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Influence of Infant Cleft Dimensions on Velopharyngeal Function in 5-Year-Old Danish Children Born With Unilateral Cleft Lip and Palate

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Abstract

Aim: To examine the association of cleft severity at infancy and velopharyngeal competence in preschool children with unilateral cleft lip and palate operated with early or delayed hard palate repair.

Design: Subgroup analysis within a multicenter randomized controlled trial of primary surgery (Scandcleft).

Setting: Tertiary health care. One surgical center.

Patients and Methods: One hundred twenty-five infants received cheilo-rhinoplasty and soft palate repair at age 3 to 4 months and were randomized to hard palate closure at age 12 or 36 months. Cleft size and cleft morphology were measured 3 dimensionally on digital models, obtained by laser surface scanning of preoperative plaster models (mean age: 1.8 months).

Main outcome measurements: Velopharyngeal competence (VPC) and hypernasality assessed from a naming test (VPC-Sum) and connected speech (VPC-Rate). In both scales, higher scores indicated a more severe velopharyngeal insufficiency.

Results: No difference between surgical groups was shown. A low positive correlation was found between posterior cleft width and VPC-Rate (Spearman = .23; $P = .025$). The role of the covariate "cleft size at tuberosity level" was confirmed in an ordinal logistic regression model (odds ratio [OR] = 1.17; 95% confidence interval [CI]:1.01-1.35). A low negative correlation was shown between anteroposterior palatal length and VPC-Sum (Spearman = −.27; $P = .004$) and confirmed by the pooled scores VPC-Pooled (OR = 0.82; 95% CI: 0.69-0.98) and VPC-Dichotomic (OR = 0.82; 95% CI: 0.68-0.99).

Conclusions: Posterior cleft dimensions can be a modest indicator for the prognosis of velopharyngeal function at age 5 years, when the soft palate is closed first, independently on the timing of hard palate repair. Antero-posterior palatal length seems to protect from velopharyngeal insufficiency and hypernasality. However, the association found was significant but low.

Keywords

nonsyndromic clefting, speech development, velopharyngeal function, hard palate, surgical technique

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Introduction

It is commonly acknowledged among cleft surgeons that a wide cleft palate challenges restoration of velopharyngeal anatomy (Yuan et al., 2016). Adequate velopharyngeal function is essential to achieving good speech, a goal of utmost importance in cleft treatment.

In persons with a repaired cleft palate, presence of velopharyngeal dysfunction (VPD) will inevitably affect speech production to different degrees (Hutters and Brondsted, 1987).

Standard assessment of cleft palate speech involves perceptual auditory assessment (Sell, 2005), although agreement between listeners has often been low, especially for the assessment of hypernasality (Zraick et al., 2000). To overcome challenges of interrater reliability, different composite scores have been developed for the assessment of velopharyngeal competence (VPC). They typically combine estimation of hypernasality and appraisal of passive and active symptoms of VPD from spontaneous speech or a naming test (see Lohmander et al., 2017a; 2017b for a detailed description).

Correlation Between Surgical Technique and Velopharyngeal Function Postsurgery

Many surgical methods have been proposed to reconstruct the palate (Teblick et al., 2018), aiming for closure of the oronasal communication, reconstruction of a physiologic muscular sling, and achievement of adequate length of the velum with minimal detrimental effect on the bony growth of the maxillofacial complex (Lin et al., 2015).

Generally, conclusions on the role of surgical methods remain tentative due to the retrospective design of observational studies (Semb, 2014; Reddy et al., 2017). Furthermore, knowledge of important factors such as surgical skills and surgeons' familiarity with the methods tested remains sparse (Shaw and Semb, 2017).

To inform the choice of surgical method for primary palatoplasty in patients unilateral cleft lip and palate (UCLP), the Scandcleft project was designed as a series of 3 parallel randomized controlled trials (RCTs) in which 10 Scandinavian and British cleft teams compare a common surgical protocol with a variation in timing or sequence of palatoplasty. Speech and dentofacial development as primary outcomes and several other aspects are currently investigated from the perspectives of different professions staffing the cleft palate craniofacial teams (Shaw and Semb, 2017).

Surprisingly, the 5-year speech results from the Scandcleft trials do not support a relation between velopharyngeal function and different surgical methods. No significant difference was reported between surgical methods for VPC or hypernasality within any of the trials. A high prevalence of marginal and incompetent velopharyngeal function was found, based on a summary score of VPD symptoms (VPC-Sum), ranging from 39% to 65%. The authors ascribed the results and the higher prevalence of fistulas to the limited experience of some surgeons with the new common method (Lohmander et al., 2017b). The prevalence of velopharyngeal insufficiency (VPI) included marginal and severe incompetence but remained relatively high compared to previous studies, although differences in methodology make direct comparisons questionable (Nyberg et al., 2014; Sell et al., 2015).

