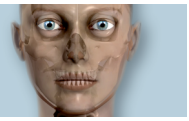
Orthodontics & Craniofacial Research



ORIGINAL ARTICLE

C. B. Staudt
W. M. Gnoinski
T. Peltomäki

Upper airway changes in Pierre Robin sequence from childhood to adulthood

Authors' affiliations:
C. B. Staudt, W. M. Gnoinski, Cleft Lip and Palate Unit, Clinic of Orthodontics and Pediatric Dentistry, Center of Dental Medicine, University of Zurich, Zurich, Switzerland
T. Peltomäki, Oral and Maxillofacial Unit, Department of Ear and Oral Diseases, Tampere University Hospital, Tampere, Finland; Department of Otorhinolaryngology, University of Tampere, Tampere, Finland

Correspondence to:
Dr Christine B. Staudt
Cleft Lip and Palate Unit
Clinic of Orthodontics and Pediatric Dentistry
Center of Dental Medicine
University of Zurich
Plattenstrasse 11
CH-8032 Zurich
Switzerland
E-mail: christine.staudt@zzm.uzh.ch

Date:
Accepted 30 December 2012

DOI: 10.1111/ocr.12019

Staudt C. B., Gnoinski W. M., Peltomäki T. Upper airway changes in Pierre Robin sequence from childhood to adulthood
Orthod Craniofac Res 2013; 16: 202–213. © 2013 John Wiley & Sons A/S. Published by Blackwell Publishing Ltd

Structured Abstract

Objectives – To investigate pharyngeal airway changes in patients with Pierre Robin sequence (PRS) longitudinally from childhood to adulthood.

Setting and Sample Population – Cleft Lip and Palate Unit, Clinic of Orthodontics, University of Zurich. Twenty-four patients born between 1970 and 1990 with non-syndromic PRS.

Materials and Methods – Lateral cephalograms at age 5 (T1), 10 (T2), 15 (T3) and 20 (T4) years were available. Variables describing pharyngeal airway dimensions, soft palate morphology, tongue and hyoid position, skeletal morphology and head posture were assessed.

Results – A significant increase in nasopharyngeal depth was found over the entire observation period (T1 10.7 to T4 19.1 mm, $p < 0.001$), especially between T2 and T3 (change 3.8 mm, $p < 0.001$), and was mainly due to adenoid recession ($r = -0.75$, $p < 0.001$; variation explained by 56%). Increase in velopharyngeal depth mainly took place between T3 and T4 (change 2.3 mm, $p < 0.01$). It was due to more anterior tongue posture ($r = 0.65$, $p < 0.001$; 42.5% of variation explained), in turn allowing the soft palate to take a more vertical position ($r = -0.52$, $p < 0.001$). Increase in oropharyngeal depth was associated with head extension and anterior mandibular positioning (36% of variation explained). However, significance was not reached (T1 8.3 to T4 9.8 mm, $p > 0.05$).

Conclusions – Upper airway dimensions in children with PRS improve with time, except for the oropharyngeal airway. Despite large interindividual variation, the mean remained in the lower reaches of normality described in other studies. Thus, further research should investigate the prevalence of obstructive sleep apnoea in adults with PRS.

Key words: airway; cephalometry; child; longitudinal; Pierre Robin sequence

Introduction

One child of 14 000 is born with Pierre Robin sequence (PRS) (1), which is defined by mandibular retro-/micrognathia, glossoptosis, cleft palate and varying degree of respiratory distress. In this sequence, mandibular retro-/micrognathia is often considered the primary cause, leading to glossoptosis, thus inhibiting the fusion of the palatal shelves (2, 3). The respiratory difficulties at birth are mainly due to obstruction of the oropharyngeal airway by posterior displacement of the tongue base. As a consequence of retro-/micrognathia, the tongue lies more posteriorly and so does the mandibular origin of the genioglossus muscle. Consequently, this muscle is less effective in protruding the tongue and holding it actively out of the pharyngeal airway (4).

It is postulated that neuromuscular immaturity, in the form of hypotonia or lack of coordination, can interplay with the described anatomic anomalies (4). Neurophysiological findings suggest dysfunction not only of the lingual but also of the pharyngeal motor organization in patients with isolated PRS (5). In these cases, resistance of the genioglossus and the parapharyngeal muscles is inadequate in maintaining pharyngeal patency against the high inspiratory negative pressures (6). As shown by nasopharyngoscopy, narrowing of the oropharynx in patients with PRS can occur by glossoptosis as well as by collapse of the pharyngeal wall (7). Any narrowing of the airway increases resistance to the inspiratory airflow and negative pressure in the pharynx, which leads to further posterior pull on the tongue, collapse of the pharyngeal muscles and increasing airway obstruction. Clinically, heavy breathing becomes noticeable with substernal retractions and stridor (unless there is complete obstruction) (8). Even in the absence of clinical signs of airway obstruction such as snoring, obstructive sleep apnoea (OSA) has been detected via polysomnography in infants with PRS (9). In addition to hypoxia, airway obstruction results in feeding difficulties and failure to thrive, because the calories necessary for adequate weight gain are mainly spent in the respiratory effort (8).

In newborns with PRS, vital problems such as severe respiratory distress and feeding difficulties have to be resolved as early as possible. Careful evaluation and management of airway obstruction are essential to prevent long-term neurologic and cardiovascular sequelae (10). Depending on the severity of the condition and on the preferences of the multidisciplinary medical team, treatment options greatly differ, including prone positioning, palatal plate insertion (11, 12), nasopharyngeal or endotracheal intubation, tongue–lip adhesion, tracheostomy and mandibular distraction osteogenesis. Based on endoscopy, the site of airway obstruction can be defined and management options can be targeted to the specific deficiency. When airway obstruction occurs at the base of the tongue, as in most children with PRS, prone positioning, tongue–lip adhesion and mandibular distraction are advocated in ascending order. When obstruction occurs below the base of the tongue (e.g. tracheomalacia), tracheostomy may become an option (13). In a recent investigation, 49% of patients with PRS were found to require non-surgical or surgical airway intervention beyond prone positioning (14).

