LEONARDO LOPES BALSALOBRE FILHO

EFEITO DA PRESSÃO POSITIVA AGUDA NA CAVIDADE NASAL

Tese apresentada à Universidade Federal de São Paulo – Escola Paulista de Medicina para obtenção do título de Doutor em Ciências

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Dedicatória

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ÍNDICE

LISTA DE ABREVIATURAS

AOS: Apneia obstrutiva do sono

CE: Corticosteroide

CPAP: Aparelho gerador de pressão positiva

EVA: Escala visual analógica

IAH: Índice de apneia e hipopnéia

NOSE: Escala de avaliação sintomática de obstrução nasal

PFI: Pressão do fluido intersticial

PFNI: Pico de fluxo nasal inspiratório

PN: Pólipo nasal

RA: Rinite alérgica

RmA: Rinometria acústica

RSCcPN: Rinossinusite crônica com pólipos nasais

TGF-β: Fator transformador de crescimento β

UNIFESP: Universidade Federal de São Paulo

RESUMO

Introdução: A influência da obstrução nasal nos distúrbios do sono e na adaptação ao CPAP tem sido amplamente demonstrada. Entretanto, poucos estudos mostram o impacto da pressão positiva contínua na cavidade nasal, seja em indivíduos normais, ou em pacientes com rinite alérgica; assim como o efeito do corticosteroide tópico na patência nasal após a exposição ao CPAP. Além disso, despeito dos poucos dados, acredita-se que o aumento da pressão hidrostática intersticial nos pólipos de pacientes com rinossinusite crônica com pólipos nasais possa diminuir o volume dos mesmos **Objetivo:** Esta linha de pesquisa teve como objetivo geral avaliar o efeito da pressão positiva contínua na cavidade nasal de indivíduos normais, com rinite alérgica e com pólipos nasais, por meio de métodos objetivos e subjetivos. **Método**: Três pesquisas foram realizadas. A primeira incluiu 27 indivíduos que foram expostos a pressão positiva nasal por 2 horas por meio de CPAP e máscara nasal com pressão de 20cm/H_2O. Um questionário sobre sintomas alérgicos nasais foi aplicado e 2 grupos foram estabelecidos – com e sem sintomas alérgicos nasais. Imediatamente antes e após a exposição à pressão positiva, escores de obstrução nasal foram obtidos pela escala visual analógica (EVA), pela escala de sintomas de obstrução nasal (NOSE), pelo pico de fluxo nasal inspiratório e por rinometria acústica. No segundo estudo, 10 pacientes com rinite alérgica nasal foram expostos a pressão positiva nasal por 1 hora com CPAP e máscara nasal com pressão de 15cm/H_2O. Os mesmos testes foram aplicados imediatamente antes e após exposição à pressão positiva. Após tratamento com budesonida tópica nasal na dose de 400mcg/dia por 4 semanas os testes foram novamente realizados antes e após a exposição à pressão positiva. No terceiro estudo, 12 pacientes com rinossinusite crônica com pólipos nasais e 27 controles foram expostos a CPAP (20cm/H_2O) por 2 horas. Os testes para mensuração dos escores de obstrução nasal, assim como a endoscopia nasal (graduação de pólipos de Meltzer) foram realizados antes e depois da intervenção. **Resultados:** No primeiro estudo, observou-se aumento da obstrução nasal tanto nos testes subjetivos (EVA e NOSE) como nas avaliações objetivas, mostrando redução do volume da cavidade nasal na rinometria

acústica e diminuição do pico de fluxo nasal inspiratório. Indivíduos com queixas alérgicas nasais, apresentaram uma piora mais acentuada nos parâmetros da permeabilidade nasal. No segundo estudo, a comparação entre os testes antes e após o uso da budesonida tópica e após a exposição à pressão positiva mostrou uma melhora nos escores de obstrução nasal e patência nasal, estatisticamente significantes. No terceiro estudo, para o grupo de pacientes com rinossinusite com pólipos nasais, EVA, NOSE e rinomanometria não diferiram significantemente ($p = 0,72$, $p = 0,73$ e $p = 0,17$, respectivamente), mas os valores do pico de fluxo nasal inspiratório pioraram ($p = 0,04$) após a exposição ao CPAP. Houve redução estatisticamente significante nos pólipos nasais ($p = 0,04$). O grupo controle apresentou piora dos parâmetros de obstrução nasal em todos os testes utilizados. **Conclusão:** A exposição aguda à pressão positiva com CPAP, deteriora a patência nasal e em indivíduos com sintomas alérgicos nasais, a piora é ainda mais acentuada. O uso do corticoide tópico é capaz de mitigar os efeitos irritativos na mucosa nasal da pressão positiva, levando a uma melhora dos parâmetros da patência nasal. Pacientes com rinossinusite crônica com pólipos nasais expostos a CPAP apresentam redução do volume dos pólipos nasais, embora a patência nasal, estabelecida pelo pico de fluxo nasal inspiratório e pela rinometria acústica não determine efeitos significativos nos sintomas de obstrução nasal.

