UNIVERSIDADE DE SÃO PAULO
HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

MICHELE GARCIA-USÓ

The upper airways in syndromic craniosynostosis: tomographic and computational fluid dynamics assessment

BAURU
2019

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Tese apresentada ao Hospital de Reabilitação de Anomalias Craniofaciais da Universidade de São para obtenção do título de Doutor em Ciências da Reabilitação, área de concentração: fissuras orofaciais e anomalias relacionadas.

Orientadora: Ivy Kiemle Trindade-Suedam

Coorientador: Luiz André Freire Pimenta

Coorientador: Cristiano Tonello

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UNIVERSIDADE DE SÃO PAULO
HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

R. Silvio Marchione, 3-20

Caixa Postal: 1501

17012-900 - Bauru – SP – Brasil

Prof. Dr. Vahan Agopyan – Reitor da USP

Prof. Dr. Carlos Ferreira dos Santos – Superintendente do HRAC /USP

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FOLHA DE APROVAÇÃO

Michele Garcia-Usó

Tese apresentada ao Hospital de Reabilitação de Anomalias Craniofaciais da Universidade de São Paulo para a obtenção do título de Doutor.
Área de Concentração: Fissuras Orofaciais e Anomalias Relacionadas

Aprovado em:

Banca Examinadora

Prof. Dr. _____
Instituição _____

Prof. Dr. _____
Instituição _____

Prof. Dr. _____
Instituição _____

_____
Profa. Dra. Ivy Kiemle Trindade-Suedam
Hospital de Reabilitação de Anomalias Craniofaciais

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Profa. Dra. Ivy Kiemle Trindade-Suedam
Presidente da Comissão de Pós-Graduação do HRAC-USP

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DEDICATÓRIA

Àqueles que são muito mais do que amostra e números nas tabelas, os quais serão verdadeiramente beneficiados pelos resultados das pesquisas desenvolvidas no HRAC/USP. Assim, dedico esse trabalho aos pacientes e familiares; cederam-se à pesquisa científica, momento no qual efetivamente colaboraram para o progresso e doaram-se à ciência, muitas vezes sem dimensionar a própria colaboração na busca pela excelência em tratamento e prevenção das mais diversas alterações craniofaciais.

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À Profa. Dra. Ivy Kiemle Trindade-Suedam

Ao ingressar no curso de Odontologia da Faculdade de Odontologia de Bauru/Universidade de São Paulo, no ano de 2010, tinha certeza que muitas boas surpresas e oportunidades estavam por vir. Desde o princípio meu respeito e admiração pela docência eram ascendentes, dia a dia alimentados ao observar meus mestres demonstrando o domínio das técnicas, da ciência e do saber.

Apenas um ano depois, no ano de 2011, iniciaram-se as primeiras aulas de Fisiologia. Naquele momento, saber como "tudo funciona" fazia mais sentido que as ciências exatas. Nesse mesmo ano, tive o privilégio de conhecer a Profa. Ivy, e por ela ser orientada em minha primeira iniciação científica. Uma jornada iniciava-se ali. Desde 2011, foram duas iniciações científicas, dois anos de mestrado, quatro anos de doutorado, estágio e sanduíche no exterior, muitos trabalhos apresentados, alguns publicados, outros submetidos, viagens, poses para foto, broncas, e muitas risadas.

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Quando criança que só quer brincar,
já mistura tudo e diz que é remédio.
Brinca de fazer curar,
até para o cachorro não sobra tédio

O pai dizia que tinha o mundo sob seus pés,
Olhava e só tinha um machucado.
E a vida brinca de ter viés,
se despediu dele do outro lado.

Sentiu gosto de água salgada,
desceu daquelas duas janelas de alma.
Escondeu a saudade arraigada,
disse pra dentro que tudo se acalma.

No seu riso fez de tudo um sonho,
voando alto e querendo sempre saber.
Não tinha medo de dia enfadonho,
sabia que tinha de crescer

E de adulto quis ser de novo criança,
que de criança sempre quis ser.
Todo adulto tem dentro de si a lembrança,
que quer ser cientista quando crescer.

Michele Garcia-Usó

RESUMO

Garcia-Usó M. Vias aéreas superiores nas craniossinostoses sindrômicas: análise por tomografia computadorizada e fluido dinâmica computacional [tese]. Bauru: Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo; 2019.

Objetivos: Estudos sugerem que as dismorfologias das vias aéreas superiores (VAS) nas Craniossinostoses Sindrômicas (CSS) são decorrentes da hipoplasia de terço médio da face e possuem estreita relação com a Síndrome da Apneia Obstrutiva do Sono (SAOS). O objetivo do presente estudo foi caracterizar a morfo-fisiologia das VAS nos indivíduos com CSS comparados a um grupo controle (CON), por meio de tomografia computadorizada (CT) e fluidodinâmica computacional (CFD). A hipótese inicial foi de que as UAW estão reduzidas e fisiologicamente impactadas nos CSS. **Métodos:** a amostra foi composta por dois grupos: 1) CON: 19 tomografias de indivíduos sem síndromes ou infecções das VAS (25±7 anos de idade); 2) SCS 10 tomografias de indivíduos com CSS (21±5 anos de idade); O volume (cm^3) (V) e área seccional mínima (mm^2) (ASm) foram aferidos por meio do software Mimics. As VAS foram divididas em VAS total (VASt), cavidade nasal (CN) e faringe (FAR). A análise cefalométrica foi realizada por meio do software Dolphin. Sete indivíduos de cada grupo foram selecionados, pareados por gênero e idade, para as simulações de CFD. As medidas foram feitas duas vezes pelo mesmo avaliador em dois momentos distintos. Valores de $p<0,05$ foram considerados significantes. **Resultados:** Valores médios de V (±Dp) para os grupos CON e CSS corresponderam a: VASt 34,3±5,9 e 24,5±9,5; CN 17,90±3,0 e 14,1±4,3; FAR 16,4±4,0 e 10,4±5,6 respectivamente. Os valores médios de ASm (±Dp) para os grupos CON e SCC corresponderam a 67,3±54,2 e 28,6±17,1, respectivamente. Dentre os principais resultados cefalométricos observou-se que as dimensões maxilomandibulares estavam significantemente reduzidas em relação ao grupo CON (Co-A (mm) 84,1±5,8 vs. 67,3±11,3; Go-Me (mm) 71,1±6,0 vs. 58,3±9,5; SNA (°) 82,8±3,8 vs. 76,4±8,5). Foi observada uma correlação positiva entre as dimensões maxilomandibulares (Co-A e Go-Me) e V. Na análise por CFD, pressões mais negativas (Pa) foram observadas no grupo CSS (-107,7±63,0) em relação ao grupo Com (-45,6±24,2). Da mesma forma, maiores valores de resistência ($Pa/(cm^2/min)$) ao fluxo inspiratório foram observadas no grupo CSS (-6,8±3,7) em relação ao grupo CON (-2,7±1,7) .

Conclusão: As dimensões das VAS dos indivíduos com CSS estão reduzidas em relação à indivíduos não sindrômicos. Esta redução pode ser justificada pela discrepância maxilo-mandibular observada. As dimensões reduzidas impactam negativamente a função das VAS. Infere-se, assim, que esta população está mais predisposta ao desenvolvimento de obstrutiva do sono e desordens relacionadas

Descritores: Obstrução das vias aéreas. Acrocefalosindactilia. Tomografia. Imagem tridimensional

ABSTRACT

Garcia-Usó M. The upper airways in syndromic craniosynostosis: tomographic and computational fluid dynamics assessment [thesis]. Bauru: Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo; 2019.

Objectives: Studies have suggested that upper airway (UAW) dysmorphologies in Syndromic Craniosynostosis (SCS) are mainly related to midface hypoplasia and consequently with obstructive sleep apnea (OSA). The aim of this study was to characterize the morphophysiology of UAW in SCS individuals as compared to controls (CON) by means of computed tomography (CT) and computational fluid dynamics (CFD). We hypothesized that UAW was reduced and physiologically impaired in SCS. **Methods:** The sample was composed by two groups: 1) CON: 19 scans of individuals without any syndrome or upper airway infections (25,26±6,67 years of age), and 2) SCS 10 CT scans of individuals with SCS (21,05±4,89 years of age); volume (cm^3) (V) and minimal cross-sectional area (mm^2) (mCSA) were assessed using Mimics software; UAW was divided into total UAW (tUAW), nasal cavity (NC), and pharynx (Phrx). Cephalometric analysis was also performed using Dolphin software. Seven individuals of each group, age and gender matched, were considered for CFD simulation. Measurements were done twice by the same evaluator at two different time points. Differences between groups were assessed at a 5% significance level. **Results:** Mean values of V (±Sd) for groups CON and SCS corresponded to: tUAW 34,31±5,97 and 24,52±9,55; NC 17,90±3,07 and 14,10±4,30; Phrx 16,46±4,60 and 10,42±5,63 respectively. Mean mCSA (±Sd) for groups CON and SCS corresponded to 67,32±54,20 and 28,66±17,14. Cephalometric findings showed significant differences between CON and SCS respectively: a smaller maxillomandibular length in SCS, represented by Co-A (mm) 84,13±5,80 and 67,36±11,30, Go-Me (mm) 71,14±6,00 and 58,37±9,50; midface retrusion in relation to the skull base, showed by SNA 82,87°±3,80 and 76,44°±8,50; greater flexure of skull base angle, from the magnitude of Ba-S-N 131,16°±6,2 and 121,85°±7,60. There was a positive correlation between the cephalometric

variables Co-A/Go-Me and V Phrx. The mCSA showed a positive correlation with V Phrx. On CFD analysis, pressure boundary condition on outlet (P_{out}), expressed in Pascals, on CON and SCS corresponded to -45,6±24,26 and -107,78±63,06. The UAW resistance (R_{es}), expressed in Pa/(L/min), corresponded to -2,74±1,77 and -6,88±3,78, on CON and SCS respectively. The actual simulated flow rate (F_{lw}), expressed in L/min, was from 17.2±2.39 and 15.8±1.88, for CON and SCS respectively. **Conclusion:** The initial hypothesis was confirmed, since the UAW dimensions were significantly reduced in SCS. The same significance was found in CFD variables. Therefore, the results suggested these individuals with SCS are at great risk for OSA.

Keywords: Airway obstruction. Acrocephalosyndactylia. Tomography. Imaging, three-dimensional

SUMMARY

1. GENERAL INTRODUCTION

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Craniosynostosis is the premature closure of the cranial sutures. Under physiological conditions, the cranial sutures progress into fusion with different initial periods, occurring between 2 and 39 months of life (GHIZONI et al., 2016). In children with syndromic craniosynostosis (SCS) this event happens earlier in life, sometimes even at birth (SAWH-MARTINEZ; STEINBACHER, 2019). When associated with syndromes, craniosynostosis comprises a rare craniofacial anomaly, affecting 1:30.000 to 1:100.000 live births (NAGY; DEMKE, 2014), with several conditions associated, such as intracranial hypertension, restrictions in skull base growth, midface hypoplasia and a high risk for sleep disorders, including obstructive sleep apnea (OSA) (CALANDRELLI et al., 2018; INVERSO et al., 2016; NASH et al., 2015; SAWH-MARTINEZ; STEINBACHER, 2019; SPRUIJT et al., 2016). Among Syndromic Craniossynostosis (SCS), Apert (AP) and Crouzon (CZ) syndromes are the most common and are determined by an autosomal-dominant inheritance, with mutations in transmembrane fibroblast growth factor receptor (FGFR2) (SAWH-MARTINEZ; STEINBACHER, 2019). Despite some differences, AP and CZ have similar phenotypes regarding midface retrusion and airway impairments (Figure 1A, B). The AP phenotype includes extremities malformations, as syndactyly, exorbitism, and gingival hypoplasia (WENGER; HING; EVANS, 2019), and CZ frequently involves the closure of multiple sutures (SAWH-MARTINEZ; STEINBACHER, 2019).

Several studies have suggested that the premature closure of the cranial sutures can lead to maxillomandibular discrepancies (CALANDRELLI et al., 2018; MATHEWS et al., 2018; SAWH-MARTINEZ; STEINBACHER, 2019), resulting in airway obstructions and consequently to OSA in SCS, with the prevalence as high as 70% (BANNINK et al., 2011; NASH et al., 2015). For instance, OSA is a sleep-related breathing disorder characterized by periodic obstruction of the pharyngeal airway during sleep (BANNINK et al., 2011). Upper airway (UAW) morphology and craniofacial skeletal pattern play an important role in the pathogenesis of OSA (OSMAN et al., 2018). Thus, some of therapies for OSA aim at correcting the anatomical issues such as those previously mentioned. According to several authors (NASH et al., 2015; SAWH-MARTINEZ; STEINBACHER, 2019; TONELLO, 2016), craniofacial surgery, by mid-face distraction, including Le Fort III and monobloc

advancement are established techniques that enlarge airway space and release the high intracranial pressure, improving sleep quality of SCS individuals.

Figure 1A: Female individual with Apert Syndrome, presenting a severe midface retrusion; **Figure 1B**: Female individual with Crouzon Syndrome, demonstrating midface retrusion and exorbitism.

Three-dimensional modeling, by means of computed tomography, has been the gold-standard morphological investigation of the UAW. This is an important method to evaluate volume and the location of minimal cross-sectional area, since pharyngeal narrowing is well associated with the propensity for pharyngeal collapse during sleep (OSMAN et al., 2018). When associated with cephalometric analysis, the characterization of craniofacial deformity and its influence on the UAW can be achieved. Even more, airway constrictions and reduced volumes is largely linked to OSA in SCS individuals (SAWH-MARTINEZ; STEINBACHER, 2019). In addition, Computational Fluid Dynamics (CFD) technique applied to UAW could be described

as the association of anatomy and physiology, simulating airflow through three-dimensional reconstructions. CFD provides several physiological parameters such as heat flux, nasal resistance, shear stress, velocity magnitude, air flow and breathing effort (KIMBELL; RHEE, 2015), and has been shown to be a promising technique for simulating and characterizing airflow behavior on the UAW.

Several studies have been published regarding SCS (CHANG et al., 2018; HU et al., 2017; MATHEWS et al., 2018; MÜLLER-HAGEDORN et al., 2018; SAWH-MARTINEZ; STEINBACHER, 2019; SAXBY et al., 2018). However, to the best of our knowledge, there is a lack of morphophysiological reports from the UAW which could guide treatment and objectively assess the outcomes.

Considering that SCS presents with a broad spectrum and with different levels of severity, the complex rehabilitation process of these individuals requires a multidisciplinary approach and an evidence-based rehabilitation protocol. Thus, the following questions raise: 1) To what extent UAW of SCS individuals are affected, compared to the population without craniofacial anomalies? 2) Does the UAW impairment relate to the high prevalence of OSA in this specific population? The present study aimed at answering these questions, assuming the hypothesis that UAW in SCS is reduced and physiologically impacted.