During infancy, the respiratory distress seems to resolve naturally, due to a dramatic increase in the airway dimensions in the first 2 years of life (3.5 times its original size) (15). This improvement has been attributed to an accelerated mandibular growth rate, combined with slower relative growth of the tongue and more anterior tongue posture (15). However, normal dimensions are not attained (15), and to the best of our knowledge, it has yet to be investigated how the airway dimensions of patients with PRS develop beyond infancy. Therefore, the aim of this study was to investigate pharyngeal airway changes in patients with PRS longitudinally from childhood to adulthood.

Materials and methods

Subjects

All children born with non-syndromic PRS between 1970 and 1990 and treated at the Uni-

Table 1. **Sample description**

	T1			T2			T3			T4		
	N	Age (mean)	SD	N	Age (mean)	SD	N	Age (mean)	SD	N	Age (mean)	SD
Male	10	5.0	0.2	10	9.8	0.4	10	15.3	0.7	9	20.3	2.5
Female	14	5.3	0.5	14	10.1	0.4	13	15.2	0.4	10	19.8	0.1
Total	24	5.2	0.4	24	10.0	0.4	23	15.2	0.6	19	20.0	1.7

versity Clinics in Zürich were selected for the study (n = 38). The diagnostic criteria for PRS were mandibular retro-/micrognathia, cleft palate and respiratory difficulties caused by glossoptosis in the neonatal period. All newborns with PRS were hospitalized in highly specialized clinics with neonatal care units, where oxygen saturation was continuously monitored.

Exclusion criteria were associated syndromes (except for Stickler syndrome) or missing initial lateral cephalograms. Six patients with PRS were excluded from this study because major cerebral disturbances were detected later in infancy, which were in all probability not due to hypoxia, but part of unnamed dysmorphic syndromes. From the remaining 32 patients, eight were excluded because the initial (n = 4) or the total (n = 4) cephalometric documentation was missing. The complete inexistence of documentation can be explained by refusal of medical care in one patient and by remigration to their country of origin of three patients between the age of 0 and 5 years. Where only the initial documentation was missing, this was due to non-compliance or change of domicile. Thus, the final sample consisted of 24 patients with PRS (10 males, 14 females).

In all 24 patients with PRS, airway obstruction was managed by prone positioning and by insertion of an orthopaedic plate with a posterior extension, which obturates the whole length of the soft palate cleft back to the uvula (11). The plate holds the tongue out of the cleft and leads it to a more physiological forward position, thus eliminating glossoptosis and ensuring a free airway as well as facilitating spontaneous advancement of the mandible with suckling. Normal bottle feeding was possible within a few days to a few weeks (removal of gastric tube in 72% of the newborns within 3 weeks, in 79% within 4 weeks). Primary surgery was performed by one surgeon (Prof. M. Perko) according to the Zürich protocol, closing the soft palate according to Widmaier-Perko at the age of 18 months and the hard palate in a second intervention with a mucoperiosteal flap at the age of about 4 years. Velopharyngoplasty was necessary in two patients (one girl at 7 years and one boy at 5 years). None of the patients had adenoidectomy or functional orthodontic appliances, and the post-operative radiographs of those who underwent orthognathic surgery (n = 2) were excluded.

At the Cleft Unit in Zürich, orthodontic records including lateral cephalograms are taken routinely in every patient with PRS at the age of 5, 10, 15 and 20 years (T1, T2, T3 and T4, respectively). In 19 of the 24 patients, lateral cephalograms were available at each time point, in four patients, the 20-year cephalogram was missing (two patients did not show up and two patients had orthognathic surgery for class III) and one patient had refused the 15- and 20-year cephalogram (Table 1). However, the documentation is complete in 60% of the children born between 1970 and 1990 (78% between 1976 and 1990).

Analysis of lateral cephalograms

Lateral cephalograms were taken orientating the Frankfurt horizontal plane parallel to the floor. Tracings including point identification were performed manually on acetate paper, always comparing the structures on all cephalograms of one patient and checking for correctness by superimposition on stable structures of the cranial base. The tracings were scanned, and a cephalometric program (Viewbox version 3.1.1.14; dHAL Software, Kifissia, Greece) was

used to adjust for magnification and assess variables describing pharyngeal airway dimensions, soft palate morphology and angulation, the position of tongue and hyoid as well as skeletal morphology and head posture (Fig. 1).

Statistical analysis

Statistical analyses were performed with the Statistical Package for Social Sciences (version 18.0; SPSS, Chicago, IL, USA). The level of significance was set at $p < 0.05$. Normal distribution was verified (Kolmogorov–Smirnov), and descriptive statistics were performed. To detect differences between the four time points (T1, T2, T3, T4), two-way ANOVA was used, followed by *post hoc* LSD test. Correlations (Pearson's correlation coefficient) were calculated between airway dimensions and the soft and hard tissue variables. Multiple linear regression analysis was performed (stepwise) to determine the predictive value of a combination of those variables on the airway dimensions.

Error of method

To test reliability, one lateral cephalogram of every second subject was redigitized after at least 2 weeks by the same examiner. A paired *t*-test was performed for each pair of replicates to detect systematic error (16). The random error and the coefficient of reliability were calculated (17).