ABSTRACT

Introduction: Many studies have shown the influence of nasal obstruction on sleep disorders and adaptation to continuous positive airway pressure (CPAP). However, data are lacking on the impact of continuous positive pressure on the nasal cavity – whether in healthy individuals or patients with allergic rhinitis – and on the effect, if any, of topical corticosteroids on nasal patency after exposure to CPAP. In addition, it has been hypothesized that increasing interstitial hydrostatic pressure within the sinonasal mucosa of patients with nasal polyposis may decrease polyp size. **Objective:** The overarching goal of this series of studies was to evaluate the effect of continuous positive pressure on the nasal cavity of healthy individuals, subjects with allergic rhinitis, and subjects with nasal polyposis by objective and subjective methods. **Methods:** Three studies were carried out. The first included 27 subjects who were exposed to 2 hours of positive nasal pressure by CPAP via nasal mask with a pressure of 20 cm/H_2O. A questionnaire on nasal allergic symptoms was applied, and participants were subsequently divided into two groups: with and without nasal allergic symptoms. Four methods were applied immediately before and after exposure to positive pressure: a visual analogue scale (VAS) of nasal obstruction; the Nasal Obstruction Symptom Evaluation (NOSE) scale; peak nasal inspiratory flow (PNIF) measurement; and acoustic rhinometry (AcRh). For the second study, 10 patients with nasal allergic rhinitis were exposed to 1 hour of positive nasal pressure by CPAP via nasal mask with a pressure of 15 cm/H_2O. VAS, NOSE, PNIF, and AcRh measurements were obtained immediately before exposure to positive pressure. Topical intranasal budesonide therapy (400 mcg/day) was administered for 4 weeks, and the aforementioned tests were performed again, now before and after exposure to positive pressure. For the third study, 12 patients with nasal polyposis and 27 controls without polyposis were exposed to CPAP (20 cm/H_2O) for 2 hours. VAS, NOSE, PNIF, AcRh, and nasal endoscopy (for polyp grading with the Meltzer Clinical Scoring System) were performed before and after the intervention. **Results:** In the first study, an increase in nasal obstruction was observed both on subjective parameters (VAS and NOSE) and on objective evaluation (reduction of nasal cavity volume on AcRh and lower PNIF). Deterioration of indicators of nasal patency was worse in subjects with nasal

allergic complaints. In the second study, comparison of VAS, NOSE, PNIF, and AcRh findings after and before topical budesonide therapy and after exposure to positive pressure showed a statistically significant improvement in nasal obstruction scores and indicators of nasal patency. In the third study, for the polyposis group, VAS, NOSE and AcRh findings did not differ significantly (p=0.72, p=0.73, and p=0.17, respectively), but PNIF worsened (p=0.04) after exposure to CPAP. There was a statistically significant reduction in nasal polyp volume (p=0.04). The control group experienced deterioration of all measured parameters of nasal obstruction. **Conclusion:** Acute exposure to positive pressure via CPAP impairs nasal patency. This effect is even more pronounced in individuals with nasal allergic symptoms. Topical corticosteroid therapy was able to mitigate the irritant effects of CPAP on the nasal mucosa, leading to improvement of nasal patency parameters. In patients with nasal polyposis, CPAP exposure reduced the size of nasal polyps, but also reduced nasal patency as measured by PNIF. However, it had no significant effects on acoustic rhinometry findings or clinical symptoms of nasal obstruction.

