UCLP and BCLP, compared to the earlier identified fistulas (20%).

Although large anterior postalveolar and perialveolar fistulas are a challenging surgical dilemma (Sohail et al., 2016, Nicol et al., 2019), most of these anterior postalveolar fistulas closed during ABG most likely represent smaller, less symptomatic fistulas than larger anterior fistulas or larger posteriorly located fistulas that require closure prior to ABG. Whereas posterior fistulas have been described to more often associated with VPI (Andersson et al. 2021). Shankar et al. (2018) described that fistulas requiring early repair are particularly challenging since they are more prone to become recurrent or persistent fistulas.

The present observations regarding fistula location differ slightly from other observations (Smith et al., 2007, Passos et al., 2014, Shankar et al., 2018, Yang et al., 2020) that reported the greatest incidence of fistulas in the hard palate (IV) amongst CLP. However, this is presumably due to interpretation errors in the documenting process, as distinguishing Pittsburgh VI from V fistulas is challenging, a fact that was already acknowledged by the authors of the original publication (Smith et al. 2007). Another explanation may be the non-intraoperative assessment, which may exclude potential unintended anterior palatal fistulas. Moreover, some fistulas were localized in the present study according to their most anterior position, whereby some IV fistulas may be counted as V fistulas.

6.5 COMPARISONS OF SURGICAL PROTOCOLS ON SECONDARY SURGERY

Surgical protocols and techniques differ significantly across cleft centers, and no protocol has demonstrated superiority over another. Accordingly, the search for the ideal protocol for cleft repair continues. Many of the techniques and protocols utilized today are a result of years of modifications of older techniques and principles. The goal of modern cleft surgery has changed from not only correcting the defect but also to achieving an optimal speech outcome and a low fistula rate without sacrificing the growth of the maxillary structures (Leow and Lo, 2008). For these reasons, staged repair protocols were developed, although controversies still exist. In Husuke, single-stage protocols were utilized for several decades. Until the SC study (Semb et al., 2017), along with the general paradigm switch in cleft surgery, the standard approach was changed toward a two-stage approach in CLP. However, single-stage repair is still in use for primary repair in ICP and is also a common procedure throughout the world (Naidu et al., 2022).

As the literature tends to focus more on the common cleft types, there is limited information on surgical management in BCLP and associated long-term outcomes. Particularly studies comparing surgical protocols or techniques in BCLP are rather limited (Landheer et al., 2010) and often have small patient numbers (Landheer et al., 2010, Klintö et al., 2018, Shankar et al., 2018). Despite the complex and considerable anatomical variations in BCLP (particularly wide clefts and protruded maxilla), it is not uncommon that surgical principles for UCLP repair are applied in BCLP. Given the range of cleft anatomy, individual variations in the applied surgical techniques are often inevitable. Therefore, a particular technique or protocol is not suitable for all types of clefts. Tailored approaches are often essential along with the experience of a skilled surgeon.

6.5.1 SURGICAL PROTOCOLS ON SPEECH OUTCOME

Although the two-flap technique was not significantly superior to the other single-stage techniques (Study I-IV). Attention was drawn to the overall rather plausible results (regarding both fistulas and SCS), considering that this technique was often used in particularly severe, complex, and wide clefts. The elevation of mucoperiosteal flaps and the anatomical muscle dissection of the pathologically positioned muscles seem to ease the release of the soft tissue structures in the soft palate, allowing retroposition and construction of a perhaps longer palate that facilitates speech. The two-flap technique had a reduced need of SCS in both UCLP (Study III) and BCLP (Study IV) compared to the staged procedures and significantly fewer SCSs were performed prior to ABG in UCLP (14.9% versus 31.7%).

