UNIVERSIDADE DE SÃO PAULO
HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

LUCAS ANTONIO DA COSTA

UPPER AIRWAYS DIFFERENCES BETWEEN PIERRE ROBIN SEQUENCE AND TREACHER COLLINS SYNDROME

DIFERENÇAS DAS VIAS AÉREAS SUPERIORES ENTRE A SEQUÊNCIA DE PIERRE ROBIN E A SÍNDROME DE TREACHER COLLINS

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Dissertação constituída por artigo apresentada ao Hospital de Reabilitação em Anomalias Craniofaciais da Universidade de São Paulo para obtenção do título de Mestre em Ciências da Reabilitação, na área de concentração Fissuras Orofaciais e Anomalias Relacionadas.

Orientador: Prof. Dr. Cristiano Tonello

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Aos meus pais, Edenilson e Maria Aparecida, que sempre me incentivaram a permanecer no caminho do conhecimento...

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“OS QUE SE ENCANTAM COM A PRÁTICA SEM A CIÊNCIA SÃO COMO OS TIMONEIROS QUE ENTRAM NO NAVIO SEM TIMÃO NEM BÚSSOLA, NUNCA TENDO CERTEZA DO SEU DESTINO”

LEONARDO DA VINCI

RESUMO

RESUMO

Costa, LA. **Upper airways differences between Pierre Robin sequence and Treacher Collins syndrome** [dissertação]. Bauru: Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo; 2021.

Introdução: A Sequência de Pierre Robin (SPR) e a Síndrome de Treacher Collins (STC) são doenças congênitas e os indivíduos podem apresentar achados clínicos semelhantes. O risco é igualmente comum em homens e mulheres para ambas as condições. A STC está associada a alterações das vias aéreas inferiores e superiores e é distinta da SPR. O objetivo deste estudo foi comparar a morfologia das vias aéreas superiores levando em consideração os volumes dos segmentos (cavidade nasal, nasofaringe e orofaringe) e área seccional mínima de sujeitos com STC e SPR não sindrômica. **Métodos:** O grupo SPR era composto por 14 indivíduos (5 homens, 9 mulheres) e o grupo STC era composto por 14 indivíduos (6 homens, 8 mulheres). Exames pré-ortodônticos de tomografia computadorizada de feixe cônico (TCFC) de todos os indivíduos foram avaliados usando o Mimics Innovation Suite 21.0. A faringe foi dividida em 3 seções: nasofaringe, orofaringe e hipofaringe. Após delimitar as regiões, foram determinados o volume total, volume da cavidade nasal, volume nasofaringe, volume orofaringe e área secional mínima para cada paciente em ambas as condições. As análises estatísticas foram realizadas por meio do teste de Wilcoxon para dados independentes, pareados e não paramétricos, para análise comparativa das variáveis entre as condições SPR e STC. Os valores médios e desvio padrão das variáveis também foram determinados para os grupos SPR e STC. Valores de $p < 0,05$ foram considerados significativos em todos os casos. **Resultados:** A idade do grupo SPR variou de 6 a 23 anos com média de 11,07 ± 5,12 anos, e no grupo STC a idade variou de 6 a 20 anos com média de 12,00 ± 4,50 anos. Em relação aos volumes dos segmentos das vias aéreas superiores, ao comparar SPR e STC, foi observada diferença significativa no volume total ($p = 0,0494$), no volume da cavidade nasal ($p = 0,0085$), no volume nasofaringe ($p = 0,0166$) e na áera seccional mínima ($p = 0,0166$). Não foi observada diferença no volume de orofaringe ($p = 0,8077$). Volume total, volume da cavidade nasal, volume da nasofaringe e área seccional mínima foram maiores em pacientes com SPR do que em pacientes com STC. **Conclusão:** Pacientes com STC apresentam maior comprometimento das vias aéreas superiores com perda significativa dos volumes total, da cavidade nasal e da nasofaringe em comparação aos pacientes com SPR não sindrômica.

Palavras-chave: Pierre Robin Sequence, Treacher Collins Syndrome, Airway obstruction.

ABSTRACT

ABSTRACT

Costa, LA. **Upper airways differences between Pierre Robin sequence and Treacher Collins syndrome** [dissertação]. Bauru: Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo; 2021.

ABSTRACT

Introduction: Pierre Robin Sequence (PRS) and Treacher Collins Syndrome (TCS) are congenital disorders and the subjects may demonstrate similar clinical findings. Risk is equally common in male and female for both conditions. TCS is associated with alterations in the lower and upper airways and is distinct from PRS. The goal of this study was to compare the morphology pharynx taking account of volumes of segments (Nasal cavity, nasopharynx and oropharynx) and minimum sectional area of TCS and patients with non-syndromic PRS. **Methods:** PRS group were composed by 14 patients (5 male, 9 female) and TCS group formed by 14 patients (6 male, 8 female). Pre-orthodontic cone-beam computed tomography (CBCT) exams of all individuals were evaluated using Mimics Innovation Suite 21.0 (Materialize, Leuven, Belgium). The pharynx was divided into 3 sections: nasopharynx, oropharynx and the hypopharynx. After delimiting the regions, the total volume, nasal cavity volume, nasopharyngeal volume, oropharynx volume and minimum sectional area were determined for each patient at both conditions. Statistical analyzes were performed using Wilcoxon test for independent, paired, non-parametric data for comparative analysis of variables between the conditions PRS and TCS. The mean values and standard deviation of the variables were also determined for the PRS and TCS groups. Values of $p < 0.05$ were considered significant in all cases. **Results:** The age of PRS group range from 6 to 23 years old with a mean of 11.07±5.12 years, and at TCS group age were between 6 to 20 years with a mean of 12.00±4.50 years. Regarding the volumes of the segments of the upper airways, when comparing PRS and TCS, a significant difference was observed in total volume ($p=0.0494$), in nasal cavity volume ($p=0.0085$), in nasopharynx volume ($p=0.0166$) and in the minimum section area ($p=0.0166$). No difference was observed in the oropharynx volume ($p = 0.8077$). total volume, nasal cavity volume, nasopharynx volume and minimum sectional area were higher in PRS patients than in TCS patients. **Conclusion:** Patients with TCS have greater involvement of the upper airways with significant loss of total, nasal cavity and nasopharynx volumes compared to patients with non-syndromic PRS.

Keywords: Pierre Robin Sequence, Treacher Collins Syndrome, Airway obstruction.