O tratamento padrão ouro para pacientes com apneia obstrutiva do sono (AOS) é a pressão positiva contínua nas vias aéreas (CPAP), que demonstrou reduzir os riscos das complicações associadas tais como doenças cardiovasculares, hipertensão arterial crônica, doença coronariana, acidente vascular encefálico, diabetes mellitus (Peppard et al. 2000) e câncer (Kent et al. 2014; Nieto et al. 2012).

A adesão variável à terapia, no entanto, limita sua eficácia geral; 46% a 83% dos pacientes não são aderentes ao tratamento (Weaver and Grunstein 2008). A interface da máscara, desconforto da pressão do ar, obstrução e secura nasal, e fatores psicológicos e sociais levam a baixa aceitação e adesão (Sawyer et al. 2011).

A obstrução nasal é um fator de risco conhecido para distúrbios respiratórios do sono secundários a mudanças da velocidade e resistência do fluxo aéreo (Young, Finn, and Kim 1997). Como o nariz representa o primeiro portal de entrada de ar, doenças nasais na forma de desvios septais, pólipos nasais, hipertrofia de conchas nasais e rinites, podem contribuir para o desenvolvimento de AOS (Georgalas 2011). Além disso, a cavidade do nariz é responsável por 50% da resistência total das vias aéreas superiores (Ferris, Mead, and Opie 1964).

Mecanismos fisiopatológicos têm sido descritos para explicar o efeito da obstrução nasal nos distúrbios respiratórios do sono. De acordo com o modelo *do resistor* de Starling, a apneia pode ocorrer quando a obstrução nasal gera pressão negativa intraluminal a jusante, suficiente para causar colapso dos tecidos moles complacentes da orofaringe (Park 1993). Além disso, a exclusão da respiração nasal leva a uma queda da ativação dos receptores nasais e do reflexo naso-ventilatório, resultando em diminuição do tônus muscular e à diminuição da ativação destes receptores (Mcnicholas, Coffey, and Boyle 1993).

Evidências clínicas e experimentais tem demonstrado uma associação entre redução da patência nasal e distúrbios respiratórios do sono.

Pacientes submetidos a tamponamento nasal apresentaram piora da qualidade do sono e aumento da frequência de episódios de apneia (Suratt, Turner, and Wilhoit 1986).

A literatura, porém, não mostra muitos estudos sobre o efeito da pressão positiva na cavidade nasal, especialmente no que diz respeito a obstrução nasal. O conhecimento e compreensão desse mecanismo são extremamente importante, pois em portadores de AOS, é provável que haja uma relação direta entre o sintoma obstrutivo e a aderência ao CPAP.

Em estudo realizado com 12 pacientes com AOS e usuários de CPAP, foram coletadas biópsias da mucosa nasal e realização do teste da sacarina (para avaliação do *clearance* mucociliar). As amostras foram coletadas antes do início do tratamento CPAP e após 3-10 meses do uso do mesmo e examinados por microscopia eletrônica. Em todos os pacientes, o epitélio nasal mostrou alterações fundamentais que se manifestaram como modificações na forma de células epiteliais, conglutinação e aglutinação das microvilosidades, e o surgimento de células imunocompetentes. O *clearance* mucociliar estava claramente prolongado em todos os casos (Constantinidis et al. 2000).

Bossi e colaboradores (Bossi et al. 2004) não observaram alteração na resistência nasal nos resultados da rinomanometria computadorizada de oito pacientes com AOS, antes e após 6 meses de tratamento com CPAP. Apenas um estudo (Willing et al. 2007) em indivíduos saudáveis, utilizando rinomanometria computadorizada, conseguiu demonstrar uma diminuição da resistência nasal após o uso de CPAP por um período de 6 horas. Entretanto, os autores não avaliaram o impacto dos sintomas alérgicos nasais na patência nasal durante a exposição à pressão positiva.

Estudos demonstraram uma associação entre rinite alérgica sazonal e diminuição da qualidade do sono e um aumento nos episódios apneicos (McNicholas et al. 1982; Stuck et al. 2004). Além disso, pacientes com rinite não alérgica apresentaram maior risco para maiores escores de IAH e escala de

sonolência de Epworth, com até 83% de queixas de sono (Kalpaklıoğlu, Kavut, and Ekici 2009).

Alguns pesquisadores acreditam que a ocorrência de rinite pelo uso de CPAP, especialmente nos pacientes com obstrução nasal preexistente ou sintomas prévios de rinite, poderia contribuir para aumentar a baixa adesão do paciente ao tratamento (Devouassoux et al. 2007).