While both two-staged protocols showed similar results concerning SCS in UCLP (Study III), the single-staged protocol showed reduced need for SCS compared with the early soft palate repair approach in both UCLP (Study III; 22.9-29.0% versus 31.7-33.3%) and BCLP (Study IV; 32.2-40.7% versus 54.5-63.6%) and compared with early hard palate repair in UCLP (Study III, 22.9-29.0% versus 31.7%),

although these results did not achieve statistical significance. Similar beneficial outcomes regarding speech following single-stage repair were reported in a recent meta-analysis by Stein and colleagues (2019) compared with two-stage repair entailing early soft palate repair and delayed hard palate repair. Moreover, Ganesh et al. (2015) and Rossell-Perry (2018) found superior speech outcomes in a single-stage repair compared to staged early hard palate repair with vomer flap. Rossell-Perry (2018) described that early vomer flap causes scar contracture in the palate, resulting in shorter palatal length compared with palates repaired with single-stage repair. One can consequently speculate if greater retroposition with improved velopharyngeal function is achieved with the single-stage approach compared with the two-stage approaches. On the other hand, the SC study revealed no significant difference in VPC, hypernasality, and VPI surgery rates between the surgical protocols in trials 2 and 3. However, fewer speech-therapy visits were required in the early hard palate repair protocol than in the early soft palate repair protocol (Trial 3). Unfortunately, due to the various variables that interfered with speech evaluation, cross-trial comparisons between different protocols were not reliable (Lohmander et al. 2017, Rautio et al., 2017).

Whereas uncertainties regarding speech outcome and surgical approach exist emerging evidence suggests that delayed closure of the palate has a deleterious impact on speech outcomes (Rohrich et al., 1996, Holland et al., 2007, Kappen et al., 2017, Willadsen et al., 2017), which suggests that early cleft repair by the first year of age is preferable (Willadsen, 2012, Klintö and Lohmander, 2017). This was also compared in the SC study (trial 1, Arm A versus Arm B), where short delayed hard palate closure (12 months) was compared with delayed repair at 36 months. Although no difference in VPC, hypernasality, or VPI surgery rates was observed, delayed repair is associated with poorer consonant proficiency and greater need for speech therapy visits by the age of 5 years.

6.5.2 SURGICAL PROTOCOLS ON FISTULA REPAIR RATES

Regarding overall fistula repair, the single-stage and the early soft palate repair protocols showed similar need for fistula repair in UCLP (Study III, 20.4% versus 20.6%), with a slightly higher incidence of fistulas in the early soft palate procedure in BCLP (Study IV, 47.5% versus 68.2%). The early hard palate repair in UCLP (Study III) had an overall lower need (9.8%), although again without statistical significance. One interesting finding was that a significant number of fistulas were closed at ABG, with an overall low fistula repair rate prior to ABG in the single-stage protocol. As such, the single-stage protocol had significantly lower fistula repair rates prior to ABG compared with early soft palate closure in both UCLP (5.9% versus 14.3%) and BCLP (20.3% versus 54.5%). A meta-analysis by Stein and colleagues (2019) and studies by Ganesh et al. (2015) and Rossell-Perry (2018) also confirmed the observations of the present study. In the SC study, significantly lower fistula repair rates were noted in early hard palate closure (Arm D; 8%) compared to the early soft palate closure protocol (Arm A; 51%) (Trial 3) while no other significant differences were reported between the other trials (Rautio et al., 2017).

Among the single-stage techniques, fistula repair was more frequently required in the V-W-K technique when compared with the two-flap, MI, and Langenbeck techniques in ICP (Study I). This same trend was also noted in UCLP (Study III) and BCLP (Study IV), although without statistical significance. This particular limitation of the V-W-K technique is also a reason why this technique has lost popularity among surgeons (Leow and Lo, 2008) and was abandoned at Husuke in 1992.

Most single-stage repaired fistulas in UCLP and BCLP were anterior, Pittsburgh V fistulas (69.4-63.3%), with a high association with a perialveolar (Pittsburgh VI-VII) fistula (43.6-43.3%). Similar observations of a high representation of anterior fistulas requiring repair during ABG following BCLP single-staged two-flap closure at 12 months of age were observed by David et al. (2011). As described earlier, although large anterior fistulas are challenging to repair, there is a reason to believe that most of the anterior fistulas following repair are small and represent clinically nonsignificant fistulas (asymptomatic, nonfunctional, or both) and are intentionally deferred to this timepoint. Large anterior fistulas would have been repaired prior to ABG as they would have interfered with the ABG. As described previously, fistulas repaired prior to ABG are more likely to represent clinically significant fistulas that require early surgical management. These anterior defects in single-stage repair reflect the challenge of stretching the mucoperiosteal vomer flaps, particularly in BCLP, to the most anterior part of the cleft and pre-maxilla, resulting in an insecure closure consisting of a one-layer closure prone to fistula development.