Relationship Between Cleft Size and Risk of VPD

Large phenotypic variation in the UCLP population's cleft dimensions at birth warrants particular attention to patient-related intrinsic factors such as cleft size and morphology before repair (Liao et al., 2010). An important clinical concern is whether there is a significant risk that larger clefts present secondary VPD. Such a risk must be communicated to parents and caregivers because it is related to the prognosis of the primary operation and subsequent treatment need.

There is paucity of evidence on the association between cleft size at birth and the risk of developing VPI. Most current studies examined the correlation between palatal fistula incidence and cleft type determined according to the Veau classification, which distinguishes between clefts of the soft and hard palate and between complete unilateral and complete bilateral clefts (Cohen et al., 1991; Muzaffar et al., 2001; Phua and de Chalain, 2008; Murthy et al., 2009). Few investigations (Parwaz et al., 2009; Landheer et al., 2010) have attempted to define cleft severity based on actual measurement of presurgical cleft size. However, the main outcome was again surgical dehiscence and not VPI. Yuan and coauthors (Yuan et al., 2016) also investigated VPI, but no information was provided about methodology used and background of the raters involved in the assessment of VPI. Furthermore, different types of palatal clefts were investigated, bringing uncertainty to the interpretation. One study examined the correlation between the size of the residual cleft in the hard palate and several speech variables, including hypernasality (Lohmander-Agerskov et al., 1997), but no measurements of the initial cleft before primary closure were included.

It has been hypothesized that wider cleft palates are associated with increased fistula formation and generally more severe VPI following surgical repair (Parwaz et al., 2009). In addition, it is well known that a UCLP population displays large variation in cleft dimensions and morphology (Reiser et al., 2010; Latief et al., 2012; Russell et al., 2015). Thus, the present study aimed to investigate the impact of infant cleft severity and surgical strategy, in terms of timing of hard palate repair, on velopharyngeal function at age 5.

Materials and Methods

Participants

A total of 125 nonsyndromic Caucasian infants born with UCLP, operated by 1 surgical team at the Department of Plastic Surgery and Burns Treatment, Copenhagen University Hospital, Denmark, were included in the Scandcleft Trial 1. Inclusion criteria, study design, and surgical methods have been reported

Table 1. Results of the Ordinal Logistic Regression Analysis to Estimate the Association Between VPC-Rate and Covariates Describing Cleft Size and Morphology.[a]

	VPC-Rate						
	Surgery			Covariate[b]			Parallelism Assessment[c]
Covariate	$OR_{c/b}$	95% CI	*P*	OR	95% CI	*P*	*P*
None	1.12	0.53-2.35	.763	–	–	–	–
Cleft size at anterior level (GL), mm	1.12	0.53-2.36	.759	1.04	0.94-1.14	.461	.922
Cleft size at canine level (cc′), mm	1.07	0.51-2.27	.849	1.07;	0.96-1.18	.198	.663
Cleft size at molar level (mm′), mm	1.00	0.46-2.15	.999	1.10	0.96-1.25	.177	.099
Cleft size at tuber level (tt′), mm	0.88	0.40-1.92	.747	1.17	1.01-1.35	.032	.167
Cleft surface, mm^2	1.05	0.50-2.24	.882	1.00	0.99-1.00	.274	.088
Palatal surface, mm^2	1.13	0.54-2.38	.748	0.99	0.99-1.00	.706	.581
3DICSR, %	1.04	0.49-2.22	.904	1.03	0.98-1.08	.192	.115
Arch length, mm	1.17	0.55-2.4	.681	0.88	0.75-1.03	.112	.649
Arch perimeter, mm	1.20	0.56-2.53	.640	0.95	0.90-1.01	.138	.731

Abbreviations: CI, confidence interval; OR, odds ratio; n.s., the CI indicates that the difference between the surgical groups is nonsignificant; VPC, velopharyngeal competence.

[a] Without adjustment for cleft dimensions (covariate: none), patients in surgical arm B had 12% (95% CI: 0.53-2.35 n.s.) higher odds to receive a worse VPC-Rate score than patients in surgical arm A. After adjustment for cleft size at tuber level, arm B presented 12% (95% CI: 0.40-1.92 n.s.) lower odds than arm A. The change indicates a significant role of the covariate, cleft size at tuber level (tt′): OR = 1.17, 95% CI = 1.01-1.35.

[b] OR gives the odds ratio for a VPC-Rate category change (averaged) associated with 1 unit increase in the covariate.

[c] The *P* value results from testing the hypothesis of the same effect of the covariate in each group.

by Semb and coauthors (2017). In trial 1, surgical variation consisted of difference in timing of hard palate surgery. Two "high-volume" cleft surgeons (more than 50 newborns/year) performed cheilo-rhinoplasty (modified Millard and McComb techniques) and soft palate repair (ad modum Gothenburg) when the babies were 3 to 4 months old. The patients were then randomized for hard palate closure at age 12 months (Arm A) or 36 months (Arm B; Rautio et al., 2017).