A rinite alérgica (RA) constitui um estado de inflamação crônica com uma taxa de prevalência de até 25% nos países europeus (Bauchau and Durham 2004). A inflamação nasal tem sido relacionada à presença de AOS e à falta de aderência ao CPAP (McNicholas et al. 1982). Portanto, faz sentido considerar que, em pacientes com AOS tratados com CPAP, a existência de uma inflamação de base, como uma rinite alérgica, poderia aumentar ou exacerbar o efeito inflamatório do CPAP e levar a uma maior intolerância ao tratamento.

Evidências sugerem que medicamentos tópicos podem ser benéficos em pacientes com obstrução nasal e com queixas relacionadas ao sono. Em ensaio clínico randomizado, Craig et al. em 1998 demonstraram melhora significativa na qualidade do sono e sonolência diurna em pacientes com rinite alérgica em tratamento com esteroides nasais tópicos. Os dados deste estudo foram então reunidos com os resultados de outros dois estudos controlados com placebo, observando-se correlação significante entre a redução na congestão nasal e melhora na qualidade do sono e da sonolência (Craig, Hanks, and Fisher 2005). Outro ensaio clínico e randomizado, (Kiely, Nolan, and McNicholas 2004) demonstrou redução significante no IAH, de 6,5 pontos em média; no entanto, a maioria dos pacientes continuou com AOS significativa. Portanto, os corticosteroides nasais podem melhorar a qualidade do sono nesta população de pacientes e podem ser um complemento útil no tratamento de pacientes com AOS leve. Esse achado contrasta com os resultados de tratamento com descongestionantes intranasais tópicos, que não se mostraram eficazes. Ensaios clínicos randomizados com o uso de oximetazolina na AOS mostraram pouca ou

nenhuma melhora na taxa de IAH (Kerr et al. 1992; McLean et al. 2005; Clarenbach et al. 2008).

A falta de controle dos sintomas de rinite foi significativamente correlacionada à baixa adesão ao CPAP em pacientes apneicos com rinite alérgica ou não alérgica (Parikh et al. 2014).

Uma revisão sistemática e meta-análise (Charakorn et al. 2017) concluíram que os CE nasais apresentam algum benefício na duração média do uso do CPAP por noite, porém sem significância estatística. Dois estudos cegos e placebo controlados foram incluídos, porém, nenhum deles separou os pacientes alérgicos dos nao alérgicos. Os autores, concluem ainda, que novos estudos devam ser realizados para avaliar o efeito dos CE na mucosa nasal de pacientes submetidos a pressão positiva.

A pressão intersticial e os pólipos nasais

Histologicamente, a rinossinusite crônica com pólipos nasais (RSCcPN) é caracterizada por intenso edema estromal, com deposição de albumina, formação de pseudocistos e infiltrado celular inflamatório subepitelial e perivascular (Van Crombruggen et al. 2011). O TGF-β é considerado um importante instrumento na imunossupressão e remodelação da via aérea. Além de apresentar papel imunossupressor, induz os fibroblastos a sintetizar proteínas da matriz extracelular implicando na formação de fibrose (Pezato et al. 2016). Esse grupo de pesquisa (Balsalobre et al. 2013) estudou também a expressão de TGF-β em pacientes com RSCcPN e seu papel no processo de remodelação da matriz intersticial. Para tanto, procedemos à análise de pólipos nasais de pacientes com RSCcPN e da mucosa nasal de controles, com a avaliação da expressão TGF-β por meio de método imunohistoquímico com anticorpo monoclonal primário de TGF-β, e da análise morfométrica microscópica do tecido. Demonstramos uma relação de inversão da área de expressão de TGF-β do epitélio em relação ao estroma (submucosa) através da

variação da expressão reafirmando a importância do TGF-β como peça fundamental no processo de remodelação tecidual. Concluímos que o TGF-β pode exercer um papel diferente no estroma e no epitélio na RSCcPN podendo alterar a resposta ao tratamento tópico.