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SUMMARY

1 INTRODUCTION

1. INTRODUCTION

Airway compromise is well described in multiple craniofacial syndromes, and early identification can be lifesaving. Immediate recognition of a constellation of anomalies that point to a syndrome or diagnosis will result in more targeted assessments and therapies for that patient (Evans et al, 2012)

Congenital craniofacial anomalies are caused by abnormal growth and/or development of the soft tissue structures of the head and face and/or bones. The most common facial abnormalities are cleft lip and cleft palate (Twigg & Wilkie, 2015). Among the existing craniofacial malformations, we will specifically address in this work the TCS and the PRS.

The PRS and the TCS are rare and important craniofacial anomalies that have much in common, mainly the presence of mandibular hypoplasia (Chung et al., 2012).

TCS is characterized by craniofacial changes caused by a defect in the development of the first and second pharyngeal arches that creates a deformity of the mandible and generates a convex profile, lack of chin projection, redundant presence of submental soft tissue, and malocclusion of Angle Class II. Mandibular alteration involves a reduction in the vertical branch point, reduction in body length and bone volume showing an incidence of 1:25,000 to 1:50,000 for live births (Chong et al., 2008).

In turn, the PRS is characterized by severe underdevelopment of the mandible (micrognathia), glossoptosis, airway obstruction, and generally cleft palate. Microretrognathia is immediately identified at birth and is a defining feature of the diagnosis (Gangopadhyay et al., 2012). The incidence is from 1:8500 to 1:14.000. PRS is considered not to be a syndrome, but an isolated change in the maxillofacial complex during development, or as part of a set of signs and symptoms of different syndromes (Redett, 2008; Sadewitz, 1992).

TCS is an autosomal dominant condition with variable expressivity and arises from alterations in the development of craniofacial structures derived from the first and second branchial arches (Magalhaes et al., 2007). TCS is associated with mutations in the TCOF1 gene (Treacher Collins Franceschetti syndrome 1) located on chromosome 5q32-q33.1 and more than 120 pathogenic mutations associated with TCS have been identified (Dixon et al, 1997), which are distributed throughout the entire gene (Splendore et al., 2000, 2002, 2005; Ellis et al., 2002; Dixon e Dixon, 2004; Teber et al., 2004; Horiuchi et al., 2005).

Risk is equally common in male and female for both conditions. PRS may appear in isolation called Isolated Robin Sequence (IRS) or associated with syndromes and other comorbidities (Costa et al., 2014; Marsella et al., 2011). TCS in more severe and rare cases may be associated with congenital heart disease and megacolon (Tsitouridis et al., 2007).

Patients with PRS may present with alternative mechanisms of airway obstruction, such as disproportionate tongue growth, tongue prolapse in the cleft palate, if present, lack of voluntary control of the tongue muscles and negative pressure pulling the tongue to the hypopharynx (Evans et al., 2011; 4, Mallory & Paradise, 1979).

Upper and lower airway aberrations are found in patients with TCS (Chung et al., 2012) and are distinct from PRS. In severe cases of airway obstruction, surgical intervention is required in cases of TCS and PRS. The different pathophysiology suggests that osteogenesis by bilateral mandibular distraction is less successful in TCS compared to PRS (Nardini et al., 2015).

Therefore, the study of the airways in patients with TCS and PRS is of great relevance in order to observe and quantify the possible differences in upper airway volumes as well as the minimum sectional area in those affected by TCS and PRS

2 OBJECTIVES

2. OBJECTIVES

Evaluate the upper airway of individuals with PRS and TCS through tomography and compare the variables (total volume, nasal cavity volume, nasopharyngeal volume, oropharyngeal volume and minimum sectional area) between the study groups, regardless of gender.

3 ARTICLE

3 ARTICLE

Article presented in this Dissertation was written according to The Cleft Palate-Craniofacial Journal instructions and guidelines for article submission (https://journals.sagepub.com/home/cpcj).

Manuscript: **Upper airways differences between Pierre Robin sequence and Treacher Collins syndrome**.

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ABSTRACT

Objectives: The goal of this study was to compare the morphology pharynx taking account of volumes of segments of upper airway and minimum sectional area of patients with TCS and non-syndromic PRS.

Design: Retrospective study.

Setting: Rehabilitation Hospital for Craniofacial Anomalies.

Patients, Participants: PRS group were composed by 14 patients (5 male, 9 female) and TCS group formed by 14 patients (6 male, 8 female).

Intervention: Pre-orthodontic cone-beam computed tomography (CBCT) exams of all individuals were evaluated using Mimics Innovation Suite 21.0 (Materialize, Leuven, Belgium).

Main Outcome Measurements(s): Volumes of upper airway segments and minimum sectional area were determined of patients with PRS and TCS. Wilcoxon test were used to compares data. Values of $p < 0.05$ were considered significant in all cases.

Results: The age of PRS group range from 6 to 23 years old with a mean of 11.07±5.12 years, and at TCS group age were between 6 to 20 years with a mean of 12.00±4.50 years. Significant differences were observed in total volume (p=0.0494), in nasal cavity volume (p=0.0085), in nasopharynx volume (p=0.0166) and in the minimum section area (p=0.0166) comparing PRS and TCS. No difference was observed in the oropharynx volume (p = 0.8077). Total volume, nasal cavity volume, nasopharynx volume and minimum sectional area were higher in patients with PRS than in patients with TCS.

Conclusion: Patients with TCS have greater involvement of the upper airways with significant loss of total, nasal cavity and nasopharynx volumes compared to patients with non-syndromic PRS.

Keywords: Pierre Robin Sequence, Treacher Collins Syndrome, Airway obstruction.

INTRODUCTION

PRS and TCS are congenital disorders and children may demonstrate similar clinical findings. Airway obstruction causing sleep apnea, glossoptosis (posterior displacement of the tongue) and micrognathia and accompanied by cleft palate can be observed (Butow et al., 2009; Costa et al., 2014; Ribeiro et al., 2019). PRS and TCS are multifactorial, with SPR having an incidence of 1:8500 to 1:14000 live births (Evans et al., 2011; Davidson et al., 2012) and TCS having an incidence of 1:40000 to 1:70000 live births (Marres et al., 1995; Posnick, 1997).

Risk is equally common in male and female for both conditions (Costa et al., 2014; Marsella et al., 2011). PRS may appear in isolation called Isolated Robin Sequence (IRS) or associated with syndromes and other comorbidities (Costa et al., 2014; Marsella et al., 2011).