Cleft Dimensions

Three-dimensional data of cleft size and morphology were collected using a novel method previously validated and judged robust in terms of reproducibility (Botticelli et al., 2018). Measurements of cleft severity were based on digital models obtained by surface laser scanning (3Shape D2000, Copenhagen, Denmark) of the plaster models collected preoperatively according to the Scandcleft protocol (mean age: 1.8 months; standard deviation: 1.5 months). Analysis comprised linear measurements, entered into a coordinate system, of cleft width at 4 anteroposterior levels (anteriorly between the margins of the greater and the lesser segments, at the level of the canines, the molars, and the maxillary tuberosities) and area measurements of cleft surface and palatal surface retrieved from the cleft volume and palatal volume. The ratio between cleft surface and palatal surface was defined as the 3D Infant Cleft Severity Ratio (3DICSR), a modification of a previously used index (Johnson et al., 2000; Russell et al., 2015). A complete list of the measurements considered is reported (as covariates in the regression model) in Table 1 and part of the analysis shown in Figure 1. For the full analysis, please refer to the technical paper (Botticelli et al., 2018). Data were available for 109 participants: 3 children were excluded from the trial; 2 infant models were missing; and in 11, the quality of the plaster models was not considered sufficient for analysis.

Speech Measures

Scandcleft speech assessment results for VPC and velopharyngeal hypernasality were retrieved with permission from 106 participants who were included in this subgroup analysis. For those participants, both cleft severity assessment and speech evaluation were available. A CONSORT flow diagram is shown in Figure 2.

Before the 5-year assessment, all speech-language therapists (SLTs) involved in the Scandcleft project had received the same training and passed a final test. Intra and interrater reliability assessment were conducted, and from each participating center, the 2 STLs with the highest intraexaminer agreement score were selected. They were blinded to randomization and assessed only participants from a different cleft palate center{Willadsen, 2017 #132} (Willadsen et al. 2017). Velopharyngeal competence was assessed from 2 different speech materials, a naming test and retelling of a story.

Based on this material, 2 VPC scores were provided: VPC-Rate and VPC-Sum. *VPC-Rate* is an overall assessment of velopharyngeal function as competent, marginally competent, or incompetent. It was assessed by 2 SLTs based on a 2-minute sample of the participants' retelling of a story. It is a categorical score: 0 = competent, 1 = competent, and 2 = incompetent.

VPC-Sum is a summary score of the VPI symptoms: (1) hypernasality, (2) passive symptoms (nasal emission, weak pressure, and nasalization of voiced consonants), and (3) active nonoral symptoms (glottal and pharyngeal consonants, active