2. OBJECTIVES

2.OBJECTIVES

The objectives of the present study were

1) To characterize the morphology of the upper airways in three-dimensions (volume and minimal cross-sectional area), in individuals with syndromic craniosynostosis and to correlate these findings with craniofacial pattern by means of cephalometric analysis and computational fluid data (pressure on the outlet, airway resistance and flow rate) – Manuscript #1.
2) To clinically describe the impact of the upper airway reduction on the sleep and breathing of an individual with syndromic craniosynostosis in a case report – Manuscript #2.

3. MANUSCRIPT #1

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Morphological findings in the upper airway of syndromic craniosynostosis: tomographic and computational fluid dynamics assessment.

To be submitted to the “Laryngoscope” journal.

ABSTRACT

Objectives: Studies have suggested that upper airway (UAW) dysmorphologies in Syndromic Craniosynostosis (SCS) are mainly related to midface hypoplasia and consequently with obstructive sleep apnea (OSA). The aim of this study was to characterize the morphophysiology of UAW in SCS individuals as compared to controls (CON) by means of computed tomography (CT) and computational fluid dynamics (CFD). We hypothesized that UAW was reduced and physiologically impaired in SCS. **Methods:** The sample was composed by two groups: 1) CON: 19 scans of individuals without any syndrome or upper airway infections (25,2±6,6 years of age), and 2) SCS 10 CT scans of individuals with SCS (21,0±4,8 years of age); volume (cm^3) (V) and minimal cross-sectional area (mm^2) (mCSA) were assessed using Mimics software; UAW was divided into total UAW (tUAW), nasal cavity (NC), and pharynx (Phrx). Cephalometric analysis was also performed using Dolphin software. Seven individuals of each group, age and gender matched, were considered for CFD simulation. Measurements were done twice by the same evaluator at two different time points. Differences between groups were assessed at a 5% significance level. **Results:** Mean values of V (±Sd) for groups CON and SCS corresponded to: tUAW 34,3±5,9 and 24,5±9,5; NC 17,9±3,0 and 14,1±4,3; Phrx 16,4±4,6 and 10,4±5,6 respectively. Mean mCSA (±Sd) for groups CON and SCS corresponded to 67,3±54,2 and 28,6±17,1. Cephalometric findings showed significant differences between CON and SCS respectively: a smaller maxillomandibular length in SCS, represented by Co-A (mm) 84,1±5,8 and 67,3±11,3, Go-Me (mm) 71,1±6,0 and 58,3±9,5; midface retrusion in relation to the skull base, showed by SNA 82,8°±3,8 and 76,4°±8,5; anterior position of hyoid illustrated by SNH 56,42°±4,50 and 62,24°±5,7; greater flexure of skull base angle, from the magnitude of Ba-S-N 131,1°±6,2 and 121,8°±7,6. There was a positive correlation between the cephalometric variables Co-A/Go-Me and V Phrx. The mCSA showed a positive correlation with V Phrx. On CFD analysis, pressure boundary condition on outlet (P_{out}), expressed in Pascals, on CON and SCS corresponded to -45,6±24,2 and -107,7±63,0. The UAW resistance (R_{es}), expressed in Pa/(L/min), corresponded to -2,7±1,7 and -6,8±3,7, on CON and SCS respectively. The actual simulated flow rate (F_{lw}), expressed in L/min, was from 17,2±2,39 and 15,8±1,88, for CON and SCS respectively. **Conclusion:** The initial hypothesis was confirmed, since the UAW dimensions were significantly reduced in SCS. The same significance was

found in CFD variables. Therefore, the results suggested these individuals with SCS are at great risk for OSA.

Keywords: Airway obstruction. Acrocephalosyndactylia. Tomography. Imaging, three-dimensional

INTRODUCTION

Craniosynostosis is the premature closure of the cranial sutures. Under physiological conditions, the cranial sutures progress into fusion with different initial periods, occurring between 2 and 39 months of life (GHIZONI et al., 2016). In children with syndromic craniosynostosis (SCS) this event happens earlier in life, sometimes even at birth (SAWH-MARTINEZ; STEINBACHER, 2019). When associated with syndromes, craniosynostosis comprises a rare craniofacial anomaly, affecting 1:30.000 to 1:100.000 live births (NAGY; DEMKE, 2014), with several conditions associated, such as intracranial hypertension, restrictions in skull base growth, midface hypoplasia and a high risk for sleep disorders, including obstructive sleep apnea (OSA) (CALANDRELLI et al., 2018; INVERSO et al., 2016; NASH et al., 2015; SAWH-MARTINEZ; STEINBACHER, 2019; SPRUIJT et al., 2016). Among Syndromic Craniossynostosis (SCS), Apert (AP) and Crouzon (CZ) syndromes are the most common and are determined by an autosomal-dominant inheritance, with mutations in transmembrane fibroblast growth factor receptor (FGFR2) (SAWH-MARTINEZ; STEINBACHER, 2019). Despite some differences, AP and CZ have similar phenotypes regarding midface retrusion and airway. The AP phenotype includes extremities malformations, as syndactyly, exorbitism, and gingival hypoplasia (WENGER; HING; EVANS, 2019), and CZ frequently involves the closure of multiple sutures (SAWH-MARTINEZ; STEINBACHER, 2019).

Several studies have suggested that the premature closure of the cranial sutures can lead to maxillomandibular discrepancies (CALANDRELLI et al., 2018; MATHEWS et al., 2018; SAWH-MARTINEZ; STEINBACHER, 2019), resulting in airway obstructions and consequently to OSA in SCS, with the prevalence as high as 70% (BANNINK et al., 2011; NASH et al., 2015). For instance, OSA is a sleep-related breathing disorder characterized by periodic obstruction of the pharyngeal airway during sleep (BANNINK et al., 2011). Upper airway (UAW) morphology and

craniofacial skeletal pattern play an important role in the pathogenesis of OSA (OSMAN et al., 2018). Thus, some of therapies for OSA aim at correcting the anatomical issues such as those previously mentioned. According to several authors (NASH et al., 2015; SAWH-MARTINEZ; STEINBACHER, 2019; TONELLO, 2016), craniofacial surgery, by mid-face distraction, including Le Fort III and monobloc advancement are established techniques that enlarges airway space, improving sleep quality of SCS individuals.

Three-dimensional modeling, by means of computed tomography, has been the gold-standard morphological investigation of the UAW. This is an important method to evaluate volume and the location of minimal cross-sectional area, since pharyngeal narrowing is well associated with the propensity for pharyngeal collapse during sleep (OSMAN et al., 2018). When associated with cephalometric analysis, the characterization of craniofacial deformity and its influence on the UAW can be achieved. Even more, airway constrictions and reduced volumes is largely linked to OSA in SCS individuals (SAWH-MARTINEZ; STEINBACHER, 2019). In addition, Computational Fluid Dynamics (CFD) technique applied to UAW could be described as the association of anatomy and physiology, simulating airflow through three-dimensional reconstructions. CFD provides several physiological parameters such as heat flux, nasal resistance, shear stress, velocity magnitude, air flow and breathing effort (KIMBELL; RHEE, 2015), and has been shown to be a promising technique for simulating and characterizing airflow behavior in the UAW.

Several studies have been published regarding SCS (CHANG et al., 2018; HU et al., 2017; MATHEWS et al., 2018; MÜLLER-HAGEDORN et al., 2018; SAWH-MARTINEZ; STEINBACHER, 2019, 2019b; SAXBY et al., 2018). However, to the best of our knowledge, there is a lack of morphophysiological reports from the UAW which could guide treatment and objectively assess the outcomes.

Considering that SCS presents with a broad spectrum and with different levels of severity, the complex rehabilitation process of these individuals requires a multidisciplinary approach and an evidence-based rehabilitation protocol. Thus, the following questions raise: 1) To what extent UAW of SCS individuals are affected, compared to the population without craniofacial anomalies? 2) Does the UAW impairment relate to the high prevalence of OSA in this specific population? The present study aimed at answering these questions, assuming the hypothesis that UAW in SCS is reduced and physiologically impacted.

OBJECTIVES

To characterize the morphology of the upper airways in three-dimensions (volume and minimal cross-sectional area), in individuals with syndromic craniosynostosis and to correlate these findings with craniofacial pattern by means of cephalometric analysis and computational fluid data (pressure on the outlet, airway resistance and flow rate).

MATERIAL AND METHODS

The present study was approved by the Institutional Review Board at the Hospital for Rehabilitation of Craniofacial Anomalies from the University of São Paulo (HRAC-USP) (Bauru, SP, Brazil), protocol number **15205413.7.0000.5441**. Researchers signed a liability form for imaging handling.

From a pool of 45 tomography scans of non-syndromic individual, 19 matched the inclusion criteria for control group (CON), which corresponded to high quality computed tomography scans of patients between 13 and 35 years of age and a field of view of at least 13cm. The same inclusion criteria were adopted to compose the SCS group and from a pool of 25 tomography scans, 10 were selected. UAW infections, imaging artifacts due to intubation, nasogastric tube or tracheostomy and body mass index greater than 30 were considered exclusion criteria. These images were imported as a DICOM (Digital Imaging and Communications in Medicine) formatted file and displayed using two different imaging software: Mimics Research 17.0 (Materialise, Leuven, Belgium), to evaluate V and mCSA, and Dolphin Imaging 11.8 software (Dolphin Imaging, Chatsworth, California, USA) to assess cephalometric landmarks.

3D image acquisition and UAW dimensions

In order to assess UAW dimension in Mimics Research 17.0 software, a mask was created, with a threshold value of -1024 to -300, consistent with the density of air. This tool allows the filling of the pharynx (Phrx) and nasal cavity (NC), distinguishing them from other structures, such as soft and hard tissues. The semiautomatic segmentation was performed, by removing noninterest structures for UAW analysis, and adding areas which, in turn, could not be selected by the threshold, in coronal,

sagittal and axial axes. To assess the different regions of the UAW, using the parasagittal axe, the segmentation was divided into 6 different parts:

1. Total Upper Airway (tUAW): anterior boundary (external nostrils); inferior boundary (most inferior point of hyoid bone)
2. Nasal cavity (NC): anterior boundary (anterior limit of tUAW); posterior boundary (most inferior posterior point at the inferior choanae).
3. Pharynx (Phrx): superior boundary (posterior boundary of NC); inferior boundary (most inferior point of hyoid bone).
4. Nasopharynx (NPhrx): anterior boundary (posterior boundary of the NC); inferior boundary (most inferior portion of the soft palate).
5. Oropharynx (OPhrx): superior boundary (inferior boundary of the NP); inferior boundary (most superior point of epiglottis valve).
6. Hipopharynx (HPhrx): superior boundary (inferior boundary of the OP); inferior boundary (most inferior point of hyoid bone).

After the selection of the region of interest (Figure 2A), the software created the 3D reconstruction, which was smoothed and compatible with colored pharyngeal airway (Figure 2B). To determine mCSA, Mimics calculated the area of each axial slice and the operator selected the smallest one (Figure 2C). This variable was calculated to the Phrx region.

Cephalometric Analysis

Dolphin Imaging 11.8 software was used to assess cephalometric landmarks. Standardization of head positioning was based on axial plane (line passing through the most inferior point of mastoid processes on both sides), coronal plane (Frankfort horizontal) and sagittal plane (line passing through the tip of nasal bone and the most inferior point of foramen magnum) with assistance of “clipping slice” tool. Using cephalograms from 3D images, 16 different craniofacial landmarks were selected, in order to access linear and angular measurements, as listed in Table 1. Cephalometric measurements were created out of sagittal plane (Figure 3).

Computational Fluid Dynamics Assessment

Seven individuals of each group were considered for CFD analysis, since tomographies with the soft palate collapsed had to be excluded. The groups were

matched by sex and age. The computational fluid dynamics simulations were performed as described by Kimbell et al. (2019). After 3D reconstruction in Mimics, the UAW models were prepared and meshed. Stereolithography (STL) files were imported into ICEM-CFD™ (ANSYS, Inc., Canonsburg, PA). Inlet, outlet, and airway wall surfaces were created separately; Computational meshes comprising approximately four million graded, tetrahedral elements were developed and smoothed until the quality of all elements was greater than 0.3, to ensure robust numerical performance. Steady-state inspiratory airflow simulations were conducted using Fluent™ v.14 (ANSYS, Inc.) for flow rates based on individual resting minute volumes which were estimated from body weight using allometric scaling. Laminar simulations were conducted for all models. Airway resistance (R_{es}) from the inlet to the last airway section was computed as the pressure drop in Pascals (Pa) divided by the flow rate in L/min: $\boxed{R_{es} = \frac{\Delta P}{L/min}}$(KIMBELL et al., 2013).

Statistical Analyses

The measurements were performed twice by the same operator (M.G.U.) with a minimum interval of thirty days between each assessment and the mean values were considered for analysis. Interclass Correlation Coefficient (ICC) was assessed to obtain intra-examiner agreement. Shapiro-Wilk test was performed to assess the normal distribution. Comparisons of quantitative variables between groups were assessed through *t test*. Chi-square or Fisher exact test were used to correlate qualitative and ordinal quantitative variables. Pearson or Spearman correlation were used to assess the quantitative variables' correlations.

RESULTS

Considering that a high intraexaminer agreement was obtained for all variables (0.97 to 0.99), results are presented as the mean values of both measurements.

The volumetric data of tUAW, NC and Phrx was significantly reduced 29%, 21% and 37%, respectively, in SCS when compared with the CON group ($p<0,05$). Mean volumes (cm^3) corresponded to: tUAW 34,31 ± 5,97 (CON), 24,52 ± 9,55 (SCS); NC 17,90 ± 3,07 (CON), 14,10 ± 4,30 (SCS); Phrx 16,46 ± 4,60 (CON), 10,42 ± 5,63 (SCS), these differences were considered significant. Mean volumes of the pharynx

division were: NC 8,80±2,23 (CON), 3,96±3,71 (SCS); OP 3,03±1,42 (CON), 3,34±1,77 (SCS); HP 4,42±1,95 (CON), 2,98±1,19 (SCS). The mCSA (mm^2) was 57% smaller in SCS (28,66 ± 17,14) compared to CON (67,32 ± 54,2) ($p<0,05$). The sample description and statistical comparisons of morphological findings, V and mCSA, are shown in Table 2. 3D reconstructions can be seen in Figure 4.

Cephalometric measurements presented statistical differences between groups in the following variables: SNA(°) 82,87±3,8 (CON), 76,44±8,5 (SCS); ANB(°) 3,43±2,70 (CON), -5,62±6,29 (SCS); Ba-S-N(°) 131,16±6,2 (CON), 121,85±7,6 (SCS); SNH(°) 56,42±4,40 (CON), 62,24±5,72 (SCS); Co-A (mm) 84,13±5,8 (CON), 67,36±11,3 (SCS) and Go-Me(mm) 71,14±6,0 (CON), 58,37±9,5 (SCS). Cephalometric findings are displayed in Table 3.