Results

Reliability

Systematic error was found for the smallest velopharyngeal depth (VP1-VP2; $p = 0.026$), for soft palate length (PNS-L; $p = 0.021$) and width (W1-W2; $p = 0.007$). The mean and SD for the first and second measurement for these variables were 5.43 (1.80) and 5.67 (1.82), 29.67 (2.88) and 29.38 (2.92), and 9.47 (1.27) and 9.80 (1.50) mm. The random errors ranged from 0.18 to 0.74 (AD3-H) mm for linear measurements and 0.48–0.96 (PNS-L/ANS-PNS) degrees for angular measurements. The coefficient of reliability was ≥ 0.95.

Pharyngeal airway

The range between minimum and maximum values (Table 2) as well as the curves connecting the four time points for every individual patient (Fig. 2) indicates large interindividual variation.

The variables describing the smallest naso- and velopharyngeal depth (NP1-NP2 and VP1-VP2) increased over the observation period, whereas the smallest oropharyngeal depth (OP1-OP2) remained fairly stable (Table 3). The soft pharynx between PNS and the adenoid deepened mainly between T2 and T3 (e.g. PNS-AD2 = 4.24 mm, $p < 0.001$) and also the adenoid decreased from T2 onwards, especially between T3 and T4 (e.g. AD2-SOS′ 1.68 mm, $p < 0.01$). Over all time periods, the soft palate increased in length (PNS-L) and from T2 to T3 slightly in thickness (W1-W2; 0.73 mm, $p < 0.05$). The angle between soft and hard palate (PNS-L/ANS-PNS) became more acute from T2 onwards (T2-T3 and T3-T4 −3.3°, $p < 0.05$, respectively). The superior point of the tongue moved more anteriorly, as indicated by the increasing distance to the vallecula (V-ST). Head posture was stable at all four time points (e.g. NS/CVT $p = 0.36$).

Correlations and regression

Increase in mandibular length (Go′-Pog, Ar-Pog) or forward mandibular positioning (SNB) correlated with decrease in soft/hard palate angulation (PNS-L/ANS-PNS; $r = -0.49$, -0.58, -0.55, respectively, $p < 0.001$) and this, in turn, with an increase in the smallest velopharyngeal airway depth (VP1-VP2; $r = -0.36$, $p < 0.001$; Table 4). Regression of the adenoid (e.g. AD3-H) was associated with an increase in nasopharyngeal depth (NP1-NP2; $r = -0.75$, $p < 0.001$) and velopharyngeal depth (VP1-VP2; $r = -0.39$, $p < 0.001$) as well as to a more acute angulation of the soft palate (PNS-L/ANS-PNS; $r = 0.30$, $p < 0.01$). More anterior posture of the superior point of the tongue (V-ST) was correlated with decrease in soft/hard palate angulation (PNS-L/ANS-PNS; $r = -0.52$, $p < 0.001$) and increase in the nasopharyngeal (NP1-NP2; $r = 0.68$, $p < 0.001$), velopharyngeal (VP1-VP2; $r = 0.65$, $p < 0.001$) and oropharyngeal