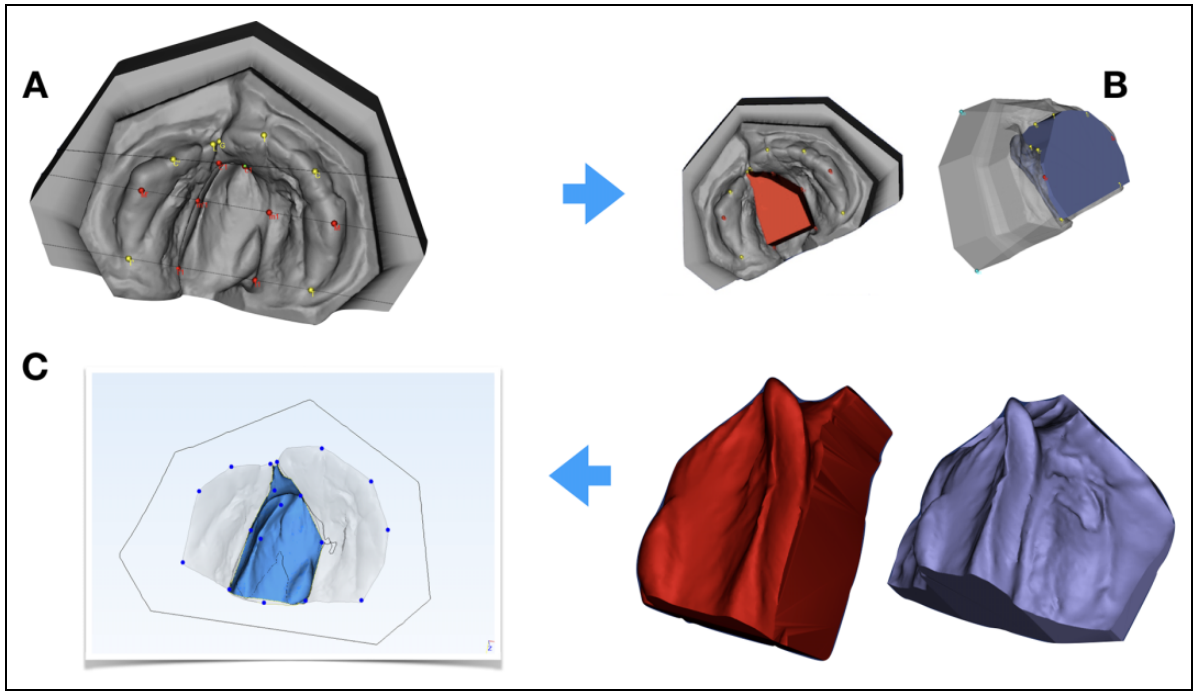

Figure 1. Analysis of cleft dimensions in infancy based on preoperative digital models. A, Linear measurements in a coordinate system. The anterior cleft (distance between the cleft margins G-L) and cleft size at canine (cc′), molar (mm′), and tuberosity (tt′) are used in the present study. B, Extraction of cleft volume and palatal volume. C, Retrieval of cleft area and palatal area and calculation of their ratio, defined 3D Infant cleft Severity Ratio (3DICSR_ modified from Johnson et al., 2000; Russell et al., 2015).

nasal fricatives, and nasal consonants for unvoiced stops) derived from a naming test encompassing 33 words including 10 target sounds /p t k b d g f s v n/. Nine of the words contained high vowels, and these words were edited into an audio string. Three SLTs independently assessed hypernasality from these strings on a 4-point ordinal scale as within normal limits, mild, moderate, or severe hypernasality.

Two SLTs phonetically transcribed the 33 target consonants of the naming test. Passive and active nonoral symptoms were derived from the phonetic transcriptions. Hypernasality, passive, and active nonoral symptoms were each given a score of 0 to 2 points depending on their severity or frequency (Lohmander et al., 2017a, 2017b). Thus, each participant received a score between 0 and 6 points, higher numbers with increasing symptoms.

The VPC-Sum scores were pooled into 3 broad categories: 0 to 1 point means competent velopharyngeal function, 2 to 3 points borderline deficit, and 4 to 6 points incompetent velopharyngeal function, called the *VPC-Pooled*.

Finally, the VPC-Sum was reported as dichotomized: 0 to 1 means VPC, and 2 to 6 means VPI (Lohmander et al. 2017b), called the *VPC-Dichotomous*.

Statistical Methods

The methods used to measure infant cleft dimensions (Botticelli et al., 2018) and to assess speech outcomes (VPC-Sum and VPC-Rate) had been previously assessed for inter-/intraexaminer reproducibility and inter-/intrarater agreement for speech outcomes (Lohmander et al., 2017a). Both were acceptable.

The association between variables describing cleft size and morphology was explored by Spearman rank correlation for all outcome variables. The association between surgical method (Arm A vs Arm B) and VPC-Rate, adjusted for covariates describing cleft dimensions at 4 anteroposterior levels and cleft size (3DICSR), was assessed using ordinal logistic regression, including 1 covariate at the time. The assumption of equal effect of the covariates in both surgical groups was checked for all covariates.

A similar analysis was performed for VPC-Pooled scores as outcome. Logistic regression was used for the prediction of VPC-Dichotomous.

Statistical significance was reported at 95% confidence level. The analysis was conducted with the STATA software package version 14.1 (Stata Corp, LP, College Station, Texas).

Results

VPC-Sum data were available for 105 patients (of 106), while VPC-Rate data were available only for 98 (of 106) due to lack of cooperation in the spontaneous speech assessment.

Association of VPC-Rate and Infant Cleft Dimensions

Auditory perceptual ratings of VPC from spontaneous speech, the VPC-Rate, showed weak but significant associations with