By closing the hard palate early with a vomer flap, have shown to decrease the width of the residual cleft and thereby provide more favorable conditions at the following soft palate repair (de Jong and Breugem, 2014). As such, the risk of subsequent fistula development is reduced (Ferdous et al., 2010; Smarius and Breugem, 2016). In the present study, similar findings were observed as the early hard palate repair, as opposed to the other protocols in UCLP, did not show any increase in fistula repair rates or anterior (Pittsburgh V) fistulas during follow up, and only clinically significant fistulas were closed prior to ABG. On the other hand, fistula repair was commonly performed at the border of the hard and soft palate and in the hard palate (Pittsburgh III-IV) in the early soft palate repair protocol. As described in the SC study (Rautio et al. 2017), the surgeons often had difficulties in constructing the posterior edge of the vomer flap at the posterior border of the hard palate during the second stage of hard palate repair. This resulted in a tendency towards dehiscence in this location.

6.5.3 OUTCOME ASPECTS AMONG SURGICAL PROTOCOLS

In this study series, none of the surgical protocols were clearly superior to another. Accordingly, small differences in outcome measures were noted. However, the single-stage protocol was associated with high dehiscence repair rates of, presumably small, fistulas in the anterior part of the palate at ABG. This protocol seems to facilitate both speech and prevention of clinically significant fistulas requiring early repair; the two-flap technique in particular has previously been shown to be reliable and safe (Rossell-

Perry et al., 2017) and offers a feasible choice of single-stage primary palatoplasty. The early hard palate repair seems to offer a watertight closure with fewer dehiscence rates. Whereas the early soft palate repair protocol seemed to be associated with the highest complication rates among the surgeons at Husuke, particularly in clinically significant fistula rates prior to ABG.

Although comparisons between protocols are challenging, especially in inter-center studies, the results in this study series can be considered fairly reliable, as most surgeries were performed by the same experienced surgeons followed by the same follow-up protocols. However, as addressed in the SC study (Rautio, 2017), due to the long learning curve, the adoption of a new surgical technique may not lead to improved outcomes, as the surgeons achieved the best results when performing a familiar technique. This calls into question the advantage of changing techniques.

To determine whether one protocol or technique is superior to another requires careful and meticulous assessment with long-term follow-up. Speech, SCS, fistulas, and fistula repair rates are important outcome variables in addition to the impact on maxillary growth. Although studies comparing surgical protocols show minimal differences, certain protocols seem to facilitate a particular outcome measure; protocol selection may be a compromise considering these factors.

Since there is a history of changing protocols at Husuke, some of the protocols and techniques evaluated in this thesis are not in general use today at Husuke. The current protocol, early hard palate closure with a vomer flap combined with a short delay in soft palate closure, has gained more attention recently and has been shown to be a reliable technique in closing the hard palate (Martin-Smith et al., 2017) with low fistula rates, as also observed in the present study. To compensate the potential scar contracture of the early vomer flap that interferes with palatal length (Rossell-Perry et al. 2018), some use the primary Furlow technique at the second stage of soft palate closure to lengthen the palate (Liao et al., 2014; Stein et al., 2019). This approach has also been utilized recently at Husuke. Since then, the common experience has been a notable reduction in SCSs. However, no further studies have yet been performed, and no major conclusions can be made due to the currently short follow-up and lack of long-term outcomes with sufficient volume. Moreover, although potentially superior speech results have been observed with this approach, a disadvantage and concern is the excessive tension during repair and the dead space between the oral and nasal lining, which is more prone to develop fistulas (Brothers et al., 1995, Gunther et al., 1998, Losee et al. 2008, Losken, 2011). However, contrasting opinions exist (Landheer 2010, Tache, 2019). However, the early vomer flap procedure has raised some concerns regarding potential subsequent detrimental effect on maxillary growth (Emami & Hashemzadeh, 2020). Moreover, in the prospective SC study, significantly better dental arch relationships were observed in Arm C (single-stage) compared to Arm D (with early vomer flap) (Heliövaara et al., 2021). However, controversial results have been observed (Ganesh et al., 2015), as beneficial outcomes on maxillary growth with the early vomer flap method were observed in the retrospective Eurocleft (Shaw et al., 2001) and Americleft (Russel et al., 2011) studies. Accordingly, careful follow-up and assessment are needed in the future.