Disproportionate tongue growth, tongue prolapse in the cleft palate if present, lack of voluntary control of the tongue muscles, and negative pressure pulling the tongue into the hypopharynx are events proposed as alternative mechanisms of airway obstruction in patients with PRS (Evans et al., 2011; Mallory & Paradise, 1979).

TCS is associated with alterations of the lower, upper and nasal airways (Chung et al., 1979) and is distinct from PRS. Airway obstructions in severe cases require surgical intervention in both TCS and PRS, the different pathophysiology suggests that osteogenesis by bilateral mandibular distraction is less successful in TCS compared to PRS (Nardini et al., 2015).

Several techniques have been used to quantify micrognathia, glossoptosis and airway obstruction in PRS and TCS (Ribeiro et al., 2019; Evans et al., 2011; van der Haven et al., 1997; Vegter et al., 1999). Upper airways cannot be accurately explored through single linear measurements provided by 2D cephalometry (Lenza et al., 2010). On the other hand, three-dimensional (3D) analysis based on cone beam computed tomography (CBCT) is able to provide a better picture of the anatomical characteristics of the upper airways and therefore result in an improvement in diagnosis (Ribeiro et al., 2019; Lenza et al., 2010; Ghoneima & Kula, 2013).

The use of the CBCT technique in patients with cleft lip and palate (CLP) showed neither airway volumes nor cross-sectional areas smaller than patients without CLP (Cheung & Oberoi, 2012). 3D analysis of patients with unilateral CLP and control group showed no differences in relation to nasopharyngeal airway volumes (Aras et al., 2012).

In this study, we assessed nasopharyngeal, oropharyngeal and total airway volumes. In addition, we determined the minimum cross-sectional area of individuals with the non-syndromic Pierre Robin Sequence (PRS) and Treacher Collins Syndrome (TCS) and performed a comparative analysis of variables (total volume, nasal cavity volume, nasopharynx volume, oropharynx volume and minimum sectional area) between group with PRS and TCS regardless of gender.

MATERIAL AND METHODS

This is a retrospective, observational and cross-sectional study consisting of 14 patients diagnosed with non-syndromic PRS being 5 male and 9 female and 14 patients diagnosed with TCS being 6 male and 8 female. All participants underwent CBCT obtained for surgical planning purposes using the i-CAT Next Generation scanner (ISI-i-CAT Imaging System, Beam Cone; Next Generation i-CAT, Hatfield, Pennsylvania), with the following specifications: 13 cm FOV, 26.9 seconds (exposure time), 120 kV, 37 mA and a resolution of 0.25 voxels or better. Images were saved as DICOM (Digital Imaging and Communications in Medicine) files. Data in DICOM format were transferred to the MIMICS image processing software (Materialise, Leuven, Belgium) and realistic upper airway models were generated and analyzed.

For the recreation of the upper airway was performed using Mimics and a mesh of -1024 and -480 Hounsfield units (HU). Two main planes were drawn to define the reference points of the upper airways: a plane that passes through the anterior and posterior nasal spine, which divides the nasal cavity/nasopharynx from the oropharynx; and a plane that passes between the anterosuperior edge of the fourth vertebra (C4) and the menton (Zheng et al., 2017).

After delimiting the upper airway (FIGURE 1A and 1D), the surrounding tissues were segmented semi-automatically, and later manual refinement was performed through the clearance of areas not perceived by the MIMICS computer software in the axial, sagittal and coronal planes and a three-dimensional image (3D) of the airway was rendered.

To determine the location of the minimum sectional area, the protocol established by Yoshihara et al., (2012) was followed. The pharynx was divided into 3 sections: nasopharynx, which comprises the pharynx with a position superior to the platinum plane parallel to Frankfort's horizontal plane; oropharynx, which is the portion of the pharynx positioned between the palatal plane and the epiglottic plane, parallel to Frankfort's horizontal plane; and the hypopharynx, which corresponds to the portion of the pharynx located inferiorly to the epiglottic plane (FIGURES 1B and 1E). After delimiting the regions, the total volume, nasal cavity volume, nasopharyngeal volume, oropharynge volume and minimum sectional area were determined for each patient at both conditions (FIGURE 1).

Statistical analyzes were performed using Wilcoxon test for independent, paired, non-parametric data for comparative analysis of variables between the conditions PRS and TCS. The mean values and standard deviation of the variables were also determined for the PRS and TCS groups. Values of $p < 0.05$ were considered significant in all cases. Furthermore, the differences in mean of volumes ($\triangle V_{PRS\text{-}TCS} = V_{PRS}\text{-}V_{TCS}$, where V is volume of total volume, or nasal cavity volume, or nasopharyngeal volume, or oropharyngeal volume) and mean of minimum sectional area ($\triangle A_{PRS\text{-}TCS} = A_{PRS}\text{-}A_{TCS}$, where A is minimum sectional area) between PRS and TCS carriers were determined.

This study was evaluated by the Research Ethics Committee at the Hospital for Rehabilitation of Craniofacial Anomalies (HRAC) of the University of São Paulo (USP) under protocol number CAAE 35247120.0.0000.5441 and approved with number 4.181.268, and the researchers involved signed a form of responsibility.

RESULTS

According to TABLE 1, the sample group for PRS consisted of 14 individuals with ages ranging from 6 to 23 years old with a mean of 11.07±5.12 years, 9 female and 5 male, and the sample group for TCS was also formed by 14 patients aged between 6 to 20 years with a mean of 12.00±4.50 years, 8 female and 6 male, with a small statistical difference in the mean age of the two groups as a function of p value = 0.0483 (FIGURE 2).

The values of minimum sectional area changed from 48.8mm^2 at 320.60mm^2 in the patients with PRS, and from 10.72mm^2 at 201.44mm^2 in the patients with TCS (TABLE 1, FIGURE 3). The variation was 6.7-fold in patients with PRS and 18.79-fold in patients with TCS. All 28 patients with TCS (n=14) and PRS (n=14) had localization of the minimum sectional area in the retroglossal region of the oropharynx.

The mean values and standard deviation for the variables in both conditions were: 30611.24±10011.59mm^3 (PRS) and 21369.47±6956mm^3 (TCS) for total volume (FIGURE 4A), 13980.66±4620.75mm^3 (PRS) and 9034.79±2361.17mm^3 (TCS) for volume of the nasal cavity (FIGURE 4B); 4830.95±2742.75mm^3 (PRS) and 2131.1060.19mm^3 (TCS) for nasopharynx volume (FIGURE 4C); 8441.88±4340.56 (PRS) and 8699.33±4640.17mm^3 (TCS) for oropharynx volume (FIGURE 4D); and 106.15±71.12mm^2 (PRS) and 61.27±47.93mm^2 (TCS) minimum sectional area (FIGURE 4E).