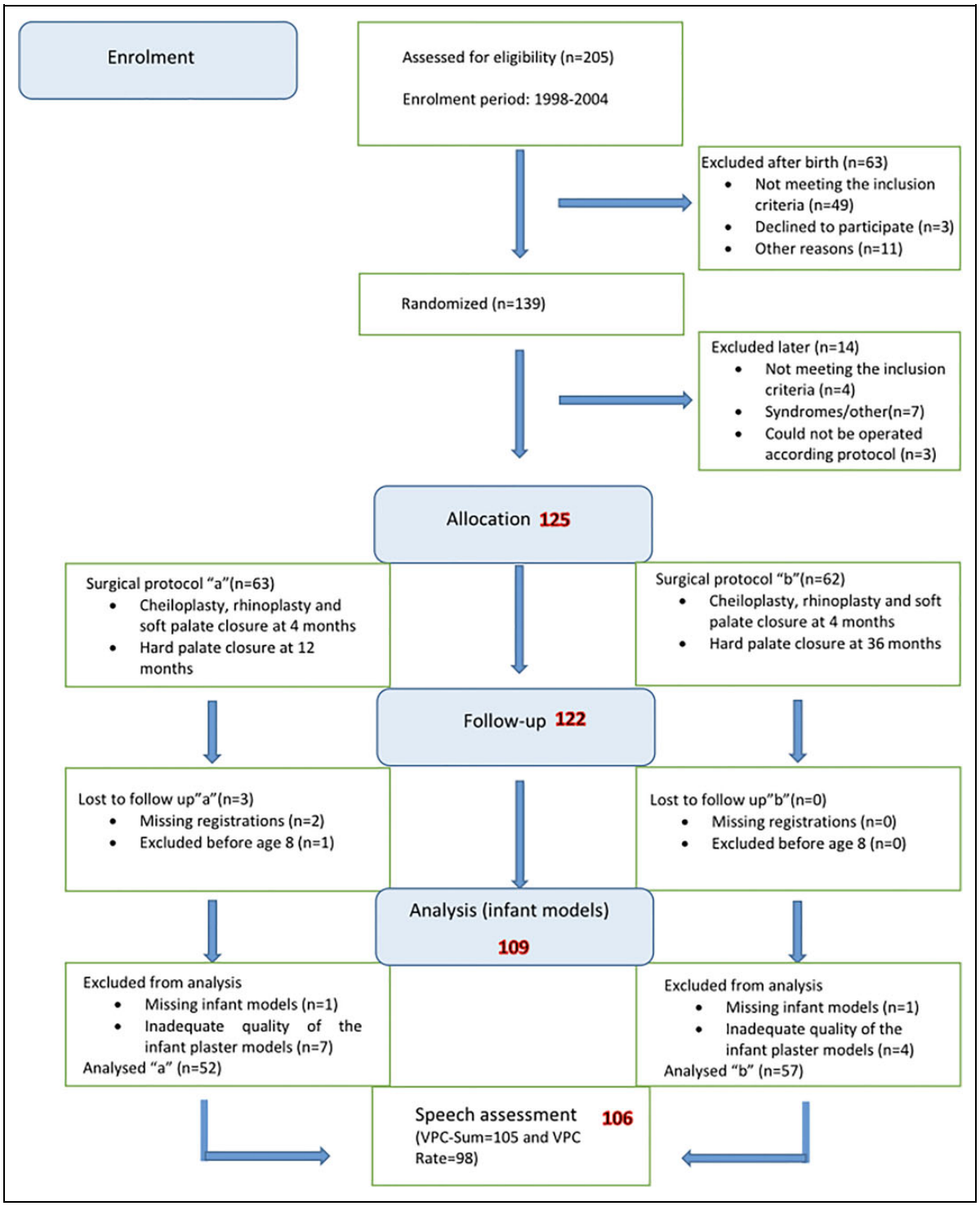

Figure 2. CONSORT flow diagram illustrating final retention of the patients participating in trial I in the Scandcleft project included in the present analysis.

posterior cleft dimensions (tuberosity level; Spearman $\rho = .23$; $P = .025$). This correlation seemed stronger (Spearman $\rho = .33$) for surgical Arm B ($P = .019$), where a significant correlation could also be identified for cleft size measured at the level of the deciduous molars ($P = .037$). The distribution of VPC-Rate scoring in relation to posterior cleft size at tuberosity levels is described in Figure 3.

The association between cleft size at tuberosity level and VPC-Rate was confirmed when adjusting the comparison between surgical groups using ordinal logistic regression.

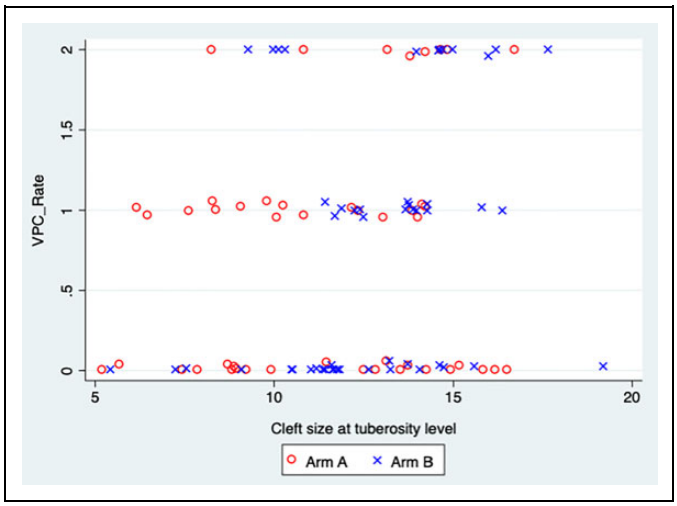

Figure 3. Correlation analysis of velopharyngeal competence (VPC)-Rate and posterior cleft dimension at tuberosity level for Arm A (hard palate closure at 12 Months) and Arm B (hard palate closure at 36 Months). One-millimeter increase in cleft size at tuberosity arm B had 17% higher odds to receive a worse VPC-Rate score than arm A. Odds ratio = 1.17; confidence interval = 1.01 to 1.35; $P = .032$.