The CFD simulation showed a pressure boundary condition on outlet (P_{out}, Pa) of -45,6±24,26 (CON) and -107,78±63,06 (SCS) ($p<0.05$); UAW resistance (R_{es}, Pa/(L/min)) of -2,74±1,77 (CON) and -6,88±3,78 (SCS); actual simulated flow rate (F_{lw}, L/min) (L/min) of 17,2±2,39 (CON) and 15,8±1,88 (SCS) ($p<0.05$). CFD data are descripted in Table 4. Figure 5 shows air flow simulations obtained with Computational Fluid Dynamics; Hot spots and more warm colors are observed in SCS group. UAW resistance presented a strong positive correlation with mCSA of 0,77 (CON) and 0,88 (SCS).

There was a positive correlation between maxillary (Co-A)/mandibular (Go-Me) body length and pharyngeal volumes. The mCSA showed a positive correlation with pharyngeal volumes. Correlation results are displayed in Figure 6.

DISCUSSION

The main finding of the present study confirms the initial hypothesis that the UAW of SCS individuals are dimensionally impaired when compared to control subjects. To the best of authors knowledge, no study compared SCS morphology with controls. The results have shown that tUAW volumes of SCS group were 29% smaller, as well as Phrx (37%) and mCSA (57%). As already suggested by Chen et al. (2016), the main UAW morphological characteristic related with the pathogenesis of OSA is the mCSA, corroborating with the high prevalence of this sleep disorder in this group (INVERSO et al., 2016; MATHEWS et al., 2018).

Surgical approach of SCS started in the 60's (TESSIER, 1967), aiming at improving physiological and aesthetics aspects. Craniofacial advancements positively impact several condition such as raised intracranial pressure, exophthalmia, narrow airway, breathing difficulties, and consequently OSA symptoms (AL-NAMNAM; HARIRI; RAHMAN, 2018; NOUT et al., 2010; SAXBY et al., 2018; TONELLO, 2016; VEYS et al., 2017).

One important feature of the sample used in this study was the supine position during imaging acquisition, similar to sleep position. Battagel et al. (2002) compared cephalograms of individuals in upright and supine positions and the results reveled reductions from 20 to 40% in the supine position, suggesting a postural retraction of the tongue and soft palate under the influence of gravity. This condition was observed in the SCS group in which total or partial collapse of soft palate was found.

Another hypothesis of this study was that UAW reduction was related to the Class III skeletal pattern, commonly observed in this population and mainly related to the maxillary retrusion in this case. Under this hypothesis, cephalometric analysis was performed, and results are discussed. Either linear or angular cephalometric measurements were reduced in SCS compared to controls. In accordance with clinical findings, linear cephalometric measurements (Co-A and Go-Me) were different in SCS and CON, indicating smaller maxillomandibular length in SCS. Moreover, a positive correlation was found between maxillomandibular length and Phrnx volume. In other words the smaller the size of de maxilla or the mandible, the smaller is the UAW, since maxillomandibular hypoplasia it's highly associated with SCS and also linked with OSA as a risk factor (HOLMES et al., 2018; MATHEWS et al., 2018). It has been suggested an etiological relationship between hard tissue dimensions and sleep disorders, indicating that the smaller the maxillomandibular enclosure, the more sever the OSA symptoms are (CHEN et al., 2016; SHELTON et al., 1993).

On cephalometric analysis, a greater flexure of cranial base angle (Ba-S-N), and a maxillary retrognathia were observed along with an anterior position of hyoid bone. The same results were described in non-syndromic individuals with Class III malocclusion (TINANO et al., 2015). The authors speculate that maxillary retrognathism could be related to cranial base flexure in this group, which leads to a Class III malocclusion, much more likely related to backward position of the maxilla than to the mandibular prognathism, since SCS mandibular bone has also a smaller

size compared to CON. The reduction observed on the skull base angle makes the UAW more curved, which combined with its shorter length (anterior/posterior measurement) increase the possibility of pharyngeal wall collapse. This finding is in accordance with literature, since maxillary/mandibular malformations reduce the UAW size, very likely playing a role in OSA etiology (CHEN et al., 2016; SCHORR et al., 2016; WATANABE et al., 2002).

Breathing is a function dependent on airway patency. The smaller are the dimensions of the UAW, the greater will be the resistance to the airflow and the reduced will be the patency. Recently, Kimbell et al. (2019) demonstrated that airway resistance could be sensitive to the UAW shape, curvature or degree of flexure, in accordance to our results. Using CFD techniques, the mean airway resistance was significantly increased in SCS. It means that SCS individuals had an increased breathing effort, in other words, more negative values of pressure on outlet. According to Berry et al. (2012), the increased effort is indicative of UAW obstructions. During sleep, it could be related to Negative Effort Dependence (NED). NED consists in decreased inspiratory flow as the downstream pressure becomes more negative (LE et al., 2019), very likely observed in OSA patients. This may suggest some link between awaken findings, as observed in SCS, and asleep observations. However, it should be confirmed by polysomnography in future studies.

There was a strong positive correlation between mCSA and R_{es}, *i.e.* as the sections of pharynx become narrower, the values of R_{es} decreased, indicating higher resistance. To our knowledge, this is the first research showing such results in this group of patients. Literature has shown smaller results in non-syndromic subjects (BACKER et al., 2007; CHANG et al., 2018). Moreover, considering R_{es} is inversely proportional to mass flow rate, and the flow was considered constant, if the pressure drops become more negative, also does the resistance. It implicates in an increased flow velocity due to the Poiseuille law, as we can observe in the third column of Figure 2B. Hence, according to our findings, the combination of high flow velocity, small mCSA and increased breathing effort, works as a predictor for collapsibility in the SCS group. As already suggested by the literature, these findings are well stablished indicators for OSA (BACKER et al., 2007; CHANG et al., 2018; HIRATA et al., 2016).

Several treatments are described for the management of airway obstruction in SCS, such as palatal surgeries, intraoral devices, continuous positive airway pressure (CPAP), adenotonsillectomy, midfacial advancements, Le Fort III osteotomy

and monobloc advancement, and even tracheostomy in specific life threatening severe obstructions (AL-NAMNAM; HARIRI; RAHMAN, 2018; MÜLLER-HAGEDORN et al., 2018; NASH et al., 2015; TAN et al., 2016; ZANDIEH; PADWA; KATZ, 2013). For instance, some authors show adverse outcomes for long-term treatment with CPAP, since positive pressure potentially exacerbates midfacial retrusion (WENGER; HING; EVANS, 2019) and in this scenario, distraction osteogenesis for maxillary advancement became an important alternative to solve in the issues related to aesthetic, breathing and sleep. In this sense, surgical approach is widely accepted, since SCS individuals tend to present multilevel obstructions of UAW, and severe backward position of maxillary bones (AL-NAMNAM; HARIRI; RAHMAN, 2018; HU et al., 2017; MEHTA et al., 2010; NASH et al., 2015; NOUT et al., 2010; TONELLO, 2016).

In face of the results obtained, it can be concluded that the upper airways are severely compromised in SCS individuals compared to controls. There is a morphological impairment of these individuals, but not only anatomy, CFD analysis showed that physiology is also anomalous. Therefore, SCS individuals are in a greater to develop UAW disorders, such as OSA, comparing to the population without craniofacial anomalies.

One limitation of this study was the reduced sample size of the SCS group. Three conditions explain this: 1) The low prevalence of this syndrome (1:30.000 to 1:100.000 live births); 2) The ethical limitation of obtaining tomographies only for research purposes; 3) The strict inclusion criteria adopted in the present study.

To the authors knowledge, this is the first study in SCS field with tomography acquired in sleep position, which associates anatomical features (cephalometric measurements; UAW dimension) with physiological CFD data, also including a control group. There is room for future studies comparing UAW dimensions after surgical interventions and the association of these data with polysomnographic findings. Investigations regarding the tongue and pharyngeal soft-tissue role in OSA etiology and the relation between air cooling and heat loss with patency perception are future studies that need to be developed.

CONCLUSIONS

In face of the results obtained, it can be concluded that the anatomy and function of the syndromic craniosynostosis individuals are severely impaired when compared to non-syndromic control subjects. This data suggests that SCS individuals are more prone to develop UAW disorders, such as OSA, that the population without craniofacial anomalies. Also, the results suggest a relation between cephalometric findings and airway constrictions. Once again, this must be confirmed by polysomnographic analysis.

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REFERENCES

1. AL-NAMNAM, N. M. N.; HARIRI, F.; RAHMAN, Z. A. A. Distraction osteogenesis in the surgical management of syndromic craniosynostosis: a comprehensive review of published papers. British Journal of Oral and Maxillofacial Surgery. 2018;56(5):353–366.

2. AL-SALEH S., RIEKSTINS A., FORREST C.R., PHILIPS J.H., GIBBONS J., NARANG I. Sleep-related disordered breathing in children with syndromic craniosynostosis. Journal of Cranio-Maxillofacial Surgery. 2011;39(3):153–157.

3. BACKER DE J.W., VANDERVEKEN O.M., VOS W.G., DEVOLDER A., VERHULST S.L., VERBRAECKEN J.A., et al. Functional imaging using computational fluid dynamics to predict treatment success of mandibular advancement devices in sleep-disordered breathing. 2007;40(16):3708–3714.

4. BANNINK N., MALIEPAARD M., RAAT H., JOOSTEN K.F., MATHIJSSEN I.M. Reliability and validity of the obstructive sleep apnea-18 survey in healthy children and children with syndromic craniosynostosis. Journal of Developmental and Behavioral Pediatrics. 2011;32(1): 27–33.

5. BANNINK, N., MALIEPAARD, M., RAAT, H., JOOSTEN, K.F.M., MATHIJSSEN,

I.M.J. Obstructive sleep apnea-specific quality of life and behavioral problems in children with syndromic craniosynostosis. Journal of Developmental and Behavioral Pediatrics. 2011;32(3):233–238.

6. BATTAGEL J.M., JOHAL A., SMITH A.M., KOTECHA B. POSTURAL variation in oropharyngeal dimensions in subjects with sleep disordered breathing: A cephalometric study. European Journal of Orthodontics. 2002;24(3):263–276.

7. BERRY R.B., BUDHIRAJA R., GOTTLIEB D.J., GOZAL D., IBER C., KAPUR V.K., et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. Journal of clinical sleep medicine. 2012;8(5): 597–619.

8. CALANDRELLI R., PILATO F., MASSIMI L., PANFILI M., D'APOLITO G., GAUDINO S., et al. Quantitative evaluation of facial hypoplasia and airway obstruction in infants with syndromic craniosynostosis: relationship with skull base and splanchnocranium sutural pattern. Neuroradiology. 2002;24(3):263–276.

9. CHANG K.K., KIM K.B., MCQUILLING M.W., MOVAHED R. Fluid structure interaction simulations of the upper airway in obstructive sleep apnea patients before and after maxillomandibular advancement surgery. American Journal of Orthodontics and Dentofacial Orthopedics. 2018;153(6): 895–904.

10. CHEN H., AARAB G., DE RUITER M.H., DE LANGE J., LOBBEZOO F., VAN DER STELT P.F. Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: A systematic review. Sleep Medicine. 2016;21(-):19–27.

11. DRIESSEN C., JOOSTEN K.F., BANNINK N., BREDERO-BOELHOUWER H.H., HOEVE H.L., WOLVIUS E.B., et al. How does obstructive sleep apnoea evolve in syndromic craniosynostosis? A prospective cohort study. Arch Dis Child. 2013;98(7):538–543.

12. FUJIMOTO T., IMAI K., MATSUMOTO H., SAKAMOTO H., NAKANO T. Tracheobronchial anomalies in syndromic craniosynostosis with 3-dimensional CT image and bronchoscopy. Journal of Craniofacial Surgery. 2011;22(5): 1579–1583.

13. GEIGER Z., GUPTA N. Adenoid Hypertrophy. StatPearls [Internet] 2019-.2019 Aug 21.

14. GENTA P.R., SCHORR F., ECKERT D.J., GEBRIM E., KAYAMORI F., MORIYA H.T. et al. Sleep. 2014;37(10):1673–1678.

15. GHIZONI E., DENADAI R., RAPOSO-AMARAL C.A., JOAQUIM A.F., TEDESCHI H., RAPOSO-AMARAL C.E. Diagnosis of infant synostotic and nonsynostotic cranial deformities: a review for pediatricians. Revista Paulista de

Pediatria (English Edition). 2016;34(4):495–502.

16. GOLD, A. R.; SCHWARTZ, A. R. The pharyngeal critical pressure: The whys and hows of using nasal continuous positive airway pressure diagnostically. Chest. 1996;110(4):1077–1088.

17. GONSALEZ S., HAYWARD R., JONES B., LANE R. Upper airway obstruction and raised intracranial pressure in children with craniosynostosis. European Respiratory Journal. 1997;10(2):367–375.

18. HIRATA R.P., SCHORR F., KAYAMORI F., MORIYA H.T., ROMANO S., INSALACO G. et al. Upper Airway Collapsibility Assessed by Negative Expiratory Pressure while Awake is Associated with Upper Airway Anatomy. J Clin Sleep Med. 2016;124(19): 1339-1346.

19. HOLMES G., O'ROURKE C., MOTCH PERRINE S.M., LU N., VAN BAKEL H., RICHTSMEIER J.T. et al. Midface and upper airway dysgenesis in FGFR2-related craniosynostosis involves multiple tissue-specific and cell cycle effects. Development [serial on the internet]. 2018 Oct 5;145(19):dev166488. doi: 10.1242/dev.166488. PMID: 30228104; PMCID: PMC6198473.

20. HU C.-H., WU C.-T., KO E. W.-C., CHEN P.K.-T. et al. Monobloc Frontofacial or Le Fort III Distraction Osteogenesis in Syndromic Craniosynostosis. Journal of Craniofacial Surgery. 2017;28(5):1344–1349.

21. INVERSO G., BRUSTOWICZ K. A., KATZ E., PADWA B. L. The prevalence of obstructive sleep apnea in symptomatic patients with syndromic craniosynostosis. International Journal of Oral and Maxillofacial Surgery. 2016;45(2):167–169.

22. KIMBELL J.S., FRANK D.O., LAUD P., GARCIA G.J.M., RHEE J.S. Changes in nasal airflow and heat transfer correlate with symptom improvement after surgery for nasal obstruction. Journal of Biomechanics. 2013;46(15):2634–2643.

23. KIMBELL J., BASU S., GARCIA G., FRANK-ITO D., LAZAROW F., SU E. et al. Upper airway reconstruction using long-range optical coherence tomography: Effects of airway curvature on airflow resistance. Lasers in Surgery and Medicine. 2019;51(2):150–160.

24. KIMBELL, S.; RHEE, J. S. Mucosal Cooling After Surgery for Nasal Obstruction. Otolaryngol Head Neck Surg. 2015;150(1):139–147.

25. LE T.B., MOGHADDAM M.G., WOODSON B.T., GARCIA G.J.M. Airflow limitation in a collapsible model of the human pharynx: physical mechanisms studied with fluid-structure interaction simulations and experiments. Physiological Reports. 2019;7(10): p. e14099.

26. MATHEWS F., SHAFFER A., GEORG M., FORD M., GOLDSTEIN J., JABBOUR N., et al. Airway anomalies in patients with craniosynostosis.