Regarding the volumes of the segments of the upper airways, when comparing PRS and TCS, a significant difference was observed in total volume (p=0.0494), in nasal cavity volume (p=0.0085), in nasopharynx volume (p=0.0166) and in the minimum section area (p=0.0166). On the other hand, there is no difference in the oropharynx volume (p = 0.8077) (FIGURE 4).

It is verified that the total volume, nasal cavity volume, nasopharynx volume and minimum sectional area were higher in patients with PRS than in patients with TCS since the difference values of volumes ($\triangle V_{PRS-TCS}$) were 9241.76mm^3, 4945.86mm^3, 2699.6mm^3 and difference values of minimum area ($\triangle A_{PRS-TCS}$) was 44.89mm^2, respectively. On the other hand, in relation to the oropharynx volume, a small increase was observed in patients with TCS in relation to PRS, but without statistical significance (FIGURE 4F).

DISCUSSION

Since its introduction in the late 1990s, there has been a high increase in interest in the use of CBCT imaging scanners for studies of oral and maxillofacial structures (Arai et al., 1999; Mozzo et al., 1998). In this sense, this technology has allowed its application in oral and maxillofacial surgical areas, dentistry and otorhinolaryngology (Guijarro-Martínez & Swennen., 2011). Therefore, the upper airways became more relevant due to the relationship between the morphological characteristics of these airways and craniofacial growth, dentomaxillofacial pathologies and obstructive sleep apnea (Arai et al., 1999; Mozzo et al., 1998).

CBCT allows physicians to avoid the limitations of conventional cephalometry, however, problems such as the influence of the breathing phase; the influence of tongue position and mandibular morphology; longitudinal and cross-sectional assessment of the upper airways; and definitions of 3D CBCT of the anatomical limits of the upper airways need to be resolved. Changes in airway size and shape during the breathing stage are known (Abbott et al., 2004; Bhattacharyya et al., 2000; Lowe et al., 1986) and should be taken into account during CBCT examinations. Airway volumetric measurements are significantly correlated with anteroposterior and vertical cephalometric variables (Iwasaki et al., 2009; Kim et al., 2010). Airway volume and shape vary significantly among patients with different anteroposterior mandibular relationships (Kim et al., 2010; Kumar et al., 2008; Grauer et al., 2009). Furthermore, the recognition of phenotypic differences between TCS and PRS is important for an adequate differential diagnosis and treatment planning (Kato et al., 2020).

Regarding gender, studies carried out by Meyer et al showed that 64.2% of patients with PRS were female (Meyer et al., 2008); Schaefer et al., (2004) and Pinheiro Neto et al., (2009) found that 66.7% and 75% were female, respectively. In our study we observed that 64.28% were female. Thus, literature data and our findings demonstrate a higher prevalence of females in non-syndromic PRS. On the other hand, the literature reports that there is no gender preference in relation to TCS (Chang & Steinbacher, 2012).

It is important to mention that there is no comparative literature on upper airway volumes and minimum sectional area in patients with PRS and TCS.

Our analyzes showed that both patients with PRS and TCS showed great variation in the values of total volume, nasal cavity volume, nasopharynx volume, oropharynx volume and minimum section area since the differences between mean and standard deviation values for patients with PRS were 32.7%, 33%, 57%, 51% and 67% and for patients with TCS they were 33%, 26%, 49%, 53% and 78%, respectively. In other words, the large percentage values denote large variation in the volume and minimum sectional area measurements of the patients (TABLE 1).

In TCS or PRS, the pathophysiology of airway obstruction is mainly due to a posteriorly located tongue, which significantly reduces the size of the posterior pharyngeal airway. Each time the baby inhales, the tongue is pulled further back and down by the force of the negative pressure generated by the breath (Mallory & Paradise, 1979). Incorrect tongue repositioning may be associated with congenital mandibular hypoplasia which may occur in patients with PRS or TCS (MacCarthy et al., 2001).

In both case PRS and TCS, patients with mandibular hypoplasia may suffer from deficits in both form and function. Mandibular hypoplasia may not only cause facial disfigurement, but also significant functional impairment with possible life-threatening airway obstruction secondary to poor positioning of the base of the tongue. Furthermore, the volume of the upper airways can be influenced by the length of the maxillary and mandibular bone, especially in the age group between 1 and 15 years in patients with TCS (Ma et al., 2014). In children with PRS, the mandibular body is small and the ramus is relatively normal, while in children with TCS, the ramus is short and the mandibular body is relatively normal (Chung et al., 2012).

Posteriorly positioned maxilla and steep mandibular plane in TCS can cause insufficient chin projection and glossoptosis with airway obstruction (Steinbacher & Bartlett, 2011).

A study by Kato et al. showed that no difference between TCS and PRS was found for the length and sagittal position of the maxilla. No difference between groups was observed in the maxillomandibular relationship (Kato et al., 2020). However, in our volumetric analyzes and comparative minimum sectional area between PRS and TCS using CBCT and MIMICS, significant differences were observed in the variables total volume, nasal cavity volume, nasopharynx volume and minimum sectional area (FIGURE 3).

In general, the total volume, nasal cavity volume, nasopharynx volume and minimum sectional area of patients with PRS were 1.43-, 1.55-, 2.67- and 1.73-fold, respectively, greater than those of patients with TCS.

Patients with TCS may present a reduction in the length of the anterior cranial base (S-N) and the length of the posterior cranial base (S-Ba), influencing the dimensions and consequently the volumes of the upper airways (Ma et al., 2014), since patients with TCS evolve with a greater chance of tracheostomy during life, more severe sleep apnea and consequently higher morbidity and mortality.

Due to the loss of total volumes, nasal cavity and nasopharynx in patients with TCS, this would imply a greater need for tracheostomy and distraction than in patients with PRS due to the greater involvement of the airways in TCS. Although TCS and PRS have micrognathia in common, there is a greater involvement in the entire length of the upper airways in TCS, which is verified by the loss of total volume compared to PRS. Furthermore, severe impairment of the craniofacial skeleton in TCS proportionally affects the airways due to impairment of the maxilla and nose. On the other hand, non-syndromic PRS presents micrognathia and glossoptosis as the only impairment that does not significantly impact airway volumes compared to TCS.