As shown in Table 1, cleft size at tuberosity level was the only covariate that changed the odds ratio (OR) of Arm B/Arm A: from 1.12 (confidence interval [CI]: 0.53-2.35) to 0.88 (CI: 0.40-1.92). Indeed, the role of the covariate was significant (OR 1.17; CI: 1.01-1.35; $P = .032$), even if the difference between the 2 surgical groups in the adjusted analysis remained nonsignificant ($P = .747$).

The hypothesis of same effect of all covariates in the surgical groups could not be rejected as all P values were larger than .05 (parallelism assessment). The complete results of the adjusted analysis can be found in Table 1.

Attempting to introduce cutoff points, we found that clefts posteriorly larger than 9 mm had 2.25 (CI: 1.20-3.31) higher odds for developing VPI (change from competent or marginally competent to incompetent). However, these patients merely accounted for 18% of the sample as reported in Table 2.

Association of VPC-Sum (VPC-Pooled and VPC-Dichotomous) and Infant Cleft Dimensions

The summary score of VPI symptoms (hypernasality, passive cleft speech characteristics, and active cleft speech characteristics) on a 6-point scale showed a moderate, negative association between "arch length" at infancy and scoring ($P = .004$; Spearman $\rho = -.27$). Again, the association was slightly stronger for the group that received hard palate closure at 36 months (Arm B; $P = .008$; Spearman $\rho = -.35$).

These results were confirmed by the VPC-Pooled score ($P = .016$; Spearman $\rho = -.23$), in particular for Arm B ($P = .015$; Spearman $\rho = -.32$). As the number of categories for this scale was limited to 3, ordinal regression analysis was considered appropriate, and analysis confirmed a significant role for the covariate "arch length" (OR: 0.82; CI: 0.69-0.98; $P = .026$).

Table 2. Tabulation With Raw Percentages of Posterior Cleft Size Dichotomized at 9 mm and VPC-Rate.

	VPC-Rate			
	0	1	2	Total
Posterior cleft size (tt′)				
≥9 mm	12 (12.2%)	5 (5.10%)	1 (1.1%)	18 (18.4%)
<9 mm	34 (34.7%)	27 (27.6%)	19 (19.4%)	80 (81.6%)
Total	46 (46.9%)	32 (32.7%)	20 (20.4%)	98 (100%)

Abbreviations: VPC, velopharyngeal competence.

The complete results of the adjusted analysis are reported in Table 3.

Finally, no difference between surgical arm A and arm B was revealed using the VPC-Dichotomous scale, but again the covariate "arch length," describing maxillary length at infancy, played a significant role in the logistic regression ($P = .039$).

Other Findings

Two patients had received pharyngeal surgeries (1 in Arm A and 1 in Arm B) and 1 patient other secondary surgery (arm A) before assessment. Nine participants were diagnosed with unrepaired fistulas before assessment (6 in Arm B and 3 in Arm A). In an explorative secondary analysis, those individuals were excluded from the data. The results did not change for any of the outcome variables, and therefore, those participants were reincluded to preserve randomization in the study design.

In an additional analysis, results were also stratified for operator, and the surgeons for stage I and stage II were introduced as covariates. No effect of those covariates could be assessed, and therefore, they were removed from the model (stepwise backward regression).

Discussion

Our findings support a modest association between presurgical cleft size in the posterior palatal regions and risk of secondary VPD at age 5. We also found that a longer maxilla apparently acts as a protective factor in relation to subsequent velopharyngeal function, although the association was weak.

Few studies investigating this association are available in the literature: Our results corroborate previous findings, but the association was noticeably weaker than reported by other authors.

In a retrospective analysis of isolated cleft palates, Lam and coauthors (2012) found an increased risk of VPI for clefts exceeding 10 mm, also after adjusting for cleft length, age at surgery, and presence of a syndrome. Although our investigation corroborates the results of Lam and coworkers, our effect size was smaller. Indeed, the results of the study by Lam et al should be interpreted with caution, since speech results were missing in 27% and no information was provided about criteria for presence or absence of VPI. In addition, VPI assessment was based on retrospective records from 1 of 2 SLTs from the

Table 3. Results of the Ordinal Logistic Regression Analysis to Estimate the Association Between VPC-Pooled and Covariates Describing Cleft Size and Morphology.[a]

	VPC-Pooled						
	Surgery			Covariate[b]			Parallelism Assessment[c]
Covariate	$OR_{B/A}$	95% CI	*P*	OR	95% CI	*P*	*P*
None	1.16	0.54-2.51	.691	-	-	-	-
Cleft size at anterior level (GL), mm	1.09	0.50-2.38	.824	0.91	0.82-1.00	.058	.956
Cleft size at canine level (cc′), mm	1.14	0.53-2.48	.730	0.93	0.85-1.02	.148	.972
Cleft size at molar level (mm′), mm	1.16	0.54-2.53	.696	1.00	0.88-1.14	.978	.485
Cleft size at tuber level (tt′), mm	1.09	0.50-2.39	.821	1.06	0.93-1.21	.368	.448
Cleft surface, mm^2	1.18	0.55-2.56	.663	1.00	0.99-1.00	.662	.177
Palatal surface, mm^2	1.22	0.56-2.65	.612	1.00	0.99-1.00	.089	.573
3DICSR, %	1.16	0.54-2.50	.709	1.03	0.98-1.08	.696	.189
Arch length, mm	1.24	0.57-2.71	.580	0.82	0.69-.98	.026	.319
Arch perimeter, mm	1.23	0.57-2.68	.592	0.97	0.91-1.03	.302	.524

Abbreviations: CI, confidence interval; OR, odds ratio; n.s., the CI indicates that the difference between the surgical groups is nonsignificant; VPC, velopharyngeal competence.