Laryngoscope. 2018;00:1–9.

27. MEHTA V., BETTEGOWDA C., JALLO G., AHN E. The evolution of surgical management for craniosynostosis. Neurosurgical Focus. 2010;26(6):1–7.

28. MÜLLER-HAGEDORN S., WIECHERS C., ARAND J., BUCHENAU W., BACHER M., KRIMMEL M. et al. Less invasive treatment of sleep-disordered breathing in children with syndromic craniosynostosis. Orphanet Journal of Rare Diseases. 2018;13(1):1–8.

29. NAGY, L.; DEMKE, J. C. Craniofacial anomalies. Facial Plastic Surgery Clinics of North America. 2014;22(4):523–548.

30. NASH R., POSSAMAI V., MANJALY J., WYATT M. The Management of Obstructive Sleep Apnea in Syndromic Craniosynostosis. Journal of Craniofacial Surgery. 2015;26(6):1914–1916.

31. NOUT E., BOUW F., VEENLAND J., HOP W., VAN DER WAL K., MATHIJSSEN I. et al. Three-dimensional airway changes after le fort III advancement in syndromic craniosynostosis patients. Plastic and Reconstructive Surgery. 2010;126(2):564–571.

32. OSMAN A., CARTER S., CARBERRY J., ECKERT D. Obstructive sleep apnea: current perspectives. Nature and Science of Sleep. 2018;10(-):21–34.

33. ROBIN, N. H.; FALK, M. J.; HALDEMAN-ENGLERT, C. R. FGFR -Related Craniosynostosis Syndromes Summary Genetic Counseling Diagnosis Clinical Diagnosis. 2019;-(-):1–33.

34. SALLES C., CAMPOS P.S.F., DE ANDRADE N.A., DALTRO C. Síndrome da apnéia e hipopnéia obstrutiva do sono: análise cefalométrica. Rev. Bras. Otorrinolaringol. [Internet]. 2005 June [cited 2019 Oct 02];71(3):369-372. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0034-72992005000300018&lng=en.

35. SAWH-MARTINEZ R., STEINBACHER D.M. Syndromic Craniosynostosis. Clinics in Plastic Surgery. [Internet]. 2019 April [cited 2019 Oct 02]; 46(2):141–155.

36. SAXBY C., STEPHENSON K.A., STEELE K., IFEACHO S., WYATT M.E., SAMUELS M. The Effect of Midface Advancement Surgery on Obstructive Sleep Apnoea in Syndromic Craniosynostosis. Journal of Craniofacial Surgery. 2018;29(1):92–95.

37. SCHORR F., KAYAMORI F., HIRATA R.P., DANZI-SOARES N.J., GEBRIM E.M., MORIYA H.T. et al. Different craniofacial characteristics predict upper airway collapsibility in Japanese-Brazilian and white men. Chest. 2016;149(3):737–746.

38. SHELTON K.E., GAY S.B., HOLLOWELL D.E., WOODSON H., SURATT P.M.

Mandible Enclosure of Upper Airway and Weight in Obstructive Sleep Apnea. American Review of Respiratory Disease. 1993;148(1):195–200.

39. SPRUIJT B., MATHIJSSEN I.M., BREDERO-BOELHOUWER H.H., CHERIAN P.J., COREL L.J., VAN VEELEN M.L. et al. Sleep Architecture Linked to Airway Obstruction and Intracranial Hypertension in Children with Syndromic Craniosynostosis. Plastic and Reconstructive Surgery. 2016;138(6): 1019e-1029e.

40. TAN H.L., KHEIRANDISH-GOZAL L., ABEL F., GOZAL D. Craniofacial syndromes and sleep-related breathing disorders. Sleep Medicine Reviews. 2016;27(-):74–88.

41. TESSIER, P. Total facial osteotomy. Crouzon's syndrome, Apert's syndrome: oxycephaly, scaphocephaly, turricephalye. Ann Chir Plast. 1967;12(4):273–286.

42. TINANO M.M., MARTINS M.A., BENDO C.B., MAZZIEIRO Ê. Base of the skull morphology and Class III malocclusion in patients with unilateral cleft lip and palate. Dental Press J Orthod. 2015;20(1):79-84.

43. TONELLO, C. Three-dimensional image evaluation of midface morphological features and growth in syndromic craniosynostosis patients following frontofacial monobloc distraction [thesis on the internet]. São Paulo (SP): University of São Paulo; 2016 [accessed 2019 April 1st]. Available at: http://www.teses.usp.br/teses/disponiveis/5/5132/tde-07032017-151610/pt-br.php

44. VEYS B., POTTEL L., MOLLEMANS W., ABELOOS J., SWENNEN G., NEYT N. Three-dimensional volumetric changes in the upper airway after maxillomandibular advancement in obstructive sleep apnoea patients and the impact on quality of life. International Journal of Oral and Maxillofacial Surgery. 2017;46(12):1525–1532.

45. WATANABE T., ISONO S., TANAKA A., TANZAWA H., NISHINO T. Contribution of Body Habitus and Craniofacial Characteristics to Segmental Closing Pressures of the Passive Pharynx in Patients with Sleep-Disordered Breathing. Am J Respir Crit Care Med. 2002;165(2):260–265.

46. WENGER, T. L.; HING, A. V; EVANS, K. N. Apert Syndrome. GeneReviews. 2019;1–26.

47. ZANDIEH, S. O.; PADWA, B. L.; KATZ, E. S. Adenotonsillectomy for obstructive sleep apnea in children with syndromic craniosynostosis. Plastic and Reconstructive Surgery. 2013;131(4):847–852.

FIGURES

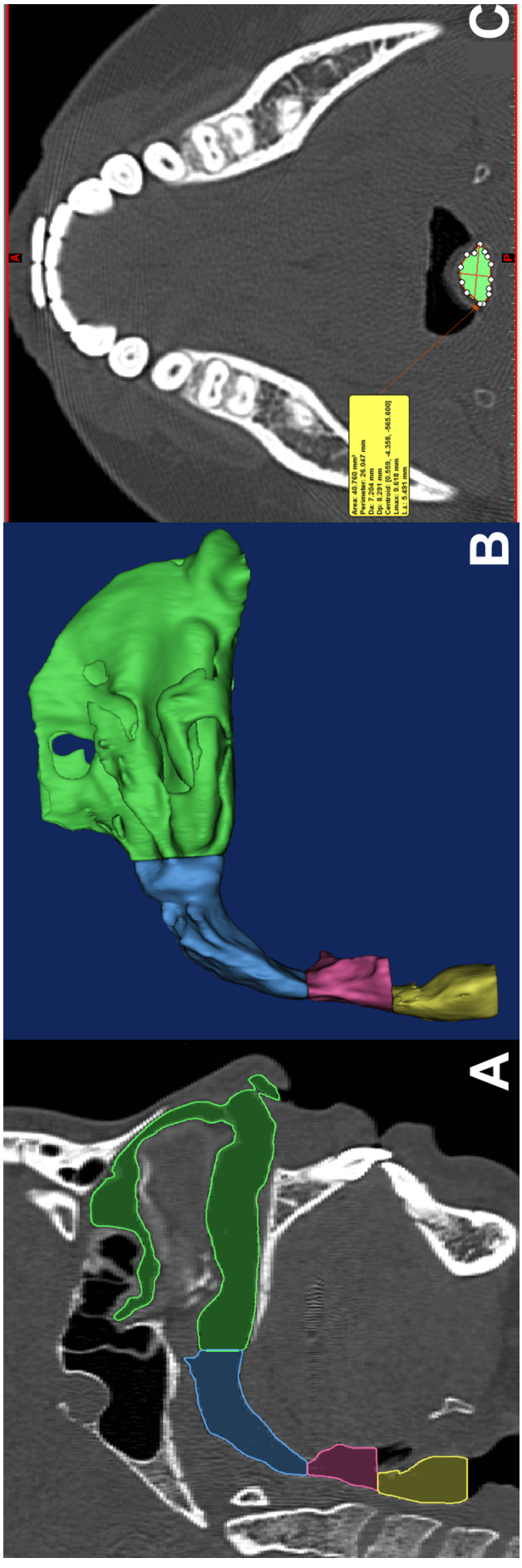


Figure 2A: Selected region of interest in the UAW; **Figure 2B**: The three-dimensional model obtained from the segmentation process; **Figure 2C**: Smallest area of the airway, representing the minimal cross-sectional area.

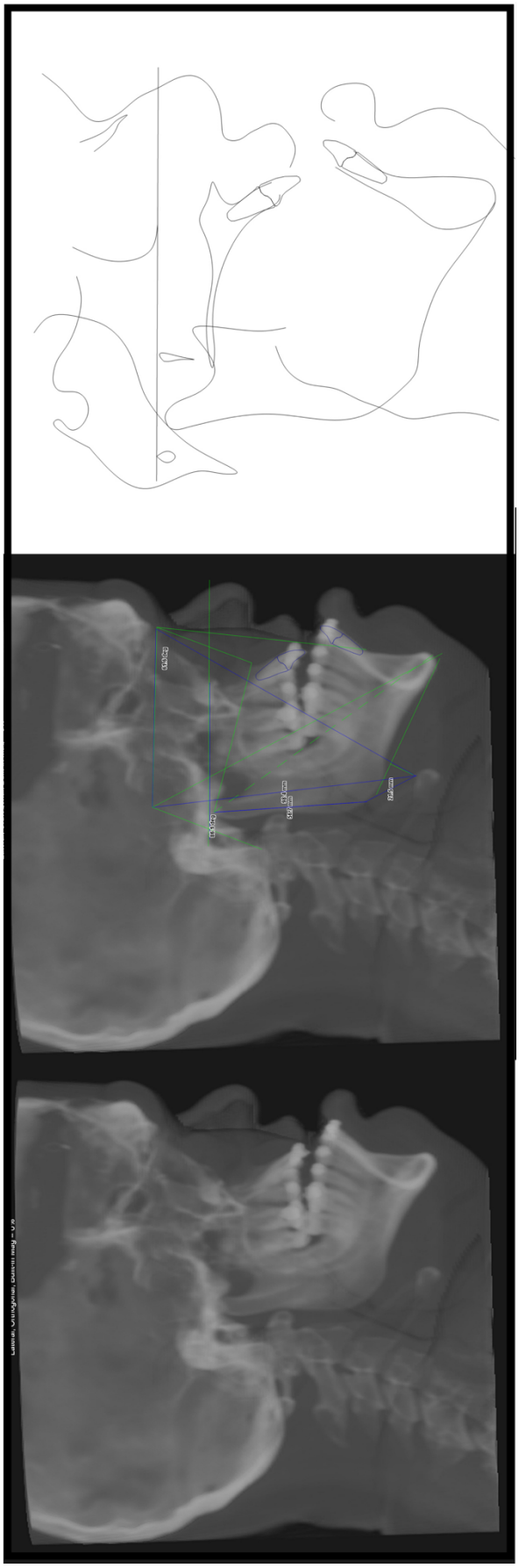


Figure 3: Cephalometric analysis performed in Dolphin software, in an individual from SCS group.

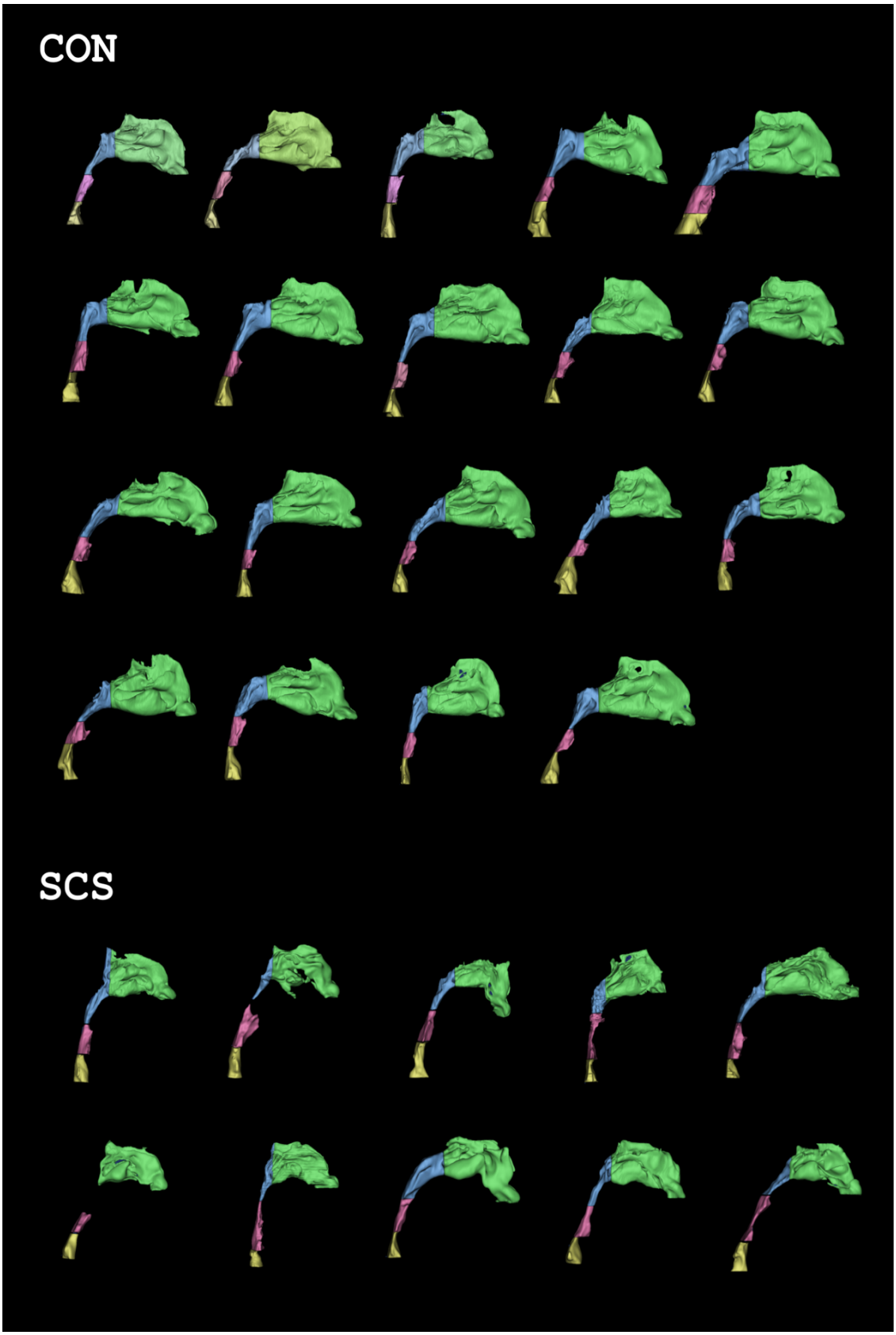


Figure 4: Three-dimensional models generated by the upper airway reconstruction of control group (CON) and craniosynostosis group (SCS). Different colors represent different anatomical division, as follow: Light green: nasal cavity. Light blue: nasopharynx. Pink: oropharynx. Yellow: hypopharynx.