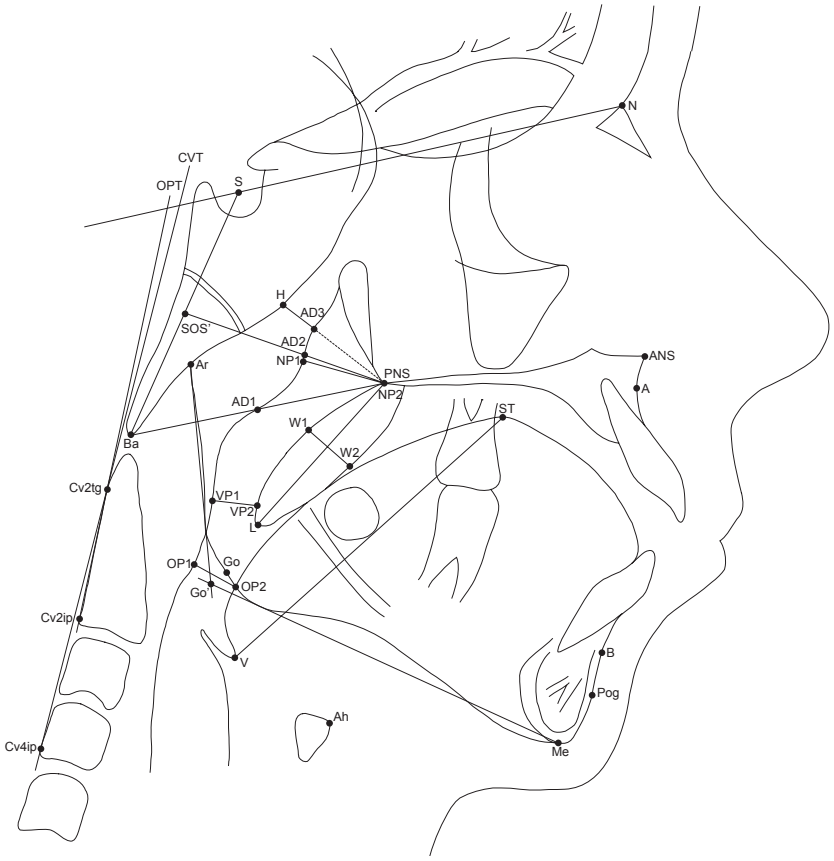


Fig. 1. Landmarks digitized on the lateral cephalograms. *Definition of landmarks:* A, A-point; AD1, intersection of PNS-Ba with adenoid tissue; AD2, intersection of PNS-SOS′ with adenoid tissue; AD3, intersection of PNS-H with adenoid tissue; Ah, anterosuperior point on the hyoid; ANS, anterior nasal spine; Ar, articulare; B, B-point; Ba, basion; Cv2ip, posteroinferior point on the corpus of the 2nd cervical vertebra; Cv2tg, dorsal contour of the odontoid process of the 2nd cervical vertebra; Cv4ip, posteroinferior point on the corpus of the 4th cervical vertebra; Go, gonion; Go′, gonion′; H, hormion (intersection of posterior border of vomer and body of sphenoidale); L, soft palate tip; Me, menton; N, nasion; NP1, point on the adenoid tissue where the distance to PNS or to the intersection of the prolongation of ANS-PNS with the soft palate (nasopharyngeal depth) is smallest; NP2, PNS or intersection of the prolongation of ANS-PNS with the soft palate; OP1, point on the posterior pharyngeal wall where the distance to the tongue base (oropharyngeal depth) is smallest; OP2, point on the tongue base where the distance to the posterior pharyngeal wall (oropharyngeal depth) is smallest; PNS, posterior nasal spine; Pog, pogonion; S, sella; SOS′, halfway S-Ba; ST, superior point of tongue; V, vallecula (depression behind root of the tongue); VP1, point on the posterior pharyngeal wall where the distance to the soft palate (velopharyngeal depth) is smallest; VP2, point on the soft palate where the distance to the posterior pharyngeal wall (velopharyngeal depth) is smallest; W1, point on nasal soft palate surface where soft palate is widest; W2, point on oral soft palate surface where soft palate is widest. *Measurements between landmarks:* Soft pharynx depth: NP1-NP2 (smallest nasopharyngeal depth); VP1-VP2 (smallest velopharyngeal depth); OP1-OP2 (smallest oropharyngeal depth); PNS-AD1; PNS-AD2. Adenoid depth: AD1-Ba; AD2-SOS′; AD3-H. Bony pharynx depth: PNS-Ba; PNS-SOS′. Soft palate: *length:* PNS-L; *width:* W1-W2; *soft/hard palate angulation:* PNS-L/ANS-PNS. Tongue posture: V-ST. Hyoid position: S-Ah. Mandible: *position:* SNB; *length:* Go′-Pog; Ar-Pog. Vertical skeletal relations: SN/Go-Me; ANS-PNS/Go-Me. Head posture: NS/OPT (OPT, odontoid process tangent = Cv2tg-Cv2ip); NS/CVT (CVT, cervical vertebra tangent = Cv2tg-Cv4ip).

depths (OP1-OP2; $r = 0.33$, $p < 0.01$). Extension of the head (NS/OPT, NS/CVT) correlated with increase in the oropharyngeal depth (OP1-OP2; $r = 0.42$ and 0.43, $p < 0.001$).

Using multiple linear regression analysis, a model containing the size of the adenoid (AD3-H, AD2-SOS′), mandibular length (Go′-Pog, Ar-Pog) and soft/hard palate angulation (PNS-L/ANS-PNS) as independent variables was found to explain 82% of the variation in the smallest nasopharyngeal airway depth (NP1-NP2; Table 5). In the case of smallest velopharyngeal depth (VP1-VP2) 46% (independent variables: tongue posture V-ST and adenoid depth AD1-Ba) and in the case of smallest oropharyngeal depth (OP1-OP2) 36% (independent variables: head posture NSL/OPT, mandibular positioning SNB) of the variation was explained.

Table 2. **Descriptive statistics at the four time points**

	T1				T2				T3				T4			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Soft pharynx depth																
NP1-NP2	10.70	3.18	5.96	17.02	13.13	3.34	6.27	21.05	16.92	4.58	4.57	24.90	19.06	3.50	12.49	24.89
VP1-VP2	4.26	2.48	0.00	8.98	5.87	2.90	1.17	13.14	6.53	2.85	2.08	12.58	8.78	4.00	3.68	19.54
OP1-OP2	8.34	2.25	3.70	12.80	8.83	4.47	2.82	19.59	7.70	2.80	3.42	12.67	9.83	4.16	4.51	20.35
PNS-AD1	15.83	4.52	6.83	23.32	18.25	4.75	8.20	26.52	21.12	4.62	13.37	29.29	23.14	4.49	13.76	32.49
PNS-AD2	11.24	3.09	5.96	16.97	13.71	3.36	6.29	21.06	17.95	3.96	10.71	25.36	20.54	3.60	13.22	26.98
Adenoid depth																
AD1-Ba	24.34	4.17	14.54	32.06	23.95	4.71	14.55	33.76	23.39	4.30	14.36	30.65	22.57	4.53	16.08	34.73
AD2-SOS′	22.11	2.79	15.90	28.79	21.99	2.81	15.29	28.09	20.47	3.62	13.32	26.63	18.79	3.10	12.37	23.71
AD3-H	11.54	3.59	4.61	19.03	11.33	3.46	4.21	18.66	9.62	4.51	2.55	20.35	7.14	3.09	0.00	14.17
Bony pharynx depth																
PNS-Ba	40.17	2.74	36.23	47.01	42.20	2.98	37.32	48.38	44.51	4.04	37.26	52.93	45.71	4.68	35.56	55.74
PNS-SOS′	33.36	1.88	30.01	36.58	35.70	2.14	31.84	40.32	38.42	2.71	33.51	43.28	39.34	3.17	33.21	45.99
Soft palate																
PNS-L	26.38	2.88	21.48	30.60	28.74	3.28	22.54	34.74	32.12	3.38	24.19	38.28	33.66	3.21	26.82	38.84
W1-W2	8.64	1.23	5.98	10.64	8.98	1.24	6.54	11.83	9.72	1.17	7.23	11.90	10.04	1.40	6.56	12.59
PNS-L/ANS-PNS	134.29	7.17	124.74	155.88	132.52	8.01	120.47	148.08	129.20	6.89	112.06	141.38	125.85	6.24	114.65	134.72
Tongue posture																
V-ST	48.64	5.02	40.12	58.03	57.88	5.11	50.25	67.53	64.62	6.94	52.14	74.69	70.35	9.29	56.38	86.74
Hyoid position																
S-Ah	81.36	6.29	69.03	98.67	94.22	8.05	80.67	119.07	108.45	8.51	92.13	124.05	111.62	10.30	93.70	135.10
Head posture																
NS/OPT	108.96	9.44	85.10	124.77	111.89	12.12	86.94	138.60	108.21	8.86	88.72	123.65	110.24	9.19	91.02	122.15
NS/CVT	110.47	8.86	92.37	129.11	114.94	12.17	86.92	141.58	111.06	8.80	91.47	125.60	113.60	8.28	97.31	127.03