[a] Without adjustment for cleft dimensions (covariate: none) patients in surgical arm B had 16% (95% CI: 0.54-2.51 n.s.) higher odds to receive a worse VPC-Pooled score than patients in surgical arm A. After adjustment for anteroposterior arch length, arm B presented 24% (95% CI: 0.57-2.71 n.s.) higher odds than arm A. The change in OR indicates a significant role of the covariate, arch length: OR = 0.82, 95% CI = 0.69 to 0.98.

[b] OR gives the odds ratio for a VPC-Rate category change (averaged) associated with 1 unit increase in the covariate.

[c] The *P* value results from testing the hypothesis of the same effect of the covariate in each group.

same center. Furthermore, palatal repair was performed at 8 to 30 months of age, which may have affected the results, as later palatal closure may be associated with higher VPI prevalence (Marrinan et al., 1998; Chapman et al., 2008). Moreover, the difference in results may be explained in light of the different cleft subtypes and patients' age at the time of cleft size measurements.

A recent retrospective study on consecutive patients treated by a single operator over a 2-year period reported an association between hypernasality and speech delay with increased cleft palate width (Wu et al., 2017). These results suffer from a high dropout rate (almost 40%), a wide age range at follow-up (approximately 16 months to 5 years of age), and complete lack of any information regarding speech outcomes and assessment procedures.

Good practice for speech evaluation includes use of audio-recorded speech samples, participants with a small age range, reporting of interrater and intrarater reliability, standardized speech material and assessment procedures, and inclusion of at least 2 blinded raters not involved in the treatment (Sell, 2005; Britton et al., 2014; Lohmander et al., 2017a).

The VPC-Sum used in this study is a composite measure including the main symptoms of VPD: hypernasality, passive VPI symptoms, and nonoral errors (Dotevall et al., 2001). As it has been previously documented that velopharyngeal closure is significantly reduced with some of the active nonoral articulations (Henningsson and Isberg, 1986), it can be argued that inclusion of nonoral errors might artificially increase the occurrence of VPD. Nonoral errors were included as they are regarded as occurring because of VPD (Hutters and Brondsted, 1987; Harding and Grunwell, 1998), and speech outcome of the 5-year-olds in the Scandcleft project supported this association (Willadsen et al. 2017). Furthermore, a validity study of the VPC-Sum by Lohmander and coworkers (2017a) showed the VPC-Sum is a reliable estimate of the overall assessment of velopharyngeal function (the VPC-Rate), in agreement with previous findings of composite velopharyngeal scores (Dotevall et al., 2002). Lohmander and co-authors (2017a) reported significant positive correlations between the VPC-Sum and each of the associated variables, which means the VPC-Sum has high *content validity*. Although nonoral errors showed the lowest correlation (Cronbach α 0.55, $P < .001$), the correlation was significant.

To consider the possible influence of nonoral errors in the present study, we examined data for the 16 of 106 Danish Scandcleft participants who produced 3 or more nonoral errors, as this influenced the VPC-Sum calculation. Only one of these participants had no other passive VPI symptoms than nonoral errors (3 active nasal fricatives) to support the presence of VPD. However, the VPC-Rate for this participant was assessed as marginally competent, which is in line with the VPC-Sum result, which also classified as marginally competent.

For the remaining 15 participants, nonoral errors always occurred in the presence of at least 1 of the 2 remaining components of the VPC-Sum, hypernasality and passive VPI symptoms. On the VPC-Rate, these participants were assessed as follows: 11 as incompetent, 4 as marginally competent, and 1 as competent. The competent child, based on the VPC-Rate, produced 6 active nasal fricatives and was assessed as mildly hypernasal on the 9-word string. Accordingly, the data from the

16 participants with at least 3 nonoral errors support that, for the present study, nonoral errors did not inflate VPD assessments artificially.

It can be considered a strength of our study that it was conducted as a subgroup analysis within the context of the Scandcleft RCT. This allowed us to take advantage of the homogeneity of the surgical team, randomization of the surgical methods, standardization of speech material with reproducible and validated assessment (Lohmander et al., 2017a), and robust 3D morphometric analysis of the cleft space (Botticelli et al., 2018).