6.6 SECONDARY SURGERIES IN ROBIN SEQUENCE

The overall high incidence of SCS observed in Study II supports the general theory of substantial speech deficits in the RS population. The findings are somewhat consistent with previous reports of VPI surgery rates (13.4-44.1%) (Witt et al., 1997; de Buys Roessingh et al., 2008; Goudy et al., 2011; Patel et al., 2012; Stransky et al., 2013; Hardwicke et al., 2016; Morice et al., 2018, Becker at al. 2021). However, it is important to note that comparisons between studies are challenging since study settings are not uniform. It is common that RS studies have small cohorts, short follow-up times, and various diagnostic criteria of the sequence and concomitant syndromes. Although no consensus exists, RS is often associated with poorer speech outcomes than in ICP (Hardwicke et al. 2016; Schwaiger et al. 2021; Becker at al. 2021, Logjes et al. 2021). Though no significant differences were observed, a similar trend was evident in the present study series comparing the SCS incidence of 47.4% in RS (Study II) with 37.3% in HSCP (Study I), considering that no SCP was present in the RS population. The difference was even more evident in comparison with ICP (HSCP and SCP). However, contrasting results, where no differences were observed, have also been reported (Taku et al. 2020, Naros et al. 2021).

Evidence suggests that cleft characteristics is a central variable that explains the speech differences between RS and ICP (Logjes et al. 2021), as the RS cleft is commonly described as more severe in terms of width (Rintala et al., 1984; Godbout et al., 2014, Logjes et al. 2021) and extent (Laitinen et al. 1997, Godbout et al., 2014, Lodges et al. 2021, Naros et al. 2021, Schwaiger et al. 2021) compared with the ICP cleft. Accordingly, no SCP was observed in the RS cohort (Study II). Interestingly, Hardwicke et al. (2016) found a significant difference in speech outcomes after matching patients with RS and ICP by age, gender, and cleft extent. This indicates that apart from the cleft extent exclusively, there are additional factors that contribute to the poorer speech outcomes in RS. Although cleft width was not assessed. Some authors postulate that the cleft extent is insufficient to predict the speech outcome exclusively, as cleft width may vary largely within the same Veau classification (Landheer et al. 2010, Logjes et al., 2021).

One can speculate if the anatomical differences are caused by the intrinsic cleft characteristics that have occurred through distinct pathogenetic mechanisms. The etiology behind ICP is believed to be multifactorial, involving both genetic and environmental factors. In contrast, the RS cleft has been described to develop due to a triad of events during embryonic development, where palatal folding is inhibited due to an upward positioned tongue that in turn is due to a retrognathic and hypoplastic mandibula (Logjes et al., 2018). This mechanical interference has described to give rise to the characteristic U-shaped morphology of the cleft (Hanson and Smith, 1975). Apart from the cleft characteristics, one can postulate that there are most likely other abnormal facial and nasopharyngeal features, apart from the hypoplastic and retrognatic mandibula, that separate RS and ICP and may further influence speech outcomes. Evidence of diverging structures of the maxilla also supports this theory (Laitinen and Ranta, 1992; Laitinen, 1993; Bacher et al., 2000; Krimmel et al., 2009; Purnell et al., 2019). However, the question regarding the

importance of these maxillary differences on speech outcomes remains unanswered. There is reason to believe that development of VPI is complex and is caused by multiple factors.