CONCLUSION

In this study, we found that the use of the CBCT technique was able to show significant differences in volumetric data in the nasal cavity, nasopharynx and total volume, as well as in the minimum sectional area between patients with PRS and TCS and that these variables had lower values in patients with TCS than in PRS carriers. Thus, in patients with TCS, it may imply a reduction in airflow with possible occurrence of increased mouth breathing, increasing the possibility of airway collapse causing risk of death as well as favoring the occurrence of repetitive infections of the upper airways.

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TABELA 1) Sumário das medições realizadas com a utilização do programa MIMICS.

Age		Gender		Total volume (mm^3)		Nasal cavity volume (mm^3)		Nasopharynx volume (mm^3)		Oropharynx volume (mm^3)		Minimum section area (mm^2)	
PRS	**TCS**	**PRS**	**TCS**	**PRS**	**TCS**	**PRS**	**TCS**	**PRS**	**TCS**	**PRS**	**TCS**	**PRS**	**TCS**
6	6	M	F	33596,80	22010,07	13027,63	9372,72	3448,92	2034,14	12479,34	9250,93	93,33	34,88
7	8	M	F	20714,63	13790,24	11333,01	7285,96	1432,10	1243,88	5843,55	3338,18	54,56	10,72
7	8	F	M	21028,12	11062,17	9019,40	6179,23	4142,41	179,06	5685,25	4926,45	76,05	44,8
8	9	F	F	37441,22	14776,06	18218,60	7672,71	8730,04	2726,03	10416,16	3988,73	160,48	28,32
8	9	F	F	24111,63	22814,4	12609,66	8482,87	3422,73	2283,93	1794,60	10256,86	102,08	201,44
8	10	F	M	23878,7	25061,25	12306,41	5360,68	2679,03	2242,39	5761,85	6133,53	93,54	26,24
9	10	F	F	23261,34	14476,48	8653,11	9820,90	6063,52	2658,26	7021,76	10184,22	71,52	101,28
10	10	F	M	19156,14	27075,42	8120,75	8720,57	3137,30	3829,89	5993,14	13417,71	61,85	63,81
10	12	M	M	47870,21	14310,47	13547,77	6205,85	3858,85	1057,84	20493,53	6646,87	320,60	49,44
11	14	M	F	19940,05	24186,85	9944,873	11730,44	1751,26	3845,89	6500,63	6823,64	61,44	46,4
12	15	F	F	44050,69	20572,85	18722,29	10948,88	10051,94	703,92	9440,76	6853,52	161,19	31,84
15	17	M	M	37836,35	23736,13	18208,23	10065,38	7542,15	1994,78	9079,09	5671,84	48,80	46,88
21	20	F	M	33598,5	34555,96	19585,23	13582,96	3325,17	2554,26	9202,74	14161,06	68,71	77,76
23	20	F	F	42072,96	30744,28	22432,23	11058	8047,81	2484,5	8473,91	20137,16	112,00	93,92

FIGURES

Figure 1: Overlapping tomographic image and three-dimensional reconstruction of the upper airway by reconstruction using MIMICS.

A and D → Representation of upper airway: A) Treacher Collins syndrome; D) Pierre Robin Sequence.

B and E→ Upper airway segmentation: B) Nasal cavity in purple, the nasopharynx in yellow, the oropharynx in red, and the hypopharynx in blue patient with TCS; E) Nasal cavity in blue, the nasopharynx in purple, the oropharynx in yellow, and the hypopharynx in violet patient with PRS.

C and F→ Upper airway segmentation: C) Nasal cavity in purple, and the nasopharynx is in yellow; F) Nasal cavity in blue, the nasopharynx in purple

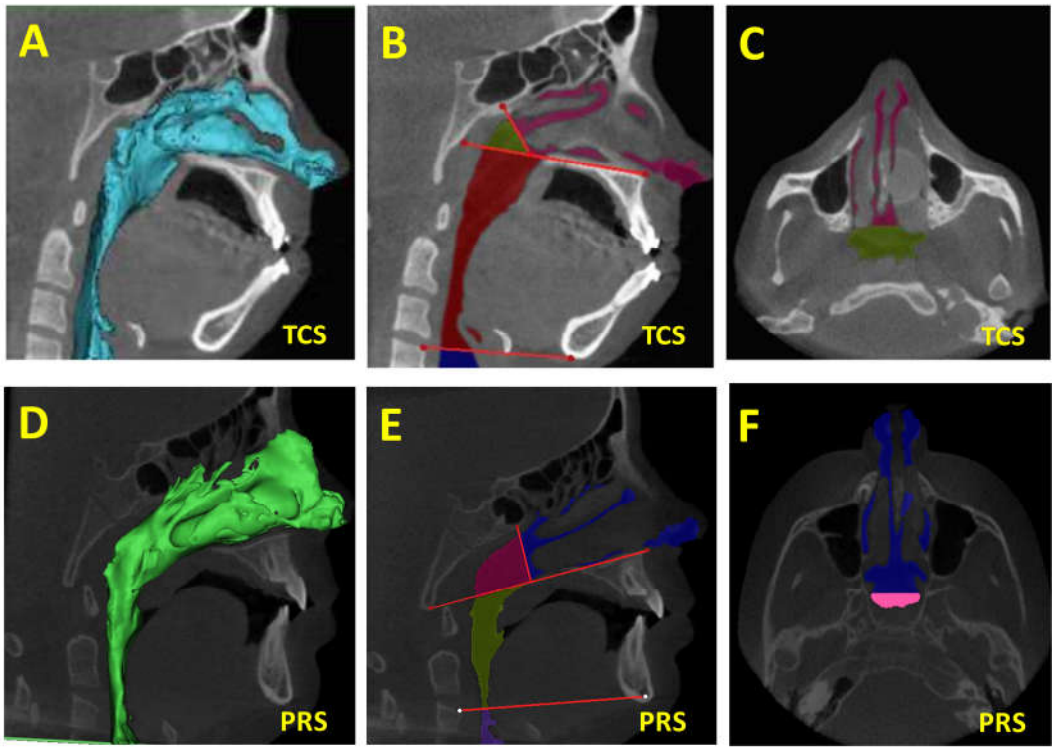


Figure 2: Comparison of mean ages of patients with PRS and TCS.