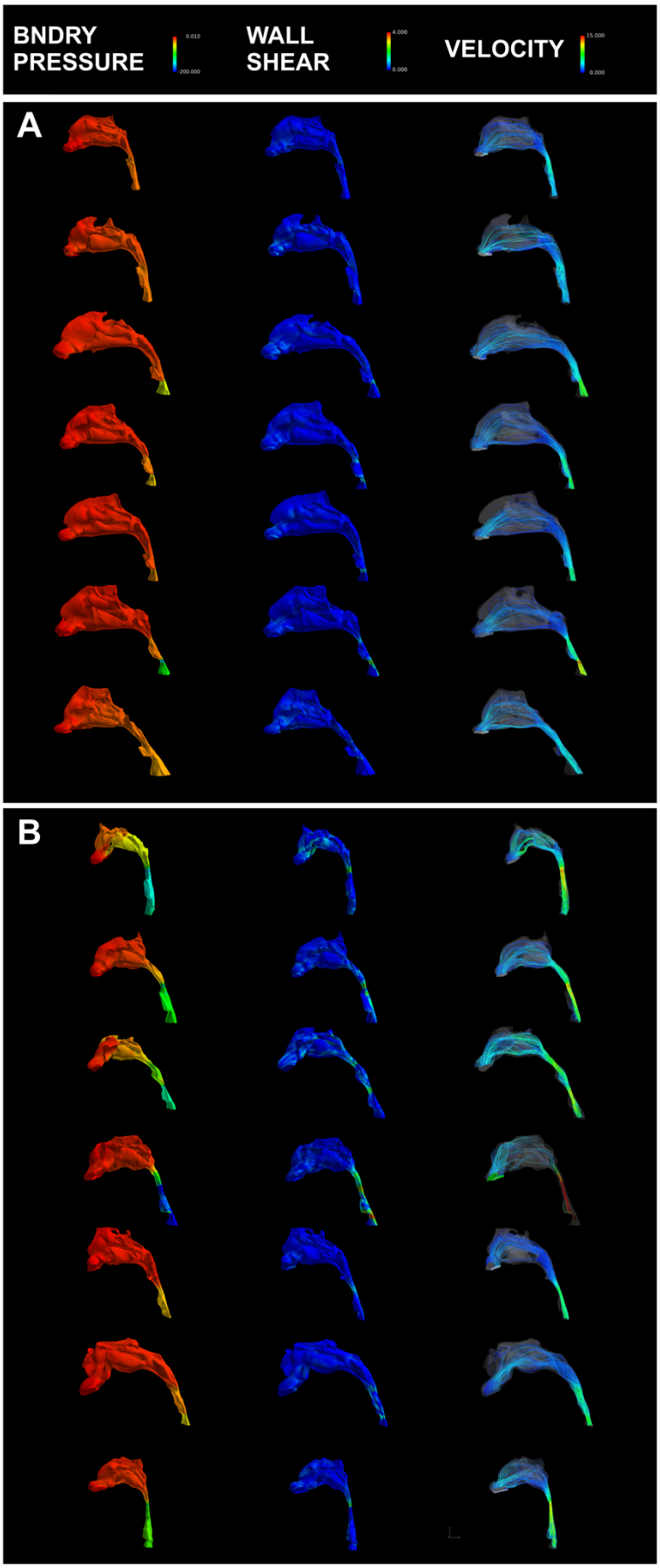


Figure 5: Post-processed images from the CFD analyses. Figure 5A represents data from CON group. Figure 5B represents data from SCS group. From left the left column to the right: pressure boundary condition; wall shear stress; velocity-magnitude streamlines.

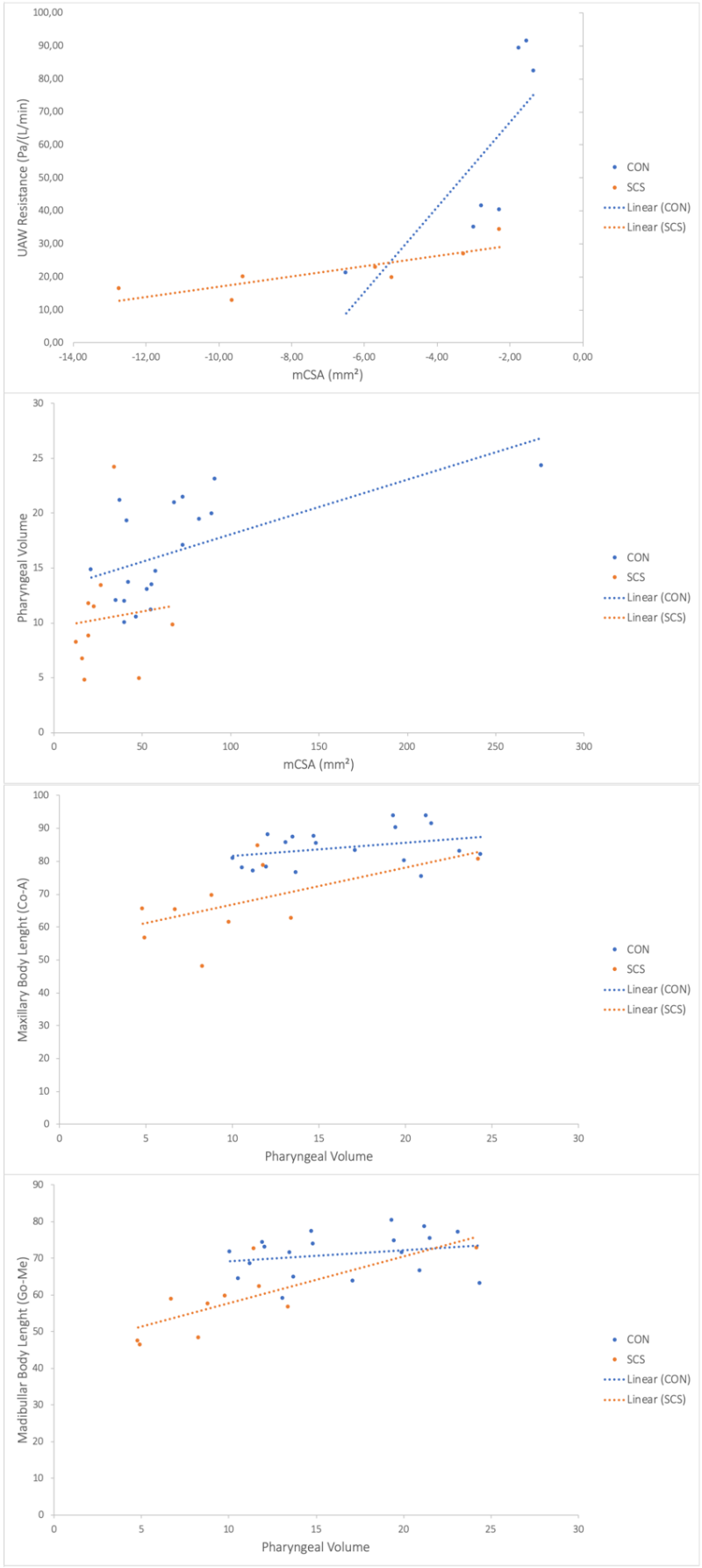


Figure 6: Correlations between different variables collected. (A) Minimal cross-sectional area *versus* airway resistance; (B) Minimal cross-sectional area *versus* pharyngeal volume; (C) Pharyngeal volume *versus* maxillary body length; (D) Pharyngeal volume *versus* mandibullar body length.

TABLES

Table 1: Description of cephalometric landmarks, linear and angular measurements considered for this study.

VARIABLE	DEFINITION
Cephalometric Landmark	
Basion (Ba)	The most inferior/posterior point on the anterior margin of the foramen Magnum
Condylion (Co)	The most posterior/superior point on the condyle of the mandible
Orbitale (Or)	The most inferior point on the lower border of the orbit
Porion (Po)	The most superior point of the surface of the external auditory meatus
Sella (S)	Point at the center of sella turcica (pituitary fossa)
Pogonion (Pg)	The most anterior point of mandibular symphysis
A point (A)	The deepest point at concavity of anterior maxilla (subspinale)
B point (B)	The deepest point at concavity of mandibular symphysis (supramentale)
Menton (Me)	The lowest point on mandibular symphysis
Nasion (N)	Point at the junction of frontal and nasal bones (frontonasal suture)
Anterior Nasal Spine (ANS)	The most anterior point on maxillary bone at the inferior margin of the piriform aperture
Posterior Nasal Spine (PNS)	Posterior limit of hard palate
Gonion (Go)	The most posterior inferior point on the outline of the angle of the mandible
H (Hyoid)	The most anterior/superior point of the hyoid
Mandibular plane (MP)	Plane from constructed Gonion (Go) to Menton (Me)
Frankfort horizontal (FHP)	Plane passing through points Orbitale (Or) and Porion (Po
Mx/Md Dimensions	
Co-A (Maxillary unit length)	Distance from Condylion (Co) to A point
Go-Me	Distance from Gonion (Go) to Menton (Me)
Mx/Md Sagittal Position	
SNA	Angle subtended from Sella (S) by means of Nasion (N) to maxillary point A
SNB	Angle subtended from Sella (S) by means of Nasion (N) to mandibular point B
ANB	Angle subtended from maxillary point A by means of Nasion (N) to mandibular point B

Table 2: Individual and mean values of both measurements (T1+T2/2) regarding volume (V, cm^3) and minimal cross-sectional areas (mCSA, mm^2), in the different regions assessed, on groups CON and SCS.

	Years of Age		Volume (cm^3) tUAW		NC		Phrx		NP		OP		HP		Minimal Cross-Sectional Areas (mm^2)	
	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS
	26	20,5	35,57	17,25	16,42	8,39	19,45	8,81	9,78	2,99	3,34	3,1	6,13	2,54	82,42	19,9
	34	21	31,59	25,92	18,77	14,39	13,08	11,47	7,56	3,64	2,43	3,37	2,82	4,33	52,71	22,86
	18,5	23	40,51	14,97	17,37	10,19	23,14	4,81	12,07	2,25	4,1	1,63	6,71	0,81	91,4	17,76
	23,5	18	38,64	17,54	17,76	12,61	20,94	4,92	12,58	0	2,54	1,92	5,3	2,91	68,18	48,65
	18	15	42,88	21,89	18,53	12,11	24,38	9,82	11,3	1,69	7,07	4,73	5,45	3,32	276,24	67,35
	34	13	40,62	20,43	19,12	12,15	21,51	8,27	8,3	1,57	6,19	3,64	6,83	2,77	73,18	12,76
	34	25,5	32,31	20,88	15,2	14,11	17,12	6,72	10,06	2,14	2,35	1,43	4,5	3,08	73,02	16,43
	35	28,5	27,17	29,06	13,45	15,6	13,71	13,42	7,72	9,07	2,45	1,69	3,44	2,5	42,16	26,79
	23	26	23,3	47,86	12,76	23,76	10,56	24,21	5,23	11,96	2,73	6,8	2,39	5,24	46,6	34,4
	23	20	40,26	29,38	20,94	17,64	19,34	11,78	10,39	4,3	2,95	5,05	5,84	2,33	41,57	19,68
	15,5		27,5		15,56		11,96		7,49		1,85		2,5		40,26	
	31		33,51		20,06		13,48		7,61		2,45		3,25		55,43	
	25		34,72		22,75		12,06		7,24		2,34		2,54		35,1	
	19,5		35,04		15,14		19,93		7,59		2,81		9,35		89,29	
	19		25,3		15,27		10,05		6,21		1,65		2,04		39,87	
	21		38,51		23,7		14,85		9,67		1,8		3,31		21,25	
	34		30,34		19,16		11,22		5,68		1,86		3,52		55,18	
	28,5		43,07		21,92		21,22		12,45		3,43		5,11		37,21	
	17,5		30,97		16,3		14,73		8,29		3,19		3,04		57,88	
Mean	21,21	22,07	34,31 [a]	24,52 [a]	17,90 [b]	14,10 [b]	16,46 [c]	10,42 [c]	8,80 [d]	3,96 [d]	3,03	3,34	4,42 [e]	2,98 [e]	67,32 [f]	28,66 [f]
SD	3,72	5,14	5,97	9,55	3,07	4,30	4,60	5,63	2,23	3,71	1,42	1,77	1,95	1,19	54,20	17,14

tUAW, total upper airway; NC, nasal cavity; Phrx, pharynx; NP, nasopharynx; OP, oropharynx; HP, hypopharynx; mCSA, minimal cross-sectional area; CON, control group; SCS, syndromic craniosynostosis group; SD, standard deviation.
Same letters mean statistical differences between groups (*p<0,05)* using *student's t-test*.

Table 3: Individual description of cephalometric measurements for control (CON) and syndromic craniosynostosis (SCS) groups

	SNA		ANB		Ba-S-N		SNH		Co-A		Go-Me	
	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS
	80,70	80,30	4,60	-2,20	133,00	120,10	57,1	65,2	90,30	69,70	74,80	57,70
	83,90	93,40	8,50	1,50	141,60	116,40	53	72,8	85,60	84,80	59,10	72,70
	78,50	83,30	-1,60	-3,30	127,70	123,90	62,7	55,6	83,10	65,60	77,10	47,60
	80,40	70,80	4,50	-14,50	138,90	109,60	57,1	61,6	75,30	56,70	66,70	46,50
	82,70	84,90	6,50	2,70	142,20	119,90	47,2	70	82,10	61,50	63,20	59,80
	87,10	71,50	2,60	-9,10	136,90	112,50	60,5	61,7	91,40	48,10	75,50	48,40
	86,50	67,70	3,10	-14,20	128,80	123,60	60,6	62,8	83,30	65,30	63,90	59,00
	78,50	68,00	4,50	-11,70	134,50	129,30	52,5	56,3	76,70	62,60	64,90	56,70
	82,20	73,30	6,60	-2,30	132,90	132,70	51,8	58,9	78,00	80,60	64,60	73,00
	89,40	71,20	3,90	-3,10	129,30	130,50	60,6	57,5	93,90	78,70	80,40	62,30
	85,70		1,70		124,70		59,1		78,20		74,40	
	84,90		5,90		132,10		53,6		87,50		71,50	
	82,40		3,00		118,20		56,2		88,00		73,10	
	76,60		-1,60		129,00		54		80,10		71,70	
	86,00		4,50		135,60		55		81,00		71,90	
	80,00		1,60		125,20		54,3		85,50		74,00	
	78,70		1,60		129,20		51,8		77,00		68,60	
	89,50		5,10		125,80		63,4		93,80		78,80	
	80,80		0,10		126,40		61,5		87,70		77,40	
Mean	82,87[a]	76,44[a]	3,43[b]	-5,62[b]	131,16[c]	121,85[c]	56,42[d]	62,24[d]	84,13[e]	67,36[e]	71,14[f]	58,37[f]
SD	3,80	8,58	2,70	6,29	6,18	7,67	4,40	5,72	5,83	11,36	5,98	9,41

SNA(º), ANB(º), Ba-S-N(º), SNH(º), Co-A(mm), Go-Me(mm); Standard Deviation (SD);
Same letters mean statistical differences between groups (*p<0,05)* using *student's t-test*.