Although controversial results regarding speech outcomes in syndromic RS (sRS) and non-syndromic RS (nsRS) (Witt et al., 1997, Patel et al., 2012, Hardwicke et al., 2016, Schwaiger et al., 2021) have been observed, some highlight the importance of distinguishing these conditions, as poorer speech outcomes may be observed in sRS (Patel et al., 2012, Morice et al., 2018, Lodges et al., 2021), suggesting that nsRS has comparable outcomes with ICP (Lodges et al., 2021). However, in line with other reports (Hardwicke et al., 2016, Becker at al., 2021) study II (nsRS) found a slightly higher incidence for SCS compared to the non-syndromic counterparts in HSCP (ICP) (Study I). However, Logjes et al. 2021 explained that the discrepancy is most likely due to the wide identification rates of additional anomalies or syndromes. There is reason to believe that a substantial proportion of syndromic patients generally remains undiagnosed (Izumi et al., 2012.), due to a prior lack of understanding of RS-associated syndromes and anomalies. Although this may be plausible, comparisons of syndromic and non-syndromic populations are may be problematic since outcome measures concerning speech may vary largely due to the possible association of severe concomitant disorders. Although study II compromised a non-syndromic population, genetic consultation was not performed in all patients mostly due to the early clinical praxis where only clinically suspected patients were further tested. Accordingly, there may have been participants with undiagnosed syndromes that may have impacted the results. Genetic consultation and appropriate investigations are currently performed regularly at Husuke.

Consistent with the commonly held belief of surgically challenging clefts in RS due to the extensive nature of the cleft, high fistula rates (24%) were observed. These results are consistent with the rather wide reported rates of 0% to 26% (Witt et al., 1997, Goudy et al., 2011, Patel et al., 2012; Stransky et al., 2013, Filip et al., 2015, Morice et al., 2018). Restoring extensive clefts is challenging due to inevitable tension occurring at repair, which results in a palate more susceptible to dehiscence and furthermore to tissue scarring that subsequently can lead to an immobile palate with poor function. Repair of wide palates has been described to cause short palates, and there is reason to believe that scar contracture may do the same and subsequently lead to VPI. Interestingly, the overall fistula repair rate in RS (10.3%) is almost identical with that of HSCP (10.7%). Although the fistulas most often occurred at the junction of the hard and soft palate, these fistulas less often required repair. However, there were no significant differences regarding fistula distribution.

In study II, potential contributing factors that may predict outcomes were further investigated. No significant differences concerning gender, surgeon, timing of primary palatoplasty, surgical technique, cleft severity, or airway obstruction in infancy were observed. Some differences in repaired fistula rates were observed between surgeons. However, these results may be due to the small size of the study population. Accordingly, no major conclusions can be made and further research with even larger cohorts is necessary. Similarly, Morice et al. (2018), found no certain predictors regarding speech outcome among anatomic variables (such as cleft width

and extent, glossoptosis, and retrognathia), respiration management at birth, or muscle deficiency (assessed with electromyography). Furthermore, Filip et al. (2015) found no significant association between cleft extent and VPI surgery rates. Moreover, no correlation between the obstruction severity in the neonatal period and speech-related outcomes has yet been found (Stransky et al., 2013, Morice et al., 2018/7, Schwaiger et al., 2021).

6.7 STRENGTHS, LIMITATIONS, AND FURTHER PERSPECTIVES

Husuke provided a unique and comprehensive database, which is a result from decades of centralized cleft care in Finland that involves long-term systematic follow-up by a multidisciplinary cleft team. Moreover, the population is unique with a high prevalence of patients with ICP. Nevertheless, this study has a few noteworthy limitations, as the retrospective study design comes with inherent potential for methodologic bias.

Orthodontic treatment was performed locally, whereby the limited treatment experience of patients with CP may have led to increased fistula formation, despite receiving instructions from the cleft team. Moreover, the universal (also at Husuke) lack of standardized documentation and classification of fistulas may have led to interpretation errors. With the aim of reducing these errors, only identified and repaired defects were included, as in the SC study (Shaw and Semb, 2017). The Pittsburgh classification system (Smith et al., 2007) is a helpful tool when assessing fistulas according to their anatomical location (particularly in documenting perialveolar fistulas from unintended palatal fistulas) and has become a more standard approach in the literature. It has shown to be particularly reliable in assessing fistulas broadly within the palate. However, this system is to some extent less reliable in particular zones (Sitzman et al., 2018). Distinguishing V from VI fistulas was challenging, particularly in the retrospective setting. Deficient and ambiguous records may have led to some VI fistulas being interpreted as a V fistula, which may also explain both the high overall incidence and the incidence of repaired fistulas in this region. These studies raised the importance of developing a routine and standardized documentation of palatal fistulas not only for further research purposes but also for clinical use.