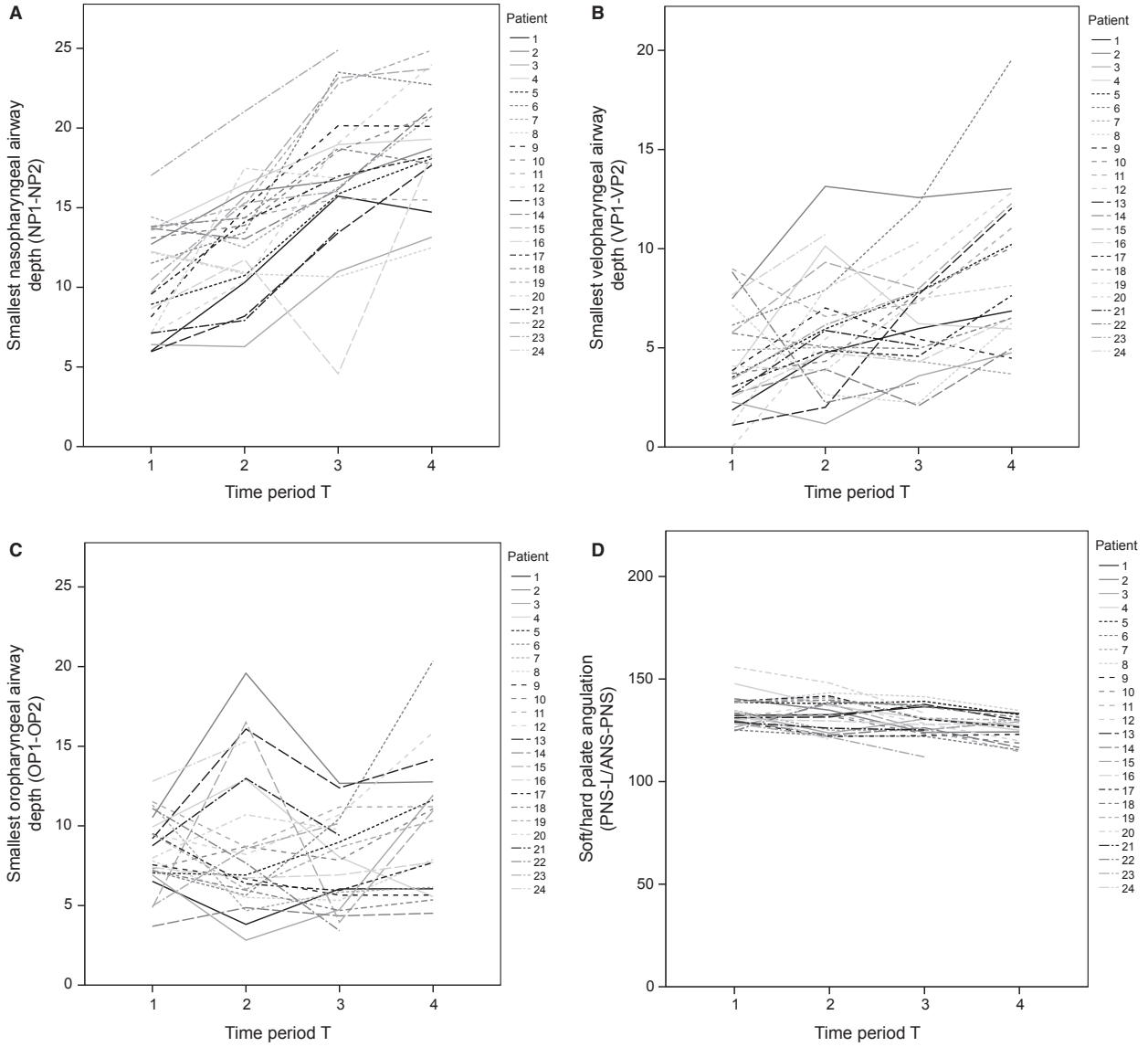


Fig. 2. Curves connecting time points T1, T2, T3 and T4 for every patient separately, exemplarily for the smallest (A) naso (NP1-NP2)-, (B) velo (VP1-VP2)-, (C) oropharyngeal (OP1-OP2) airway depth and (D) the soft/hard palate angulation (PNS-L/ANS-PNS).

Discussion

Despite the initial respiratory difficulties in newborns with PRS, regular breathing is usually established in the neonatal period. According to the literature (15), during the first 2 years of infancy, the oropharyngeal airway depth increases dramatically, from 2.9 mm at 2.8 months to 7.2 mm at 11.0 months and to 8.9 mm at 21.5 months; age-related normality (11.4 mm), however, is not reached at this age. As demonstrated by the present study, further increase is associated with head extension and a more anterior mandibular position. However, through childhood (5 years: 8.3 mm; 10 years: 8.8 mm) and adolescence (15 years: 7.7 mm) until adulthood (20 years: 9.8 mm), the increase in oropharyngeal depth did not reach statistical significance. The mean in our PRS sample remained below that found in a study with 'normal' subjects from the same geographic area (18), where no significant increase had been observed either in the same age bracket (10 years: 10.0 mm; 15 years: 9.8 mm; 22 years: 10.4 mm). Similarly, in Finnish adults with PRS (19), the