Table 4: Data description of anthropometric values used for simulations and Computational Fluid Dynamics (CFD) analysis.

	Gender		Weight (kg)		Height (m)		Body Mass		Age (years)		Flow Rate (L/min)		Pressure Boundary Condition on Outlet (Pa)		Airway Resistance (Pa/(L/min))	
	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS	CON	SCS
	1	1	82,00	67,00	1,79	1,75	25,59	21,88	26,00	26,00	18,69	17,46	-25,00	-40,00	-1,34	-2,29
	1	1	74,00	61,00	1,77	1,72	23,62	20,62	18,50	21,00	18,08	16,72	-27,60	-95,00	-1,53	-5,68
	1	1	96,00	70,00	1,94	1,68	25,51	24,80	23,00	25,50	20,15	17,87	-56,00	-227,50	-2,78	-12,73
	2	2	67,00	73,00	1,69	1,67	23,46	26,18	25,00	28,50	14,68	14,83	-43,80	-48,50	-2,98	-3,27
	2	2	56,00	44,00	1,73	1,61	18,71	16,97	15,50	13,00	13,88	12,78	-31,80	-123,00	-2,29	-9,63
	2	2	78,00	64,00	1,79	1,55	24,34	26,64	21,00	20,50	15,38	14,24	-100,00	-132,82	-6,50	-9,33
	1	1	90,00	63,00	1,80	1,70	27,78	21,80	19,50	20,00	20,00	16,76	-35,00	-87,70	-1,75	-5,23
Mean	-	-	77,57[a]	63,14[a]	1,79[b]	1,67[b]	24,14	22,70	21,21	22,07	17,27	15,81	-45,60[c]	-107,79[c]	-2,74[d]	-6,88[d]
SD	-	-	13,56	9,41	0,08	0,07	2,81	3,43	3,73	5,14	2,59	1,89	26,21	63,07	1,77	3,78

Same letters mean statistical differences between groups (*p<0,05)*, using *Student's t-test*.
CON, control group; SCS, syndromic craniosynostosis group; Gender 1, male; Gender 2, female.

4. MANUSCRIPT #2

4. MANUSCRIPT #2

Polysomnographic and tomographic assessment of the upper airways in syndromic craniosynostosis: A Case Report

To be submitted to “Nature and Science of Sleep”

ABSTRACT

Objectives: Previous study has demonstrated that maxillary retrusion and upper airway (UAW) dimensional reduction are common and related conditions observed in subjects with syndromic craniosynostosis (SCS). These conditions can lead to sleep disorders, such as Obstructive Sleep Apnea (OSA). The aim of the present study was to assess the impact of SCS on the UAW, by means morphophysiological evaluation using computed tomography and polysomnography (PSG). **Case Report**: 28-years-old female diagnosed with SCS, with a body mass index of 28,6 kg/m2, referring frequent snoring, nasal obstruction and daytime excessive somnolence. The patient was submitted to 12 PSG exams over the years, from 12 to 26 years of age, performed by two different craniofacial centers. PSG findings indicated severe OSA (AHI12y = 33,6 / minSatO2 = 61%, AHI19y = 38,3 / minSatO2 = 62%, AHI19y = 99,4 / minSatO2 = 76%). CPAP was the chosen treatment and PSG results during CPAP use corresponded to AHI14y = 0,5 / minSatO2 = 79%, AHI26y = 18,9 / minSatO2 = 78%. Although OSA was still observed on PSG with the use of CPAP, OSA indexes were reduced, improving quality of sleep. The tomographic assessment was performed at eighteen years, using Dolphin Imaging Software 11.95. Reduced volume (cm3) and minimal cross-sectional area (mm^2) were observed when compared to literature controls as follows: total UAW volume: 17,5 cm3, Nasal Cavity volume: 12,6 cm3, Pharyngeal volume: 4,9 cm3 (reference value: 28,2 [10,0] cm^3) (83% reduction), Nasopharyngeal volume: 0,0 cm3, Oropharyngeal volume: 1,9 cm3, Hypopharyngeal volume: 2,9 cm3; and minimal cross-sectional area of 48,65 mm2 (reference value: 203,3 [114.2] mm2) (76% reduction) (Trindade-Suedam et al. 2017). Monobloc craniofacial surgery was performed. **Conclusion**: Based on our findings, this subject with SCS presented with a severely reduced UAW, which probably explains the severe apnea observed throughout her life. This case stresses out the need for multidisciplinary approach in order to improve quality of life in this specific craniofacial anomaly.

Keywords: Airway obstruction. Acrocephalosyndactylia. Tomography. Imaging, three-dimensional

INTRODUCTION

Syndromic Craniosynostosis (SCS) is the premature closure of cranial sutures along with relatively rare genetic conditions, frequently associated with fibroblast growth factor receptor (FGFR) gene mutations (HOLMES et al. 2018, SAWH-MARTINEZ et al. 2019). Apert syndrome (AS) is one of the SCS types, with the prevalence of 1:65.000-100.000 (SAWH-MARTINEZ et al. 2019). It is characterized by the presence of multisuture craniosynostosis, high intracranial pressure, midface retrusion, exorbitism, syndactyly, and, in some cases, a cleft palate. There is a close relationship between AS and upper airway (UAW) multilevel obstructions, due to midface hypoplasia, predisposing this group of individuals to several respiratory related disorders, such as obstructive sleep apnea (OSA) and UAW resistance syndrome (WENGER et al. 2019, MATHEWS et al. 2018).

The prevalence of OSA in SCS individuals has been reported to be as high as 68% (BANNINK et al. 2011). This breathing disorder is characterized by the reduction or cessation in airflow during sleep, associated with an increase in respiratory breathing effort (CHESSON et al. 2017). Some of the common AS anatomical findings may play an important role in OSA etiology, such as maxillary hypoplasia, reduced internal nasal volumes, abnormal hyoid position and diminished pharyngeal minimal cross-sectional area (CHEN et al. 2016).

Moreover, the holistic approach by the multidisciplinary team is mandatory for SCS individuals, aiming to release intracranial pressure, advance the retruded maxillary bones, resulting in sleep improvement and higher life quality. Therefore, the gold standard to relief high intracranial pressure, reduce maxillofacial discrepancies and treat airway obstructions is the surgical craniofacial advancement (SAWH-MARTINEZ et al. 2019). Thus, tomographic assessment of these individuals provides three-dimensional data, giving important information to support surgical planning. Modeling the UAW shows the relationship of anatomy and airway blockage, indicating constricted regions prone to collapse during sleep, and also providing volumetric values of UAW. However, some severely impacted cases demand supplementary long-term treatments, such as the continuous positive airway pressure (CPAP) and

polysomnography (PSG) is the sleep study indicated for CPAP titration in patients with sleep related breathing disorders (CHESSON et al. 2017).).

Several studies have shown the presence of airway anomalies in SCS (SAWH-MARTINEZ et al. 2019, WENGER et al. 2019, MATHEWS et al. 2018), however there is a lack of information in literature, regarding the anatomical and physiological UAW characteristics in this population. The main purpose of this paper is to report the UAW findings in a SCS case, emphasizing anatomical e physiological relationship with sleep disorders and its relevance to long-term treatment for sleep disorders.

CASE REPORT

Ethical approval was obtained from the local Institutional Review Board, the informed consent was signed by the parents and the assent term was signed by the girl. The authors present the case of a 28-years-old female in good state of health, who had clinical and genetic confirmed diagnosis of AS. Currently admitted to our sleep clinic for excessive daytime sleepiness, excessive snoring, breathing distress, dizziness and diagnosed OSA. Her parents described loud snoring during sleep and several apneic episodes during the sleep night. The girl was referred to the rehabilitation hospital for treatment since she was a newborn. However, due to the need of rigorously accomplish the treatment protocol, the sleep study was conducted between two different reference centers.

During physical evaluation, the body mass index (BMI) was 28,6 kg/m^2, (weight = 75,0Kg. height = 1,62m) compatible with overweight obesity classification. Chronic diseases were denied, and a sedentary lifestyle was reported. A tomography was taken at 18 years of age for purposes of surgical panning. According to medical records, during surgical protocol the girl went through midface advancement in mid-2013. Also, clinical findings were compatible with AS, such as midface retrusion, exorbitism, and syndactyly. Morphological characteristics were confirmed by cephalometric analysis.

In order to assess cephalometric measurements, Dolphin Imaging 11.8 software (Dolphin Imaging, Chatsworth, California, USA) was used. The head was positioned based on axial, coronal and sagittal plane. Cephalometric findings, volumes and minimal cross-sectional area are shown in Table 6 and reveled the following data: midfacial retrusion, represented by the negative ANB angle (-14,5°) and diminishes

SNA angle (70,8°); anterior position of the posterior wall of the pharynx, identified by the flattened SN-Ba angle (109,6°) small mandibular body length with a diminished linear measurements (mm) of midface length (CoA 56,7), mandibular length (Co-Gn 99,0) and mandibular body length (Go-Me 46,5) There was a collapse of the soft palate, isolating the nasal cavity (NC) from the pharynx (Phrx).

Tomographic assessment allowed 3D reconstruction in Mimics Research 17.0 (Materialise, Leuven, Belgium) into different regions: total airway (tUAW): from the nostrils to the most inferior point of hyoid bone in mid-sagittal slice; nasal cavity (NC): from the anterior limit of tUAW to the most posterior-inferior point of the inferior turbinate; total pharynx (Phrx): from the posterior limit of NC to the inferior limit of tUAW; nasopharynx (NPhrx): from the anterior limit of Phrx to the most posterior-inferior point of soft palate in the mid-sagittal slice; oropharynx (OPhrx): from the inferior limit of NPhrx to the most superior point of epiglottis; hypopharynx (HPhrx): from the superior limit of OPhrx to the inferior limit of the Phrx. From this anatomical division, volume (V)(cm^3) and minimal cross-sectional area from the Phrx (mCSA) (mm^2) were obtained. Measurements were taken twice (T1 and T2) by the same operator, and the mean between T1/T2 was considered for the analysis. The volumetric findings are following: tUAW 17,5, NC 12,6, Phrx 4,9, NPhrx 0,0, OPhrx 1,9, HPhrx 2,9 (Figure 7). From the pharyngeal region, the most constricted area was 48,6. However, it is important to emphasize that the soft palate was completely obstructing the airway from the nasal cavity to downstream, therefore the patient was a mandatory mouth breather, at least during the tomographic procedure. The V and mCSA were reduced when compared to literature controls: total UAW volume: 17,5 cm3, Nasal Cavity volume: 12,6 cm3, Pharyngeal volume: 4,9 cm3 (reference value: 28,2 [10,0] cm^3) (83% reduction), Nasopharyngeal volume: 0,0 cm3, Oropharyngeal volume: 1,9 cm3, Hypopharyngeal volume: 2,9 cm3; and minimal cross-sectional area of 48,65 mm2 (reference value: 203,3 [114.2] mm2) (76% reduction) (Trindade-Suedam et al. 2017).

Polysomnographic follow-up was taken from 12 to 26 years of age. These assessments are displayed in Table 5. Over the four-teen years, twelve PSG were performed in order to evaluate sleep quality. From that, eight exams were with CPAP and four without the appliance. The mean values of mean oxyhemoglobin saturation ($SatO_2$) was 92% and minimum of 75%. Obstructive events were predominant, with a mean of 166,83 events nightly, and the AHI varying from 0,5 to 99 events/h. The mean

arousals were also elevated (54,92 events), with the arousal index varying from 0,8 to 33,7, indicative of sleep fractionation. Even though PSG findings indicated severe OSA over the years, with impact of sleep architecture, the patient and her parents have great adherence to the treatment, referring improvement of snoring and life quality. The tomographic assessment was performed at eighteen.

DISCUSSION

Apert syndrome and other SCS are systematically linked with breathing disorders, specially OSA (WENGER et al. 2019, MATHEWS et al. 2018, TAN et al. 2016 –10). Although multifactorial, the midface retrusion could be considered a predominant factor for the development of this condition in the referred population (TAN et al. 2016). The case described in this study showed reduced UAW dimensions and literature supports the etiological role played by anatomical factors in OSA. Considering our findings showed general reduced values for UAW parameters, the literature supports the etiological role played by anatomical factors in OSA (HOLMES et al. 2018, CHEN et al. 2016, TAN et al. 2016). An important predictor of airway collapsibility is the backward position of the maxilla which can restrict nasopharyngeal volume as observed in this case. Besides maxillary retrusion, pharyngeal compliance is also impacted by the greater flexure of the skull base (TINANO et al. 2015), represented by a more acute Ba-S-N angle, compared to normal anatomical parameters. It means that the more acute is the Ba-S-N angle, the more anteriorly positioned is the posterior wall of the pharynx. The mCSA, which represents the most constricted site of the pharynx, is another important anatomical condition that can favor pharyngeal collapse. As the velocity airflow increases, the internal pressure drops, due to Bernoulli effect, leading to pharyngeal collapse (LE et al. 2019).

These factors, altogether enclose the pharyngeal soft tissue, leading to a narrower lumen (CHEN et al. 2016), explaining the soft palate collapse observed during tomographic assessment. In physiological conditions, muscle tone during awake periods is capable to maintain the airway patency. However, during REM sleep there is a decrease in muscle tone, leading to a narrow pharynx diameter *i.e.* the lower muscle tone causes an approximation of UAW walls, increasing the risk of breathing

distress and pharyngeal collapse, specially at narrower sites. On the other hand, some authors minimized the anatomical role in sleep related disorder, associating normal sleep architecture to SCS individuals, thereby stating a theory which unifies disturbed sleep architecture, OSA and intracranial hypertension (SPRUIJT et al. 2016). The results highlight the need of more studies in this field.

Despite anatomy represents a major physical obstructive factor to air flow, central apnea could not be set aside, since it is highly reported in SCS individuals (TAN et al. 2016). One year before the surgery for intracranial pressure relief, the patient presented 29 central apneas (1,4/hour) detected by PSG. This occurrence was not observed after surgery, only obstructive events. There is evidence showing the relationship between central sleep apnea and elevated intracranial pressure (SPRUIJT et al. 2016). In cases of central apnea predominance, more conservative approaches, as the CPAP, are less probable to improve sleep quality, even for individuals with less severe anatomical obstructions. For this reason, both UAW anatomy and elevated intracranial pressure symptoms should be considered by craniofacial team during surgical planning, as well as in post-surgery following evaluation.

Aesthetics complaints associated with SCS might become secondary when compared to the impact that severe OSA has in quality of life (BANNINK et al. 2011). The severity of OSA was described as related to breathing effort arousals and consequently reducing sleep efficiency (SPRUIJT et al. 2016). In accordance to this data, the PSG findings showed several arousals episodes over the years. However, considering the severity of some referred arousals episodes, oxyhemoglobin desaturation and the disturbed sleep architecture, there was a considerable maintenance of the sleep efficiency. Therefore, the long-term treatment with CPAP could have overcome in a moderate manner the severe hypoplasia e diminished UAW dimensions, as already suggested in the literature (MÜLLER-HAGEDORN et al. 2018). It could implicate that some conservative approaches should be considered as much as craniofacial advancements, since there is a growing evidence of its benefits, when well indicated (CHESSON et al. 2017, MÜLLER-HAGEDORN et al. 2018).