Both groups consisted of 14 patients, 9 females and 5 males in the PRS group and 8 females and 6 males in the TCS group. P=0.0483.

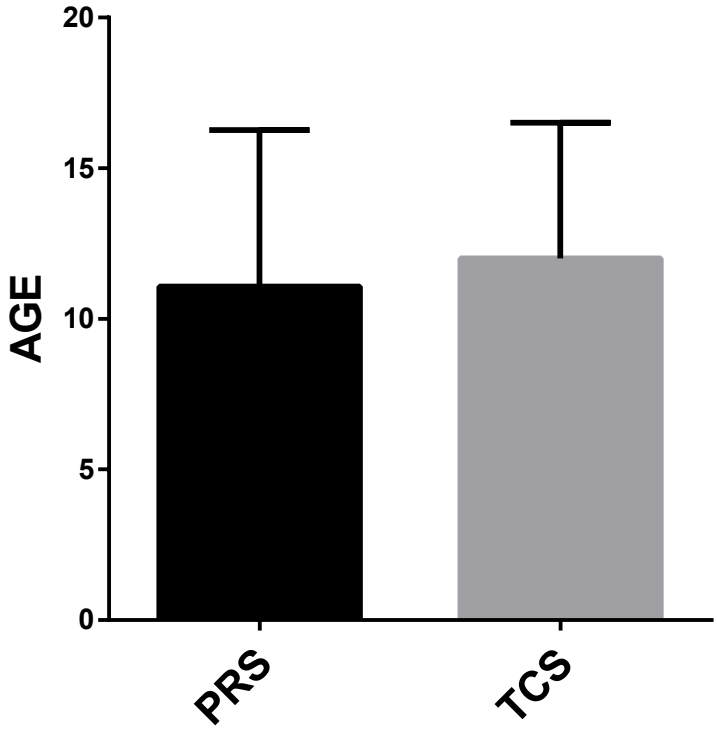


Figure 3: Comparison between the airways of patients with TCS and PRS.

Three-dimensional reconstruction of the upper airway of patients: TCS→ 8 years and 8 months (A, E, I); and 9 years and 2 months (B, F, J). PRS →15 years and 11 months (C, G, L); and 10 years and 4 months (D, H, M). Line 1: Upper airway: Minimum sectional area in the retroglossal region of the oropharynx. Line 2: Overlay of TC and upper airway and Minimum sectional area (red dot). Line 3: Minimum sectional area of upper airway seen in an axial section of the cone beam tomography. I→10.72 mm^2; J→201.44 mm^2; L→48.80mm^2, M→320.60mm^2.

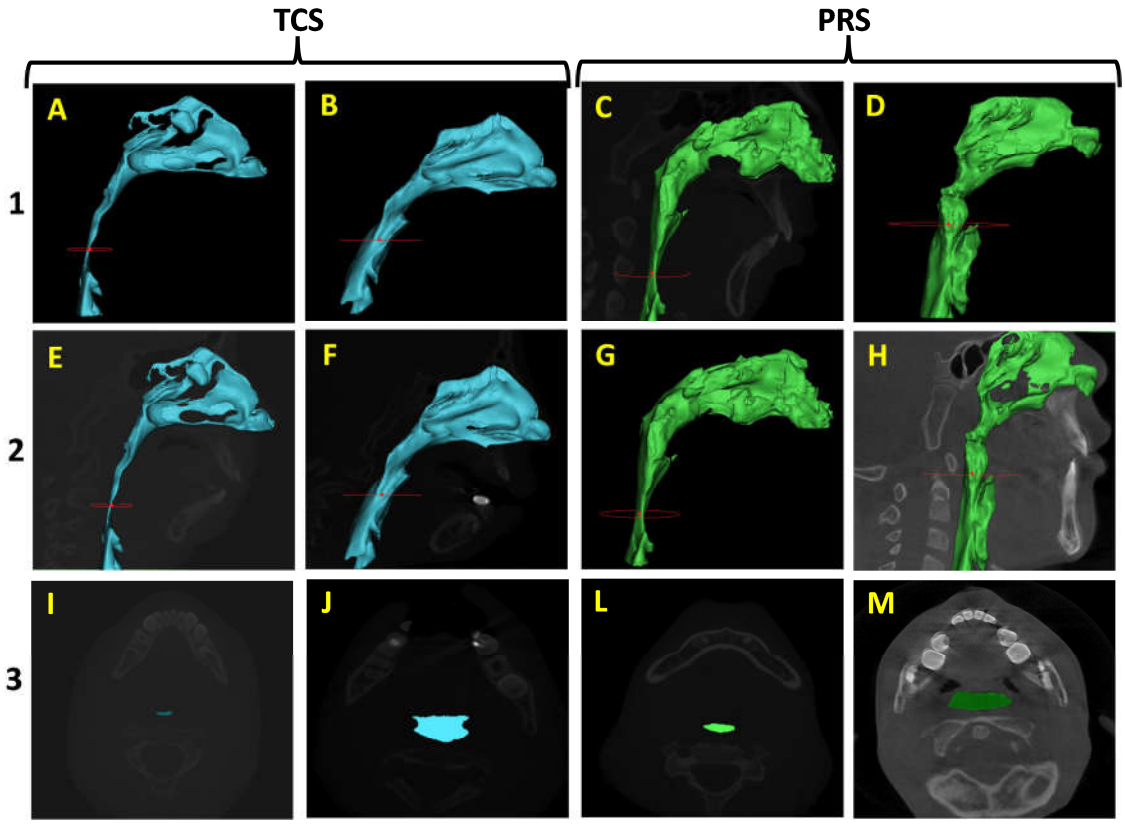
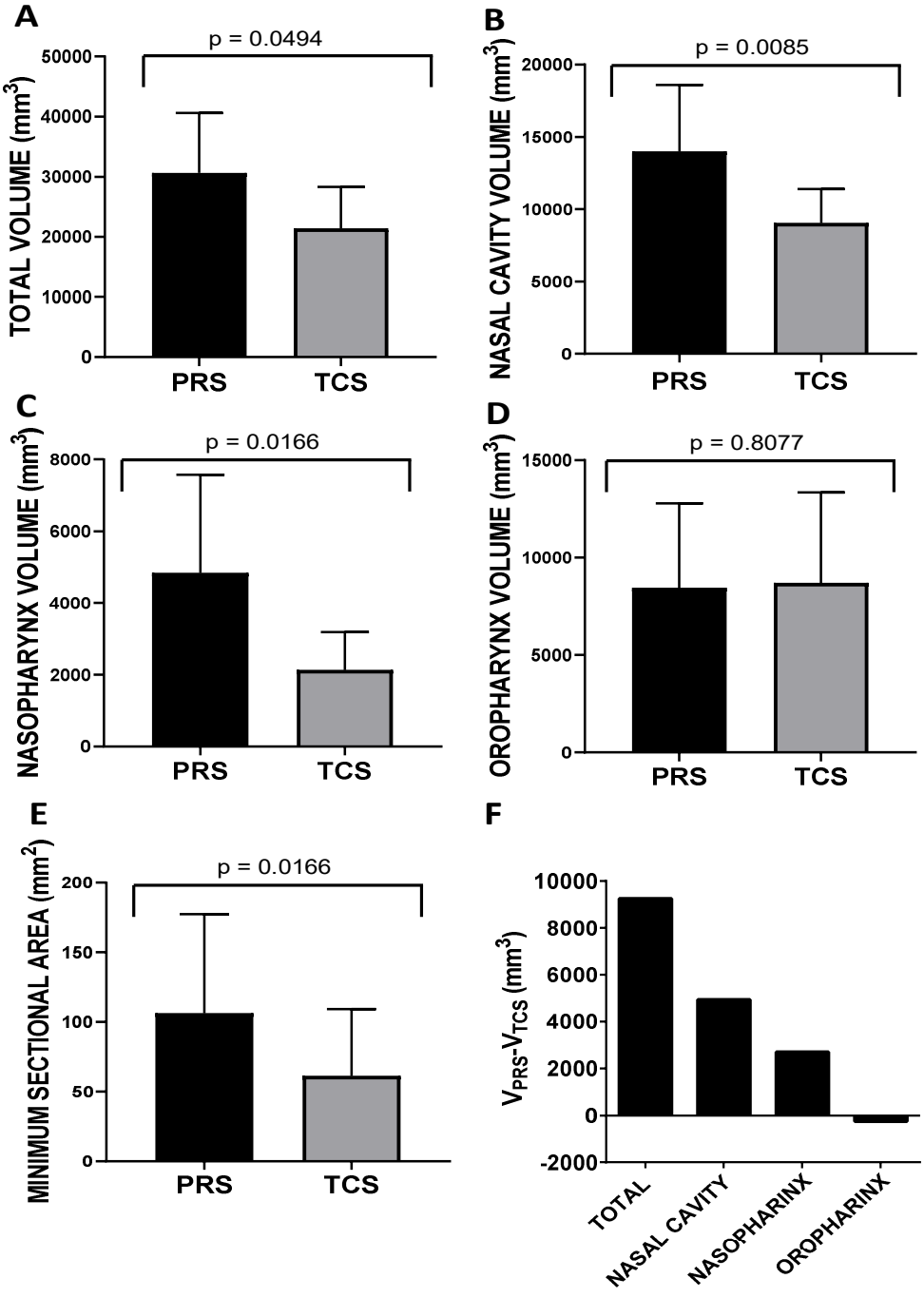