Table 3. **Longitudinal mean changes, tested for significance by two-way ANOVA (1) and post hoc LSD test (2)**

		T2-T1		T3-T2		T4-T3		T3-T1		T4-T1		T4-T2	
	p (1)	Mean change	*p* (2)	Mean change	*p* (2)	Mean change	*p* (2)	Mean change	*p* (2)	Mean change	*p* (2)	Mean change	*p* (2)
Soft pharynx depth													
NP1-NP2	0.000	2.43	**	3.79	***	2.14	**	6.22	***	8.36	***	5.93	***
VP1-VP2	0.000	1.61	*	0.67	n.s.	2.25	**	2.27	**	4.52	***	2.91	***
OP1-OP2	0.078	0.49	n.s.	−1.13	n.s.	2.13	n.s.	−0.64	n.s.	1.50	n.s.	1.00	n.s.
PNS-AD1	0.000	2.42	**	2.87	***	2.02	*	5.30	***	7.32	***	4.89	***
PNS-AD2	0.000	2.46	***	4.24	***	2.59	***	6.71	***	9.30	***	6.84	***
Adenoid depth													
AD1-Ba	0.019	−0.39	n.s.	−0.57	n.s.	−0.82	n.s.	−0.96	n.s.	−1.78	**	−1.39	*
AD2-SOS′	0.000	−0.12	n.s.	−1.52	**	−1.68	**	−1.65	**	−3.32	***	−3.20	***
AD3-H	0.000	−0.22	n.s.	−1.71	**	−2.47	***	−1.93	**	−4.40	***	−4.18	***
Bony pharynx depth													
PNS-Ba	0.000	2.03	***	2.31	***	1.20	n.s.	4.34	***	5.54	***	3.51	***
PNS-SOS′	0.000	2.34	***	2.72	***	0.92	n.s.	5.06	***	5.98	***	3.64	***
Soft palate													
PNS-L	0.000	2.36	***	3.37	***	1.54	**	5.74	***	7.28	***	4.92	***
W1-W2	0.000	0.34	n.s.	0.73	*	0.32	n.s.	1.08	***	1.40	***	1.05	**
PNS-L/ANS-PNS	0.000	−1.77	n.s.	−3.33	*	−3.34	*	−5.10	***	−8.44	***	−6.67	***
Tongue posture													
V-ST	0.000	9.24	***	6.74	***	5.74	***	15.98	***	21.72	***	12.48	***
Hyoid position													
S-Ah	0.000	12.9	***	14.2	***	3.2	*	27.1	***	30.3	***	17.4	***
Head posture													
NS/OPT	0.490	2.93	n.s.	−3.68	n.s.	2.02	n.s.	−0.75	n.s.	1.28	n.s.	−1.65	n.s.
NS/CVT	0.364	4.48	n.s.	−3.88	n.s.	2.54	n.s.	0.60	n.s.	3.14	n.s.	−1.34	n.s.

n.s., nonsignificant.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 4. **Correlation analysis of the smallest naso (NP1-NP2)-, velo (VP1-VP2)- and oropharyngeal (OP1-OP2) airway depths as well as the soft/hard palate angulation (PNS-L/ANS-PNS) with soft and hard tissue variables**

	NP1-NP2		VP1-VP2		OP1-OP2		PNS-L/ANS-PNS	
	Coefficient	*p*	Coefficient	*p*	Coefficient	*p*	Coefficient	*p*
Adenoid								
AD1-Ba	−0.48	***	−0.33	**	−0.12	n.s.	−0.07	n.s.
AD2-SOS′	−0.72	***	−0.46	***	−0.16	n.s.	0.21	*
AD3-H	−0.75	***	−0.39	***	−0.03	n.s.	0.30	**
Soft palate								
PNS-L	0.54	***	0.37	***	0.04	n.s.	−0.40	***
W1-W2	0.46	***	0.26	*	0.17	n.s.	−0.41	***
PNS-L/ANS-PNS	−0.27	**	−0.36	***	−0.09	n.s.		
Tongue								
V-ST	0.68	***	0.65	***	0.33	**	−0.52	***
Mandible								
SNB	0.35	***	0.34	**	0.21	*	−0.55	***
Go′-Pog	0.67	***	0.53	***	0.15	n.s.	−0.49	***
Ar-Pog	0.70	***	0.53	***	0.17	n.s.	−0.58	***
Vertical								
SN/Go-Me	−0.36	***	−0.31	**	−0.01	n.s.	0.38	***
ANS-PNS/Go-Me	−0.38	***	−0.30	**	0.01	n.s.	0.45	***
Head posture								
NS/OPT	−0.06	n.s.	0.07	n.s.	0.43	***	0.29	**
NS/CVT	−0.03	n.s.	0.08	n.s.	0.42	***	0.23	*

n.s., nonsignificant.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

lower pharyngeal depth was narrower than in normal controls [9.0 vs. 11.3 mm for females and 13.5 mm for males (20)].

For the nasopharyngeal airway depth, significant increase was observed throughout the entire study period, especially between age 10 and 15. This increase was mainly associated with adenoid recession (correlation up to $r = -0.75$; variation explained by 56%), which progressed until the age of 20 years. Compared to the Finnish PRS sample (19), the airway depth in our adult patients was hardly narrower (PNS-AD1 = 23.1 mm both; PNS-AD2 = 20.5 vs. 21.9 mm), although the adenoids were larger (AD1-Ba = 22.6 vs. 20.0 mm; AD2-SOS′ = 18.8 vs. 16.9 mm). In comparison with published normal data (21), the present 15-year-old patients with PRS had a narrower nasopharynx (PNS-AD1: 21.1 vs. 23.0 mm; PNS-AD2 = 17.9 vs. 19.5 mm) and more adenoidal tissue (AD1-Ba = 23.4 vs. 18.6 mm; AD2-SOS′ = 20.5 vs. 19.0 mm).