We found no difference in VPC results between early (Arm A) and delayed (Arm B) hard palate closure (DHPC), either in the included subgroups or in the entire trial (Trial 1).

The absence of any differences makes a compelling argument for studying cleft dimension covariates in an attempt to determine whether cleft size and morphology predict speech outcomes.

The fact that the Scandcleft results at age 5 revealed no association between timing of hard palate closure and VP function tallies with findings reported by Lohmander and coworkers in a retrospective longitudinal study. In their study, 26 participants who received DHPC at different ages (38-89 months) were followed for velopharyngeal function; interestingly, in this study, no association between DHPC and VPI could be shown, but persistency of a hard palate residual cleft was associated with nasal escape and retracted oral articulation of anterior consonants (Lohmander et al., 2006).

The challenges associated with the surgical procedures invite a hypothesis concerning the correlation between wider posterior clefts and VPC. Hence, wider clefts command more extensive dissection to mobilize tissues and achieve ideal tension-free closure, or operating areas have to be left raw which will entail increased scarring during healing. Contraction of the scars or simply difficulty in lengthening the velum may lead to a larger velopharyngeal gap.

Future studies applying new methodologies such as functional dynamic magnetic resonance imaging for the evaluation of the velopharyngeal space and perhaps intraoral scanning to acquire direct information about intraoral cleft dimensions will add further knowledge about the relation of preoperative cleft severity and velum length and function.

Similar clinical explanations have been proposed in several studies describing the association of cleft width with surgical outcome and have been used as arguments for choosing one surgical technique over another (Landheer et al., 2010; Lin et al., 2015). In the majority of observational studies, this may represent a methodological flaw in itself because patients were often clustered for the type of surgery performed in relation to dimensions of the cleft.

This methodological bias is not present in the Scandcleft Trial 1 because all patients were operated with the same technique and sequence of closure and were randomized for timing. The technique applied was a modification of the one that has been used in Gothenburg for many years (Lohmander et al., 2012), involving a posteriorly based vomer flap and muscular soft palate reconstruction, followed by a second phase to close the hard palate. Details about the modification of the original technique and surgical steps have been explained in the 5-year surgical report (Rautio et al., 2017). Since this method starts with closure of the posterior regions of the cleft, it can well be imagined why outcomes are influenced by posterior cleft dimensions. However, despite its statistical significance, the strength of the association remains weak. Furthermore, the definition of a large cleft has to be considered in relation to relative dimensions of the greater and lesser segment providing tissue available for repair. However, in our analysis, 3DICSR did not play a significant role as covariate, probably due to the fact that this ratio is also influenced by anterior cleft dimensions and cleft dimensions in the central palate.

The present study shows a rather high prevalence of VPD in the sample and a relatively small effect size of the associations. Based on our findings, we do not consider cleft size to be a sufficiently strong VPI predictor to warrant a change in clinical protocols or sufficient justification for changing the information given to parents and caregivers. A large cleft in infancy does not mean that the child will necessary develop VPI or require secondary surgery, as much as a smaller cleft or a longer maxilla does not protect against that. Other factors such as surgical skills, speech therapy, size of the hard palate residual cleft, individual healing pattern with possibility of establishing a functional muscular sling, and individual adaptation capacity to the anatomical condition could play an important role as well.

Limitations

The major limitation of the present study is that we examined 1-point time speech registration at age 5 years, while long-term follow-up is needed to establish firmly the long-term interaction of surgery and cleft severity on speech. We have planned to do follow-up registrations on the same sample, but the role of secondary pharyngeal surgeries will have to be considered as well to understand the new anatomical boundaries housing individual velopharyngeal function. Longitudinal evaluations are needed to assess if larger clefts could be associated with increased incidence of dehiscence and need for secondary surgeries.

Furthermore, speech therapy interventions will also have to be considered in relation to speech outcomes, burden of care, and influence on the functional adaptation of the child with a unilateral cleft.

Conclusions

Patients born with UCLP with large posterior clefts, operated according to a protocol with simultaneous closure of the lip and soft palate, presented a modestly increased risk of secondary VPI independent of the timing of hard palate closure. Increased length of the maxilla, implying less tissue deficiency, seemed to be a protective factor.

Considering the weak association of cleft severity and maxillary length with velopharyngeal dysfunction and the high prevalence of VPI in the sample, our findings showed that cleft size and maxillary length may be indicators but cannot be considered certain, lone predictors of the individual's risk of developing VPI.

Authors' Note

The Scandcleft protocol (Trial reg. no: ISRCTN29932826) was approved by the Central Denmark Regional Committee on Health Research (journal number: 1997/4121). Parental informed consent was signed for all patients included, and permission to use the participants' registrations and charts was obtained from the Data Protection Agency (n.1-16-02-616-15). Trial ID random numbers were used for identification of the participants to secure anonymization. The study abides by the principles outlined in the Declaration of Helsinki and its later amendments or comparable ethical standards.

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