Figure 4: Comparative analysis between PRS and TCS in relation to airway segments.
A) Total volume, B) Nasal cavity volume, C) Nasopharyngeal volume, D) Oropharyngeal volume, E) Minimum section area and F) Differences of volumes of (V_{PRS}-V_{TCS}) segments of PRS and TCS patients.



4 FINAL CONSIDERATIONS

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1. We found that both patients with PRS and TCS had minimal sectional area in the retroglossal region.
2. Patients with TCS had smaller total volumes, nasal cavity and nasopharynx than patients with PRS.
3. There was no significant difference in oropharyngeal volume between the two groups.
4. Patients with TCS had a smaller minimal sectional area.

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ANNEXES

ANEXO 1 – Declaração de uso exclusivo de artigo a ser publicado em periódico de língua inglesa

DECLARATION OF EXCLUSIVE USE OF THE ARTICLE IN DISSERTATION/THESIS

We hereby declare that we are aware of the articles (**Upper airways differences between Robin sequence and Treacher Collins syndrome**.) will be included in Dissertation of the student LUCAS ANTONIA DA COSTA were not used and may not be used in other works of Graduate Programs at the Bauru School of Dentistry, University of São Paulo.

Bauru, 24 de agosto de 2021

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ANEXO 2 - Termo de Permissão para uso de registros para fins científicos (fotografias, radiografias, tomografias e respectivos laudos odontológicos e médicos, vídeo imagens, amostra de voz/fala, registros clínicos, imagens de órgãos e espécimes para pesquisa, fins didáticos e publicação de artigos científicos)

Eu, _____, brasileir__, residente no endereço _____, na cidade de _____ - ___, RG nº_____, CPF nº _____ permito a captação, o uso e publicação de meus registros (**fotográficos, radiografias, tomografias e respectivos laudos odontológicos e médicos, vídeo imagens, amostra de voz/fala, registros clínicos, imagens de órgãos e espécimes) para pesquisa, fins didáticos e publicação de artigos científicos** especificamente relacionados ao projeto de pesquisa/ comunicação científica intitulado(a) "Caracterização maxilomandibular de indivíduos com Sequência de Robin isolada: avaliação tridimensional", sob responsabilidade das pesquisadoras Profª. Drª. Daniela Gamba Garib e Drª. Roseli Maria Zechi Ceide. Estou ciente de que não serei remunerado(a) pelo uso desses registros.

Entendo que poderei ser reconhecido(a) por terceiros e que as minhas documentações clínicas poderão ser publicadas exclusivamente para fins científicos, resguardando o sigilo das minhas informações pessoais.

Estou ciente de que, caso não aceite assinar este termo, receberei dos profissionais citados acima a mesma qualidade de atendimento e tratamento.

_____, _____ de _____ de 20___.

Assinatura: _____

Nome do Paciente:_____

Em caso de paciente menor de 18 anos:

Eu, _____, brasileir__, residente no endereço _____, na cidade de _____ - ___, RG nº_____, CPF nº _____, responsável legal pelo paciente_____, permito a captação, o uso e publicação de seus registros para fins científicos, de acordo com as condições expressas acima, que foram explicadas de forma clara.