Increase in velopharyngeal airway depth took place mainly between 15 and 20 years and was mainly due to more anterior tongue posture ($r = 0.65$; 42.5% of variation explained), in turn allowing the soft palate from 10 years onwards to take a more vertical position. In the present PRS sample, increase in velopharyngeal depth from 15 to 20 years (2.25 mm) was over twice the amount found in a study with 'normal' subjects from the same geographic area (1.0 mm) (18). However, at all time points, depth of the velopharynx was lower in our PRS sample (10 years: 5.9 vs. 7.9 mm; 15 years: 6.5 vs. 8.3 mm; 20 vs. 22 years: 8.8 vs. 9.3 mm) (18).

It is to be emphasized that the results of the present investigation are based on mean values that do not necessarily reflect development in

Table 5. **Multiple linear regression analysis for longitudinal changes in the smallest naso (NP1-NP2)-, velo (VP1-VP2)- and oropharyngeal (OP1-OP2) airway depths (=dependent variables) and predictor variables, which entered in the model with significant F change**

	r^2 change	Coefficient B	SE	Sig.	Sig. *F* change
NP1-NP2					
(r^2 adjusted = 0.82)					
AD3-H	0.564	−0.30	0.13	0.03	0.00
Go′-Pog	0.194	0.05	0.08	0.54	0.00
PNS-L/ ANS-PNS	0.025	0.15	0.04	0.00	0.02
AD2-SOS′	0.020	−0.57	0.15	0.00	0.03
Ar-Pog	0.034	0.22	0.07	0.00	0.00
VP1-VP2					
(r^2 adjusted = 0.46)					
V-ST	0.425	0.20	0.03	0.00	0.00
AD1-Ba	0.050	−0.18	0.08	0.03	0.03
OP1-OP2					
(r^2 adjusted = 0.36)					
NS/OPT	0.188	0.23	0.04	0.00	0.00
SNB	0.193	0.52	0.13	0.00	0.00

the individual patient. Very large interindividual variation was found among patients with PRS, which might partly be due to the fact that males and females were analysed together. In the future, prospective intercentre studies providing sufficient patients for subtype analysis would be valuable, regrouping patients within the same diagnostic category and thus reducing interindividual variation.

Part of the observed variation in airway dimensions and the inconsistency of longitudinally assessed variables in several patients may depend on varying muscular tonus during radiograph taking, for example, due to breathing or swallowing. Especially variables describing dynamic structures as the tongue, the soft palate or the hyoid bone (VP1-VP2, V-ST, PNS-L/ANS-PNS, S-Ah) could be very different at any given moment. However, repeated radiograph taking in a previous study has shown high reproducibility for similar variables, as long as attention was given to head posture (22), which has also been stable in our sample.

Concerning tracing and measurement error, reliability in our study was good, although the boundaries for landmark identification were not always undoubtedly visible at first sight. The fact that we disposed of longitudinal cephalograms was probably helpful, allowing us to compare the structures on all cephalograms of one patient and also to corroborate accuracy by superimposition. Although all measured variables have been used in former studies and reliability has been tested (except for V-ST, PNS-L/ANS-PNS), information on validity exists only on few of them, whereby various gold standards were used. A systematic review (23) describes correlations of cephalometric velopharyngeal depth (VP1-VP2) with real adenoid volume ($r = -0.67$) and of adenoid depth (AD1-Ba) with subjectively graded adenoid size ($r = 0.57$). Three-dimensional imaging studies have found significant correlations of cephalometric nasopharyngeal (PNS-AD1, PNS-AD2) and velopharyngeal depths (VP1-VP2) with airway area on MRIs (up to $r = 0.49$) (24) as well as of oropharyngeal depth (OP1-OP2) with airway volume on CTs ($r = 0.92$) (25). Thus, despite the limitations of two-dimensional lateral cephalometry in depicting three-dimensional structures, lateral cephalograms are considered valid for measuring pharyngeal airway dimensions (24).

The oropharyngeal airway depth is of special interest in patients with PRS, given that in many patients, respiratory distress in the neonatal period is primarily due to airway constriction at the base of the tongue. In the present sample, this parameter did not increase significantly throughout development and remained below that found in a study with ‘normal’ adults from the same geographic area (9.8 vs. 10.4 mm) (18). It is well known that oropharyngeal airway depth is significantly narrower in patients with OSA than in those without (9.0 vs. 10.4 mm) (26). In addition, increase in soft palate thickness, as found in our patients with PRS [10.0 vs. 8.8 mm in controls from the literature (27)], seems to be a common characteristic in patients with OSA (10.6 vs. 9.5 mm in controls) (26). Thus, it would not be surprising if patients with PRS were more prone to OSA. In fact, there are publications to

this point, however, based on samples of infants with PRS, expressly referred to polysomnography (9, 28). Thus, systematic research is necessary to investigate the prevalence of OSA in adult patients with PRS.

Conclusions

Upper airway dimensions in patients with PRS improve from childhood to adulthood, although the original site of respiratory distress in most PRS newborns, that is, the oropharyngeal airway at the base of the tongue, was found to remain stable throughout development. Compared to the literature, the pharyngeal airway at all levels (naso-, velo- and oropharynx) remained in the lower reaches of normality. Further research might test the clinical relevance of these findings by investigating whether adults with PRS are particularly prone to suffering from OSA. However, the interindividual variation for the airway parameters examined was very large, thus limiting for the individual patient the weight of conclusions based on mean values.