Finally, this case report demonstrated the expected phenotype characteristics of reduced UAW dimensions and severe midface retrusion in SCS individuals. The association of CPAP with midface advancement for a severe case of OSA improved sleep and breathing of the patient. Hence, the authors do believe that the multidisciplinary team should consider the use of CPAP even in severely impacted

cases, in which surgical planning is mandatory. Therefore, the harmful effects of disturbed sleep and impaired life quality of SCS individuals could be minimized.

The presented case shows that anatomy and physiology of UAW are severely impacted in SCS, stressing out the mandatory need of multidisciplinary approach, aiming at improvements in quality of life for these impaired individuals.

ACKNOWLEDGEMENTS

The authors would like to thank the Coordination for the Improvement of the Higher Education Personnel (CAPES), for its contribution in funding this study. The grant protocol number was 88881.188742/2018-0. Also, Santander Bank, which also funded this study with a short period scholarship “International Mobility Support Santander” PRPG number 03/2017, thank you for this opportunity.

REFERENCES:

1. BANNINK N., MALIEPAARD M., RAAT H., JOOSTEN K.F., MATHIJSSEN I.M. Reliability and validity of the obstructive sleep apnea-18 survey in healthy children and children with syndromic craniosynostosis. Journal of Developmental and Behavioral Pediatrics. 2011;32(1): 27–33.

2. BANNINK, N., MALIEPAARD, M., RAAT, H., JOOSTEN, K.F.M., MATHIJSSEN, I.M.J. Obstructive sleep apnea-specific quality of life and behavioral problems in children with syndromic craniosynostosis. Journal of Developmental and Behavioral Pediatrics. 2011;32(3):233–238.

3. CHEN H., AARAB G., DE RUITER M.H., DE LANGE J., LOBBEZOO F., VAN DER STELT P.F. Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: A systematic review. Sleep Medicine. 2016;21(-):19–27.

4. CHESSON J, FERBER RA, FRY JM, GRIGG-DAMBERGER M, HARTSE KM, HURWITZ TD, et al. Practice parameters for the indications for polysomnography and related procedures. Sleep. 2017;20(6):406–22.

5. HOLMES G., O'ROURKE C., MOTCH PERRINE S.M., LU N., VAN BAKEL H., RICHTSMEIER J.T. et al. Midface and upper airway dysgenesis in FGFR2-related craniosynostosis involves multiple tissue-specific and cell cycle effects. Development [serial on the internet]. 2018 Oct 5;145(19):dev166488. doi: 10.1242/dev.166488. PMID: 30228104; PMCID: PMC6198473.

6. LE T.B., MOGHADDAM M.G., WOODSON B.T., GARCIA G.J.M. Airflow limitation in a collapsible model of the human pharynx: physical mechanisms studied with fluid-structure interaction simulations and experiments. Physiological Reports. 2019;7(10): p. e14099.

7. MATHEWS F., SHAFFER A., GEORG M., FORD M., GOLDSTEIN J., JABBOUR N., et al. Airway anomalies in patients with craniosynostosis. Laryngoscope. 2018;00:1–9.

8. MÜLLER-HAGEDORN S., WIECHERS C., ARAND J., BUCHENAU W., BACHER M., KRIMMEL M. et al. Less invasive treatment of sleep-disordered breathing in children with syndromic craniosynostosis. Orphanet Journal of Rare Diseases. 2018;13(1):1–8.

9. SAWH-MARTINEZ R., STEINBACHER D.M. Syndromic Craniosynostosis. Clinics in Plastic Surgery. [Internet]. 2019 April [cited 2019 Oct 02]; 46(2):141–155.

10. SPRUIJT B., MATHIJSSEN I.M., BREDERO-BOELHOUWER H.H., CHERIAN P.J., COREL L.J., VAN VEELEN M.L. et al. Sleep Architecture Linked to Airway Obstruction and Intracranial Hypertension in Children with Syndromic Craniosynostosis. Plastic and Reconstructive Surgery. 2016;138(6): 1019e-1029e.

11. TAN H.L., KHEIRANDISH-GOZAL L., ABEL F., GOZAL D. Craniofacial syndromes and sleep-related breathing disorders. Sleep Medicine Reviews. 2016;27(-):74–88.

12. TINANO M.M., MARTINS M.A., BENDO C.B., MAZZIEIRO Ê. Base of the skull morphology and Class III malocclusion in patients with unilateral cleft lip and palate. Dental Press J Orthod. 2015;20(1):79-84.

13. TRINDADE-SUEDAM I.K., LIMA T.F., CAMPOS L.D., YAEDÚ R.Y.F., FILHO H.N., TRINDADE I.E.K. Tomographic pharyngeal dimensions in individuals with unilateral cleft lip/palate and class III malocclusion are reduced when compared with controls. Cleft Palate Craniofacial Journal. 2017;54(5):502-508.

14. WENGER, T. L.; HING, A. V; EVANS, K. N. Apert Syndrome. GeneReviews. 2019;1–26.

FIGURES

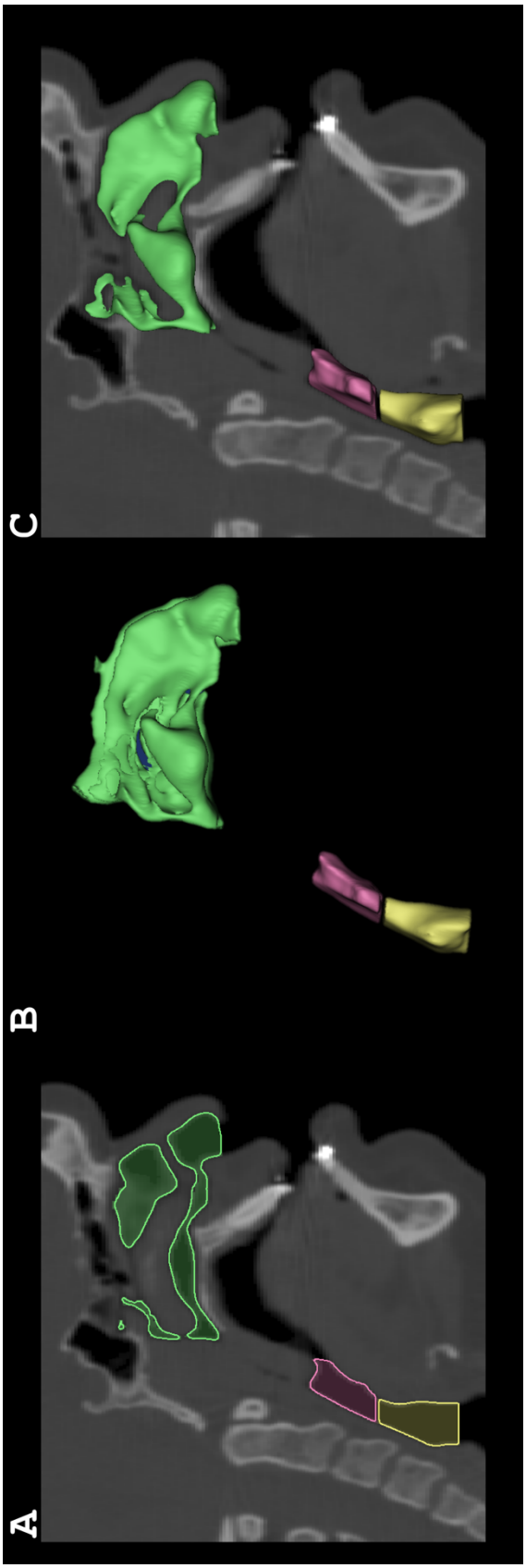


Figure 7A: 2D view of nasal cavity and the oral and hypo subdivisions of pharynx; **B:** 3D reconstruction of the upper airway; **C:** Superimposition of 3D reconstruction over a parasagittal view of computed tomography. *Light green: nasal cavity; Pink: oropharynx; Light yellow: hypopharynx.*

Table 5: Main polysomnographic (PSG) variables observed in SCS female, from 12 years of age to 26 years of age.

Year	2003			2004	2005	2006	2007	2008	2010		2015	2017	Mean	SD	Min.	Max.
Month	*10*	*11*	*12*						*2*	*9*						
Arousal	253	64	36	63	22	49	26	70	8	2	61	5	**54,92**	67,05	2	253
Arousal Index (event/h)	33,7	9,4	6,2	9,6	3,7	6,7	4,3	13,8	3,5	0,62	15,1	0,8	**8,95**	9,05	0,8	33,7
Apnea + Hypopnea	252	257	242	126	3	35	68	69	88	609	141	112	**166,83**	162,83	3	609
Central Apnea	0	0	0	0	0	0	0	29	0	0	0	0	**2,42**	8,37	0	29
Obstructive Apnea	0	99	138	62	1	7	0	7	0	481	49	97	**78,42**	135,57	0	481
Central Hypopnea	0	0	0	0	0	0	0	0	0	0	0	0	**-**	-	-	-
Obstructive Hypopnea	252	158	104	64	2	28	68	23	88	127	90	15	**84,92**	70,70	2	252
AHI	33,6	37,7	41,5	19,2	0,5	4,8	11,4	13,6	38,3	99,4	35	18,9	**29,49**	26,06	0,5	99
Mean SatO2	84%	85%	-	92%	95%	97%	96%	96%	85%	93%	97%	96%	**92%**	0,05	84%	97%
Min. SatO2	61%	61%	-	68%	79%	90%	88%	79%	62%	76%	81%	78%	**75%**	0,10	61%	90%
CPAP	NO	YES	YES	YES	YES	YES	YES	NO	NO	NO	YES	YES	**-**	-	-	-
Total Sleep Time (min)	450	410,5	350	394	377	449	359	354	138	383,5	282,5	355,5	**358,58**	83,12	138	450
Sleep Efficiency	94,20%	96,70%	96,70%	98,50%	94,80%	91,70%	92,80%	75,10%	73,60%	95,80%	55,30%	92%	**88%**	0,13	55,30%	98,50%

Mean: mean values from the observed parameters; SD: Standard deviation; Min.: Minimum value over the years presented; Max.: Maximum values over the years presented; CPAP: Continuous Positive Airway Pressure..

Table 6: Cephalometric variables of angular and linear measurements, compared to parameter of a non-discrepant anatomy.

Cephalometric Measurements	Values	N.P.	SD	D.N.P.
SNA (°)	70,8	82	0,35	-3,2
SNB (°)	85,3	80,9	3,4	1,3
ANB (°)	-14,5	1,6	1,4	-10,8
FMA (MP-FH) (°)	24,8	23,9	4,5	0,2
IMPA (L1-MP) (°)	97,5	95	7	0,4
Gonial/Jaw Angle (Ar-Go-Me) (°)	118,5	122,9	6,7	-0,7
SN - Basion (°)	109,6	131	4,5	-4,8
Y-Axis (SGn-SN) (°)	60,6	67	5,5	-1,2
Hyoid Angle (H-Gonion) to (H-Menton) (°)	114,4	N/A	N/A	N/A
Midface Lenght (Co-A) (mm)	56,7	93,2	4	-9,1
Mandibular Lenght (Co-Gn) (mm)	99	122,3	4	-5,8
Mandibular Body Lenght (Go-Me)(mm)	46,5	71	5	-4,9
Co-Go (mm)	62,8	55	3	2,6
Posterior Cranial base (S-Ba) (mm)	43,1	N/A	N/A	N/A
Hyoid-MP Perp (mm)	9,3	N/A	N/A	N/A
Hyoid - S (mm)	96,8	N/A	N/A	N/A
Pog-NB (mm)	1,4	2,4	1,7	-0,6
Morphological Variable	**Values**			
tUAW (cm^3)	17,50			
NC (cm^3)	12,60			
Phrx (cm^3)	4,90			
NPhrx (cm^3)	-			
OPhrx (cm^3)	1,90			
HPhrx (cm^3)	2,90			
mCSA (mm^2)	48,65			
Local of mCSA	Hypopharynx			

Abbreviations: N.P. Normal parameters; SD Standard deviation; D.N.P. Deviation from the normal parameter; tUAW total upper airway; NC nasal cavity; Phrx pharynx; NPhrx nasopharynx; OPhrx oropharynx; HPhrx hypopharynx; mCSA minimal cross-sectional area.

5. GENERAL CONCLUSIONS

5. GENERAL CONCLUSIONS

The UAW dimensions were reduced in SCS individuals compared to controls. This reduction could be explained by the significant maxillomandibular discrepancy also observed. The UAW physiology is compromised by the impact of reduced dimension, leading to more negative inspiratory pressures and consequently to elevated UAW resistance. Thus, this population might be more prone to develop obstructive sleep apnea and other sleep related disorders.

REFERENCES

REFERENCES

1. BANNINK N., MALIEPAARD M., RAAT H., JOOSTEN K.F., MATHIJSSEN I.M. Reliability and validity of the obstructive sleep apnea-18 survey in healthy children and children with syndromic craniosynostosis. Journal of Developmental and Behavioral Pediatrics. 2011;32(1): 27–33.

2. BANNINK, N., MALIEPAARD, M., RAAT, H., JOOSTEN, K.F.M., MATHIJSSEN, I.M.J. Obstructive sleep apnea-specific quality of life and behavioral problems in children with syndromic craniosynostosis. Journal of Developmental and Behavioral Pediatrics. 2011;32(3):233–238.

3. CALANDRELLI R., PILATO F., MASSIMI L., PANFILI M., D'APOLITO G., GAUDINO S., et al. Quantitative evaluation of facial hypoplasia and airway obstruction in infants with syndromic craniosynostosis: relationship with skull base and splanchnocranium sutural pattern. Neuroradiology. 2002;24(3):263–276.

4. CHANG K.K., KIM K.B., MCQUILLING M.W., MOVAHED R. Fluid structure interaction simulations of the upper airway in obstructive sleep apnea patients before and after maxillomandibular advancement surgery. American Journal of Orthodontics and Dentofacial Orthopedics. 2018;153(6): 895–904.

5. GHIZONI E., DENADAI R., RAPOSO-AMARAL C.A., JOAQUIM A.F., TEDESCHI H., RAPOSO-AMARAL C.E. Diagnosis of infant synostotic and nonsynostotic cranial deformities: a review for pediatricians. Revista Paulista de Pediatria (English Edition). 2016;34(4):495–502.

6. HU C.-H., WU C.-T., KO E. W.-C., CHEN P.K.-T. et al. Monobloc Frontofacial or Le Fort III Distraction Osteogenesis in Syndromic Craniosynostosis. Journal of Craniofacial Surgery. 2017;28(5):1344–1349.

7. INVERSO G., BRUSTOWICZ K. A., KATZ E., PADWA B. L. The prevalence of obstructive sleep apnea in symptomatic patients with syndromic craniosynostosis. International Journal of Oral and Maxillofacial Surgery. 2016;45(2):167–169.