Assinatura do responsável pelo paciente:_____

Nome do responsável pelo paciente:_____

Assinatura das Pesquisadoras Responsáveis:_____

_____

Term_Perm_Uso_Registro_V2.1 aprovado pelo CEP em 26/07/2016

USP - HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS DA UNIVERSIDADE DE SÃO PAULO -HRAC/USP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANA¿LISE DAS VIAS AE¿REAS SUPERIORES NA SI¿NDROME DE TREACHER COLLINS E SEQUE¿NCIA DE ROBIN

Pesquisador: Cristiano Tonello

Área Temática:

Versão: 1

CAAE: 35247120.0.0000.5441

Instituição Proponente: Hospital de Reabilitação de Anomalias Craniofaciais da USP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.181.268

Apresentação do Projeto:

O projeto de pesquisa com o título:"ANALISE DAS VIAS AÉREAS SUPERIORES NA SÍNDROME DE TREACHER COLLINS E SEQUENCIA DE ROBIN" do pesquisador Lucas Antonio da Costa sob orientação do Prof.Dr.Cristiano Tonello é apresentado a este Comitê para ser avaliado em seus aspectos éticos.

O pesquisador anexou o seguinte resumo:

"A Sindrome de Treacher Collins (STC) e a Sequencia de Robin (SR) compartilham a deficiência mandibular como um achado clinico similar e consequente obstrução da via aérea superior e insuficiência respiratória. Volumes de via aérea e informações sobre a dinâmica do fluxo aéreo de indivíduos com essas condições clinicas ainda não foram estudados e comparados com indivíduos com mandíbulas morfologicamente normais.

O objetivo deste estudo será comparar a morfologia, dimensões e volume da via aérea superior bem como a dinâmica do fluxo aéreo de indivíduos com STC e SR e indivíduos com mandíbula de morfologia normal.

A amostra consisti de tomografias computadorizadas (TC) provenientes do arquivo

do Hospital de Reabilitação de Anomalias Craniofaciais da Universidade de São Paulo. O Grupo STC

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será composto por 17 indivíduos com STC e apresenta idade media de 11,5 anos (7 do sexo masculino, 10 do sexo feminino). O Grupo SR foi pareado em número de participantes, por sexo e idade com o grupo STC bem como o GRUPO CONT (controle). Avaliações quantitativas serão realizadas em reconstruções tridimensionais da face e via aérea posterior utilizando o software Mimics Innovation Suite 17.0 (Materialize, Leuven, Belgium). A realização das mensurações de fluidodinamica computacional serão realizados no software Fluent (ANSYS).

A comparação intergrupos será realizada por meio do teste t independente/Mann-Whitney e do teste ANOVA e Tukey para a analise bidimensional e tridimensional, respectivamente ($p<0.05$)."

Objetivo da Pesquisa:

O pesquisador descreve como objetivo:

"Objetivo Primário:

O objetivo deste estudo será comparar as dimensões e a morfologia das vias aéreas bem como os achados a fluidodinamica computacional de indivíduos com Síndrome de Treacher Collins (STC) e Sequencia de Pierri Robin (SPR) comparados a um grupo controle (CONT).

Objetivo Secundário:

Avaliação de imagens 3D de Tomografia computadorizada das vias aéreas superiores.

Avaliação Computacional da Dinâmica de Fluidos com pareamento das informações dos participantes por sexo e idade."

Avaliação dos Riscos e Benefícios:

O pesquisador anexou a seguinte informação:

"Riscos:

Não haverá risco direto aos participantes uma vez que serão avaliados prontuários e exames de diagnósticos por imagem os quais se encontram nos arquivos do HRAC-USP, porém há o risco de exposição de informações dos participantes, mas será de todas as formas preservadas de acordo com as normas vigentes.

Benefícios:

Não haverá benefício direto, contudo o melhor entendimento da dinâmica dos fluidos-fluxo de ar e nos indivíduos comprometidos e suas possíveis diferenças permitida melhor acompanhamento e tratamento clínico."

Comentários e Considerações sobre a Pesquisa:

O projeto de pesquisa apresenta mérito e encontra-se bem estruturado.

O pesquisador utilizará em sua amostra as tomografias do período de janeiro de 2005 a janeiro de 2020,que se encontram disponíveis nos arquivos da instituição.

Considerações sobre os Termos de apresentação obrigatória:

Foram anexados os seguintes termos:

- TERMO DE COMPROMISSO DE TORNAR PÚBLICOS OS RESULTADOS DA PESQUISA E DESTINAÇÃO DE MATERIAIS OU DADOS COLETADOS;
- TERMO DE COMPROMISSO DO PESQUISADOR RESPONSÁVEL;
- CADASTRO DOS PESQUISADORES;
- FOLHA DE ROSTO DO HRAC;
- CARTA DE ENCAMINHAMENTO;
- TERMO DE COMPROMISSO, CONFIDENCIALIDADE E AUTORIZAÇÃO DE UTILIZAÇÃO DE DADOS EM PROJETOS DE PESQUISA;
- SOLICITAÇÃO DE DISPENSA DO TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO.

Recomendações:

Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:

Uma vez que o referido projeto não apresenta envolvimento ético recomendo sua aprovação por esse colegiado.

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.

USP - HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS DA UNIVERSIDADE DE SÃO PAULO -HRAC/USP

Continuação do Parecer: 4.181.268

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	DISPENSA_v2.pdf	30/07/2020 00:00:40	Renata Paciello Yamashita	Aceito
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1584501.pdf	16/07/2020 19:19:00		Aceito
Outros	Termo_Tornar_publico.pdf	16/07/2020 19:17:23	Cristiano Tonello	Aceito
Outros	esclarecimentos_pendencias.pdf	15/07/2020 19:34:14	Cristiano Tonello	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_V2.pdf	15/07/2020 18:05:20	Cristiano Tonello	Aceito
Outros	TERMO_COMPROMISSO.pdf	15/07/2020 17:47:14	Cristiano Tonello	Aceito
Outros	CADASTRO_PESQUISADORES_HRAC.pdf	15/07/2020 17:43:03	Cristiano Tonello	Aceito
Folha de Rosto	folha_de_rosto.pdf	15/07/2020 17:41:28	Cristiano Tonello	Aceito
Outros	Carta_Encaminhamento_CEP.pdf	02/07/2020 11:01:23	Cristiano Tonello	Aceito
Declaração de Instituição e Infraestrutura	AUTORIZACAO_USO_DADOS.pdf	02/07/2020 10:52:18	Cristiano Tonello	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	DISPENSA.pdf	02/07/2020 10:46:11	Cristiano Tonello	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BAURU, 30 de Julho de 2020

Assinado por:
Renata Paciello Yamashita
(Coordenador(a))

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