Clinical relevance

Respiratory distress in newborns with PRS is caused by glossoptosis leading to obstruction of the oropharyngeal airway that can be life-threatening. In the first 2 years of life, the respiratory distress commonly resolves naturally due to dramatic increase in the airway dimensions. This study showed that upper airway dimensions increase until adulthood (except the oropharyngeal airway), but compared to the literature, they remain in the lower reaches of normality. Although a high interindividual variation was observed, the clinician should pay attention to a potentially increased risk of OSA in the individual adult patient with PRS.

Acknowledgement: We thank Mrs. R. Gilbert for the scanning of the tracings.

References

1. Printzlau A, Andersen M. Pierre Robin sequence in Denmark: a retrospective population-based epidemiological study. *Cleft Palate Craniofac J* 2004;41:47–52.
2. Hanson JW, Smith DW. U-shaped palatal defect in the Robin anomalad: developmental and clinical relevance. *J Pediatr* 1975;87:30–3.
3. Schubert J, Jahn H, Berginski M. Experimental aspects of the pathogenesis of Robin sequence. *Cleft Palate Craniofac J* 2005;42:372–6.
4. Sher AE. Mechanisms of airway obstruction in Robin sequence: implications for treatment. *Cleft Palate Craniofac J* 1992;29:224–31.
5. Renault F, Flores-Guevara R, Soupre V, Vazquez MP, Baudon JJ. Neurophysiological brainstem investigations in isolated Pierre Robin sequence. *Early Hum Dev* 2000;58:141–52.
6. Cozzi F, Pierre A. Glossoptosis-apnea syndrome in infancy. *Pediatrics* 1985;75:836–43.
7. Sher AE, Shprintzen RJ, Thorpy MJ. Endoscopic observations of obstructive sleep apnea in children with anomalous upper airways: predictive and therapeutic value. *Int J Pediatr Otorhinolaryngol* 1986;11:135–46.
8. Singer L, Sidoti EJ. Pediatric management of Robin sequence. *Cleft Palate Craniofac J* 1992;29:220–3.
9. Anderson IC, Sedaghat A, McGinley B, Redett R, Boss E, Ishman S. Prevalence and severity of obstructive sleep apnea and snoring in infants with Pierre Robin sequence. *Cleft Palate Craniofac J* 2011;48:614–8.
10. Gozal D, O'Brien LM. Snoring and obstructive sleep apnoea in children: why should we treat? *Paediatr Respir Rev* 2004;5(Suppl A):S371–6.
11. Hotz M, Gnoinski W. Clefts of the secondary palate associated with the "Pierre Robin syndrome". Management by early maxillary orthopaedics. *Swed Dent J Suppl* 1982;15:89–98.
12. Bacher M, Sautermeister J, Urschitz M, Buchenau W, Arand J, Poets C. An oral appliance with velar extension for treatment of obstructive sleep apnea in infants with the Pierre Robin sequence. *Cleft Palate Craniofac J* 2011;48:331–6.
13. Schaefer RB, Gosain AK. Airway management in patients with isolated Pierre Robin sequence during the first year of life. *J Craniofac Surg* 2003;14:462–7.
14. Meyer AC, Lidsky ME, Sampson DE, Lander TA, Liu M, Sidman JD. Airway interventions in children with Pierre Robin Sequence. *Otolaryngol Head Neck Surg* 2008;138:782–7.
15. Figueroa AA, Glupker TJ, Fitz MG, BeGole EA. Mandible, tongue, and airway in Pierre Robin sequence: a longitudinal cephalometric study. *Cleft Palate Craniofac J* 1991;28:425–34.
16. Houston WJB. The analysis of errors in orthodontic measurements. *Am J Orthod* 1983;83:382–90.
17. Dahlberg G. *Statistical Methods for Medical and Biological Students*. New York: Interscience Publications; 1940.
18. Hänggi MP, Teuscher UM, Roos M, Peltomäki TA. Long-term changes in pharyngeal airway dimensions following activator-headgear and fixed

appliance treatment. *Eur J Orthod* 2008;30:598–605.
19. Laitinen SH, Heliövaara A, Ranta RE. Craniofacial morphology in young adults with the Pierre Robin sequence and isolated cleft palate. *Acta Odontol Scand* 1997;55:223–8.
20. McNamara JA Jr. A method of cephalometric evaluation. *Am J Orthod* 1984;86:449–69.
21. Linder-Aronson S, Leighton BC. A longitudinal study of the development of the posterior nasopharyngeal wall between 3 and 16 years of age. *Eur J Orthod* 1983;5:47–58.
22. Malkoc S, Usumez S, Nur M, Donaghy CE. Reproducibility of airway dimensions and tongue and hyoid positions on lateral cephalograms. *Am J Orthod Dentofacial Orthop* 2005;128:513–6.
23. Major MP, Flores-Mir C, Major PW. Assessment of lateral cephalometric diagnosis of adenoid hypertrophy and posterior upper airway obstruction: a systematic review. *Am J Orthod Dentofacial Orthop* 2006;130:700–8.
24. Pirilä-Parkkinen K, Löppönen H, Nieminen P, Tolonen U, Pääkkö E, Pirttiniemi P. Validity of upper airway assessment in children: a clinical, cephalometric, and MRI study. *Angle Orthod* 2011;81:433–9.
25. Riley R, Powell N, Guilleminault C. Cephalometric roentgenograms and computerized tomographic scans in obstructive sleep apnea. *Sleep* 1986;9:514–5.
26. Johal A, Patel SI, Battagel JM. The relationship between craniofacial anatomy and obstructive sleep apnoea: a case-controlled study. *J Sleep Res* 2007;16:319–26.
27. Subtelny JD. A cephalometric study of the growth of the soft palate. *Plast Reconstr Surg* 1957;19:49–62.
28. Bravo G, Ysunza A, Arrieta J, Pamplona MC. Videonasopharyngoscopy is useful for identifying children with Pierre Robin sequence and severe obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol* 2005;69:27–33.