8. KIMBELL, S.; RHEE, J. S. Mucosal Cooling After Surgery for Nasal Obstruction. Otolaryngol Head Neck Surg. 2015;150(1):139–147.

9. MATHEWS F., SHAFFER A., GEORG M., FORD M., GOLDSTEIN J., JABBOUR N., et al. Airway anomalies in patients with craniosynostosis. Laryngoscope. 2018;00:1–9.

10. MÜLLER-HAGEDORN S., WIECHERS C., ARAND J., BUCHENAU W., BACHER M., KRIMMEL M. et al. Less invasive treatment of sleep-disordered breathing in children with syndromic craniosynostosis. Orphanet Journal of Rare Diseases. 2018;13(1):1–8.

11. NAGY, L.; DEMKE, J. C. Craniofacial anomalies. Facial Plastic Surgery Clinics of North America. 2014;22(4):523–548.

12. NASH R., POSSAMAI V., MANJALY J., WYATT M. The Management of Obstructive Sleep Apnea in Syndromic Craniosynostosis. Journal of Craniofacial Surgery. 2015;26(6):1914–1916

13. OSMAN A., CARTER S., CARBERRY J., ECKERT D. Obstructive sleep apnea: current perspectives. Nature and Science of Sleep. 2018;10(-):21–34.

14. SAWH-MARTINEZ R., STEINBACHER D.M. Syndromic Craniosynostosis. Clinics in Plastic Surgery. [Internet]. 2019 April [cited 2019 Oct 02]; 46(2):141–155.

15. SAXBY C., STEPHENSON K.A., STEELE K., IFEACHO S., WYATT M.E., SAMUELS M. The Effect of Midface Advancement Surgery on Obstructive Sleep Apnoea in Syndromic Craniosynostosis. Journal of Craniofacial Surgery. 2018;29(1):92–95.

16. TONELLO, C. Three-dimensional image evaluation of midface morphological features and growth in syndromic craniosynostosis patients following frontofacial monobloc distraction [thesis on the internet]. São Paulo (SP): University of São Paulo; 2016 [accessed 2019 April 1st]. Available at: http://www.teses.usp.br/teses/disponiveis/5/5132/tde-07032017-151610/pt-br.php

17. WENGER, T. L.; HING, A. V; EVANS, K. N. Apert Syndrome. GeneReviews. 2019;1–26.

APPENDIX

APPENDIX

APPENDIX 1: Declaration of exclusive use of the article in thesis; Portuguese version.

DECLARAÇÃO DE USO EXCLUSIVO DE ARTIGO EM TESE

Declaramos estarmos cientes de que o trabalho “Vias aéreas superiores nas craniossinostoses sindrômicas: análise por tomografia computadorizada e fluido dinâmica computacional” será apresentado na Tese do aluno Michele Garcia-Usó e que não foi e nem será utilizado em outra dissertação ou tese dos Programas de Pós-Graduação do HRAC/USP.

Bauru, 06 de setembro de 2019.

Michele Garcia-Usó
Nome do autor **Assinatura**

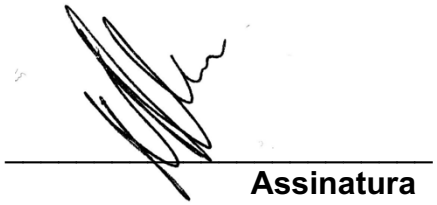
Ivy Kiemle Trindade-Suedam
Nome do autor **Assinatura**

APPENDIX 2: Declaration of exclusive use of the article in thesis; English version.

DECLARATION OF EXCLUSIVE USE OF THE ARTICLE IN THESIS

We hereby declare that we are aware of the article “The upper airway in syndromic craniosynostosis: tomographic and computational fluid dynamics assessment” will be included in Thesis of the student Michele Garcia-Usó was not used and may not be used in other works of Graduate Programs at the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo.

Bauru, September 6th, 2019



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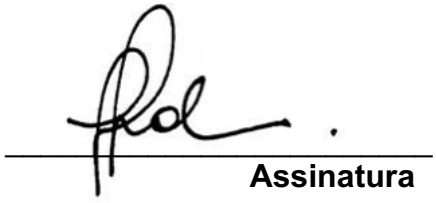

Ivy Kiemle Trindade-Suedam
Nome do autor **Assinatura**

ANNEXES

ANNEXES

ANNEXE 1: Local Institutional Review Board approval file.

USP - HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: VIAS AÉREAS SUPERIORES NOS PACIENTES COM FISSURA LABIOPALATINA: ANÁLISE TRIDIMENSIONAL POR TOMOGRAFIA COMPUTADORIZADA DE FEIXE CÔNICO.

Pesquisador: IVY KIEMLE TRINDADE SUEDAM

Área Temática:

Versão: 8

CAAE: 15205413.7.0000.5441

Instituição Proponente: Hospital de Reabilitação de Anomalias Craniofaciais da USP

Patrocinador Principal: FUNDACAO DE AMPARO A PESQUISA DO ESTADO DE SAO PAULO

DADOS DO PARECER

Número do Parecer: 2.620.557

Apresentação do Projeto:

Nona emenda de estudo transversal retrospectivo no qual os pesquisadores se propõem a avaliar o volume da faringe de indivíduos com e sem fissuras labiopalatinas por meio de tomografias computadorizadas de feixe cônico.

Segundo os autores pouco se sabe sobre o efeito das fissuras sobre a faringe. Telerradiografias em norma lateral de crianças com fissura labiopalatina foram comparadas com as de indivíduos sem fissura e demonstrou-se uma redução das dimensões faríngeas nos pacientes com fissura (Smahel e Müllerová, 1992). Esses autores associaram essa redução ao retroposicionamento da maxila comum nas crianças com fissura levando à uma redução da nasofaringe esquelética e consequentemente do espaço aéreo faríngeo.

Controversalmente, Cheung e Oberoi (2012) demonstraram, por meio de estudo volumétrico, utilizando imagens tomográficas de feixe cônico, que a faringe dos pacientes com fissura apresentava dimensões similares à de pacientes sem fissura. Os mesmos resultados foram observados por Aras, Olmez e Dogan (2012), à exceção do volume da cavidade nasal que, na população estudada, estava significantemente diminuída em relação aos pacientes sem fissura. Os pesquisadores atuais alegam que em nenhum dos estudos supracitados houve um controle do padrão facial esquelético estudado. Isto significa que, em uma mesma amostra, aqueles autores podem ter avaliado pacientes classe I de Angle, que apresentam uma relação maxilomandibular

Endereço: Rua Silvio Marchione, 3-20
Bairro: Vila Nova Cidade Universitária **CEP:** 17.012-900
UF: SP **Município:** BAURU
Telefone: (14)3235-8421 **Fax:** (14)3234-7818 **E-mail:** cephrac@usp.br

normal ou pacientes classe II ou III, que apresentam reconhecidamente uma redução do espaço aéreo posterior inerente à discrepância maxilomandibular (Claudino et al., 2013). Dessa maneira, na pesquisa atual pretende-se avaliar tomografias computadorizadas de feixe cônico de pessoas com e sem fissuras labiopalatinas que possuem o padrão classe III de Angle.

Objetivo da Pesquisa:

Segundo os autores:

Objetivo Primário:

Este estudo tem como objetivo caracterizar tridimensionalmente a via aérea superior de indivíduos com fissura labiopalatina e com anomalias relacionadas, utilizando imagens de tomografia computadorizada de feixe cônico.

Objetivo Secundário:

Avaliar, comparar e correlacionar, nos indivíduos com fissura labiopalatina e com anomalias relacionadas, as seguintes variáveis:

1. O volume total da via aérea
2. Os volumes nasais
3. Os volumes faríngeos
4. Os volumes dos diferentes segmentos faríngeos
5. As áreas seccionais mínimas faríngeas
6.O padrão facial esquelético horizontal e vertical
7. A posição da maxila e da mandíbula em relação à base do crânio
8. O comprimento faríngeo
9. Fluxo aéreo
10. Comparar resultados obtidos de Software Comercial (Dolphin Imaging 11.8) e Softwares gratuitos (ITK-Snap (Yushkevich et al., 2006) e
3DSlicer);
11. O volume do seio maxilar de ambos os lados.

Avaliação dos Riscos e Benefícios:

Riscos:

Parte do estudo, classificado como transversal retrospectivo, utilizará tomografias de banco de dados já obtidas para fins de tratamento. Em outro momento, parte da amostra (pacientes classe II) será submetidas à aplicação de questionário sobre a qualidade do sono e questionário de sintomas respiratórios. Todos os dados individuais serão mantidos em sigilo, a identidade dos sujeitos não será revelada em nenhum momento e o questionário será aplicado em ambiente

Endereço: Rua Silvio Marchione, 3-20
Bairro: Vila Nova Cidade Universitária **CEP:** 17.012-900
UF: SP **Município:** BAURU
Telefone: (14)3235-8421 **Fax:** (14)3234-7818 **E-mail:** cephrac@usp.br

individualizado, apenas quando os pacientes estiverem no HRAC para retorno ambulatorial. Desta forma, não existem riscos associados.

Benefícios:

Com este estudo pretende-se caracterizar as possíveis alterações existentes nas vias aéreas superiores do paciente com fissura labiopalatina e anomalias relacionadas, estabelecendo uma correlação positiva entre a via aérea estreita e a presença da fissura per se.

Comentários e Considerações sobre a Pesquisa:

Os autores, nessa nova emenda do projeto guarda chuva, acrescentaram mais dois nomes à equipe de pesquisa (Caroline Akemi Hassegawa e Beatriz Quevedo) e acrescentaram a avaliação dos seios maxilares aos objetivos da pesquisa.

Todos os documentos do projeto foram adaptados com as novas mudanças.

Considerações sobre os Termos de apresentação obrigatória:

Foram apresentados no projeto original.

O TERMO DE COMPROMISSO, CONFIDENCIALIDADE E AUTORIZAÇÃO DE UTILIZAÇÃO DE DADOS EM PROJETOS DE PESQUISA foi assinado pelos novos integrantes da pesquisa.

Recomendações:

Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:

Como as alterações propostas não ferem a ética, sugiro aprovação das emendas.

Considerações Finais a critério do CEP:

O pesquisador deve atentar que o projeto de pesquisa aprovado por este CEP refere-se ao protocolo submetido para avaliação. Portanto, conforme a Resolução CNS 466/12, o pesquisador é responsável por "desenvolver o projeto conforme delineado", se caso houver alterações nesse projeto, este CEP deverá ser comunicado em emenda via Plataforma Brasil, para nova avaliação.

Cabe ao pesquisador notificar via Plataforma Brasil o relatório final para avaliação. Os Termos de Consentimento Livre e Esclarecidos e/ou outros Termos obrigatórios assinados pelos participantes da pesquisa deverão ser entregues ao CEP. Os relatórios semestrais devem ser notificados quando solicitados no parecer.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação

Continuação do Parecer: 2.620.557

Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1112898_E4.pdf	13/04/2018 14:00:08		Aceito
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1112898_E4.pdf	13/04/2018 13:52:49		Aceito
Outros	Term_Comp_Conf_Aut_Dados.pdf	13/04/2018 13:42:19	Michele Garcia Usó	Aceito
Outros	Oficio_emenda_9.pdf	13/04/2018 13:36:11	Michele Garcia Usó	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_EMENDA_9.pdf	13/04/2018 13:34:52	Michele Garcia Usó	Aceito
Outros	Of_Pendencia.docx	20/12/2017 15:04:18	IVY KIEMLE TRINDADE SUEDAM	Aceito
Cronograma	CRONOGRAMA_EMENDA_7.pdf	11/07/2017 15:06:58	Michele Alves Garcia	Aceito
Outros	OFC_EMENDA_7.pdf	11/07/2017 15:06:04	Michele Alves Garcia	Aceito
Outros	Emenda4oficio.pdf	08/06/2017 12:51:18	IVY KIEMLE TRINDADE SUEDAM	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TERMO_DE_ASSENTIMENTO.pdf	25/10/2016 17:54:23	Silvia Maria Graziadei	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_SUEDAM.pdf	25/10/2016 17:53:55	Silvia Maria Graziadei	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	ASSENTIMENTO.pdf	23/09/2016 14:19:30	IVY KIEMLE TRINDADE SUEDAM	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	23/09/2016 14:19:13	IVY KIEMLE TRINDADE SUEDAM	Aceito
Declaração de Instituição e Infraestrutura	MANUSEIO.pdf	23/09/2016 14:16:19	IVY KIEMLE TRINDADE SUEDAM	Aceito
Declaração de Instituição e Infraestrutura	UNC.pdf	20/09/2016 09:20:54	IVY KIEMLE TRINDADE SUEDAM	Aceito
Declaração de Instituição e Infraestrutura	HNARY.pdf	20/09/2016 09:20:46	IVY KIEMLE TRINDADE SUEDAM	Aceito
Cronograma	CRONOGRAMA.pdf	20/09/2016 09:20:04	IVY KIEMLE TRINDADE SUEDAM	Aceito
TCLE / Termos de	TCLE_SUEDAM.docx	27/06/2016	IVY KIEMLE	Aceito

Endereço: Rua Silvio Marchione, 3-20
Bairro: Vila Nova Cidade Universitária **CEP:** 17.012-900
UF: SP **Município:** BAURU
Telefone: (14)3235-8421 **Fax:** (14)3234-7818 **E-mail:** cephrac@usp.br

Assentimento / Justificativa de Ausência	TCLE_SUEDAM.docx	17:45:32	TRINDADE SUEDAM	Aceito
Declaração de Pesquisadores	Form_HRAC_SUEDAM.pdf	27/06/2016 17:44:28	IVY KIEMLE TRINDADE SUEDAM	Aceito
Outros	Ofício nº 72-2015-SVAPEPE-CEP.pdf	13/05/2015 12:32:49		Aceito
Outros	CARTA DE ENCAMINHAMENTO EMENDA CEP.jpg	28/08/2014 17:25:37		Aceito
Outros	THIAGO FORMULARIO HRAC_20131001131727.pdf	01/10/2013 15:40:35		Aceito
Outros	THIAGO OFICIO_20131001131632.pdf	01/10/2013 15:40:06		Aceito
Outros	THIAGO CRITERIOS_20131001132223.pdf	01/10/2013 15:38:31		Aceito
Outros	THIAGO TC MANUSEIO DE IN_20131001131948.pdf	01/10/2013 15:38:02		Aceito
Folha de Rosto	THIAGO PLATAFORMA BRASIL_20131001131819.pdf	01/10/2013 15:32:56		Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BAURU, 25 de Abril de 2018

Assinado por:
Renata Paciello Yamashita
(Coordenador)

Endereço: Rua Silvio Marchione, 3-20
Bairro: Vila Nova Cidade Universitária **CEP:** 17.012-900
UF: SP **Município:** BAURU
Telefone: (14)3235-8421 **Fax:** (14)3234-7818 **E-mail:** cephrac@usp.br