Cross-study comparisons regarding speech and VPI surgery are inherently challenging due to various reasons, particularly due to the absence of a universal standardized and validated VPC scale. As mentioned, although SCS may be a crude means of assessing speech, it is a clear and easy to understand indicator that reflects unfavorable outcomes of cleft speech, describing the most severe cases and surgical burden of the child. It is therefore particularly useful, since speech assessment is complex, challenging to understand, and requires years of practice. However, the drawback with SCS as an outcome variable is the potential for bias for different impacting factors. As observed in this study series, the surgeon performing >90% of the SCS procedures had significantly higher SCS rates than the other “high-volume”

surgeon, although no difference in fistula rates (Study III and IV) was observed. Although there may be several explanations behind this, such as surgical skill, experience, technique familiarity, and cleft severity, it raises a question on the impact of the surgeon's threshold for SCS rather than surgical skill alone.

Specific surgical techniques are often difficult to compare, as modified techniques are not uncommon as the surgeon must adapt to the severity and anatomy of the cleft. As concluded in the SC study (Rautio et al., 2017, Shaw and Semb, 2017) the learning curve is long while the surgeons' experience and skill are essential and may outweigh the surgical protocol or technique applied.

As described before, a few years ago the Furlow method was implemented as the second stage for primary soft palate repair in combination with early hard palate repair. Due to the limited number of patients and currently short follow up, no investigation has yet been performed on this technique regarding speech outcomes. However, this will be investigated in the future. Speech, SCS, fistula, and fistula repair are important factors when assessing the outcomes and success of various primary repair protocols. Hearing, occlusion, and craniofacial growth are also essential factors. This study did not address these outcome variables. However, in the future, the primary palatoplasty methods` effect on maxillary growth will be investigated to provide a comprehensive review of the different treatment protocols on long-term outcomes.

6.8 CLINICAL RELEVANCE

This thesis highlights the fact that the surgical burden of care for children with OFCs extends beyond the primary repair. Over the long-term, children with OFCs have a high incidence of SS to improve speech, repair palatal defects commonly known as fistulas, or both. As such, the need for adequate and long-term follow-up is essential when reporting SS rates. In particular, severe cleft deformity and associated RS are prone to require secondary repair, reflecting the challenges the surgeon faces at primary repair. Moreover, a large number of fistulas were repaired at ABG, highlighting the possible lengthening effect on perioperative time at ABG.

SS is an important measure that describes not only the direct burden of care for the patient and family (such as additional pain, suffering, fear, and time off work) but also the financial burden for society. Accordingly, knowledge on the need for secondary corrective procedures is relevant and important to improve the preparedness of the family and caregivers and to provide proper information regarding potential future procedures.

Different surgical protocols and techniques seem to result in minimal clinically significant differences on long-term outcomes. This questions the benefits of changing the predictability of a familiar and prevailing technique for a surgical innovation or trend.

7 CONCLUSION

I. The long-term surgical burden of care for secondary surgeries is high and ranges widely between 23.6% to 46.9% for speech-correcting surgeries (SCS) and 0.8% to 53.1% for fistula repair depending on cleft type.

II. A high burden of care in the form of SCS is to be anticipated in patients with cleft palate and RS (Robin Sequence).

III. Extensive clefts, partly or totally detached from the vomer as HSCP (inclusive RS) and BCLP, are more likely to need corrective surgery for speech. Fistula repair follows the severity range of the cleft hierarchy, with a high need for fistula repair in severe clefts, such as BCLP.

IV. No surgical protocol or technique is superior to another regarding the long-term need for SCS or fistula repair. Early hard palate repair with a vomer flap seems to decrease the need for fistula repair in the palate, particularly at ABG. Early soft palate repair combined with short delayed hard palate repair resulted in the least favorable long-term outcomes. Despite the high rates for fistula repair at ABG, attention was drawn to the overall plausible outcomes of the single-stage protocol, which seem to offer a feasible approach for CP repair.

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