Estudos recentes vem demonstrando que, mais que uma doença inflamatória crônica, a RSCcPN é também uma doença caraterizada por uma disfunção mecânica do tecido da mucosa nasal caraterizada pela incapacidade da mucosa do tecido polipoide em aumentar a pressão hidrostática intersticial em resposta ao extravasamento de exsudato durante um processo inflamatório, rompendo o equilíbrio pressórico entre pressão hidrostática e oncótica, responsáveis pela limitação do edema (Pezato et al. 2014; Pezato et al. 2016; Pezato and Voegels 2012).

Pezato e colaboradores (Pezato et al. 2014) demonstraram a diferença no comportamento da infusão de liquido na mucosa nasal de pacientes com RSCcPN quando comparados à mucosa saudável. Os autores, através de uma injeção controlada de solução salina em tecido retirado de pólipos de pacientes com RSCcPN e de tecidos de controle (áreas sem doença nasossinusal), compararam o comportamento da pressão intersticial hidrostática e observaram que a relação pressão/volume nos pólipos nasais era menor em relação ao tecido normal. O pólipo requer três vezes mais infusão de solução salina para alcançar a mesma pressão hidrostática intersticial encontrada na mucosa do meato médio.

Os autores identificaram que essa diferença de pressão era acompanhada pela falta de matriz extracelular e diminuição da expressão de TGF-β nos pólipos dos pacientes com RSCcPN. E concluíram que o desequilíbrio entre a pressão osmótica e hidrostática na mucosa dos pólipos pode atuar como fator contribuinte para o seu desenvolvimento e que novas terapias que vão além do uso de imunomoduladores e anti-inflamatórios poderiam ser utilizadas para aumentar a resistência da mucosa e prevenir o seu aumento descontrolado.

Nessa mesma linha de pesquisa, Gregório e colaboradores (Gregório

et al. 2017), através do mesmo método, observaram que o aumento da pressão em resposta à injeção de solução salina foi menor no tecido dos pólipos nasais quando comparado com o grupo controle da mucosa do meato médio e o grupo fibrose (tecido proveniente de sinéquias nasais). Não houve diferença estatisticamente significante na resposta pressórica durante a injeção de solução salina entre os grupos fibrose e meato médio (controle). Os autores concluem que a disfunção mecânica encontrada na mucosa nasal de pacientes com pólipos nasais corroboram com essa nova teoria da formação do edema do mesmo. E concluem ainda, que os achados permitem acreditar que a fibrose possa ter um potencial papel no aumento da pressão hidrostática intersticial e consequentemente, poderia mitigar a formação do edema no PN.

A pressão intersticial

O espaço intersticial compreende cerca de um sexto de todo o volume corporal. Seus fluidos apresentam um gradiente de pressão denominado pressão do fluido intersticial (PFI), que corresponde à resultante entre pressão oncótica e hidrostática do capilar e do interstício. A pressão oncótica resulta em movimento de fluidos no sentido de entrada ao continente referido, enquanto que a pressão hidrostática resulta em movimento de fluidos em sentido oposto, ou seja, de saída de fluidos do continente estudado. A PFI pode ser ativamente controlada pelo tecido conectivo frouxo intersticial, possivelmente por um mecanismo onde os fibroblastos exerçam tensão sobre a rede microfibrilar de colágeno da matriz extracelular, via integrinas, contrapondo-se à tendência em extravasamento causada pela pressão oncótica intersticial (Heldin et al. 2004).

A completa falência do mecanismo de equilíbrio pressórico (pressão hidrostática/pressão osmótica) entre o vaso e o tecido durante um processo inflamatório levaria a completa depleção do volume do sistema vascular levando a choque hipovolêmico do organismo vivo ou rompimento tecidual devido ao extravasamento de volume para o interstício.

Na PN ocorre uma perda parcial da capacidade do tecido polipoide em elevar a pressão hidrostática intersticial em resposta ao aumento da pressão osmótica intersticial secundária ao extravasamento de proteínas durante o processo infamatório (Figura 1), favorecendo a formação de edema e alterando o processo de remodelação.

Na prática médica diária, o aumento da pressão hidrostática é o tratamento de alguns desequilíbrios hídricos, como no caso do edema de membros inferiores, onde a meia compressiva aumenta a pressão hidrostática intersticial, minimizando o extravasamento de liquido para o espaço intersticial.

A partir dessas observações, tem-se sugerido que o aumento da pressão intersticial hidrostática poderia mitigar o desenvolvimento de pólipos nasais (Gregório et al. 2017).

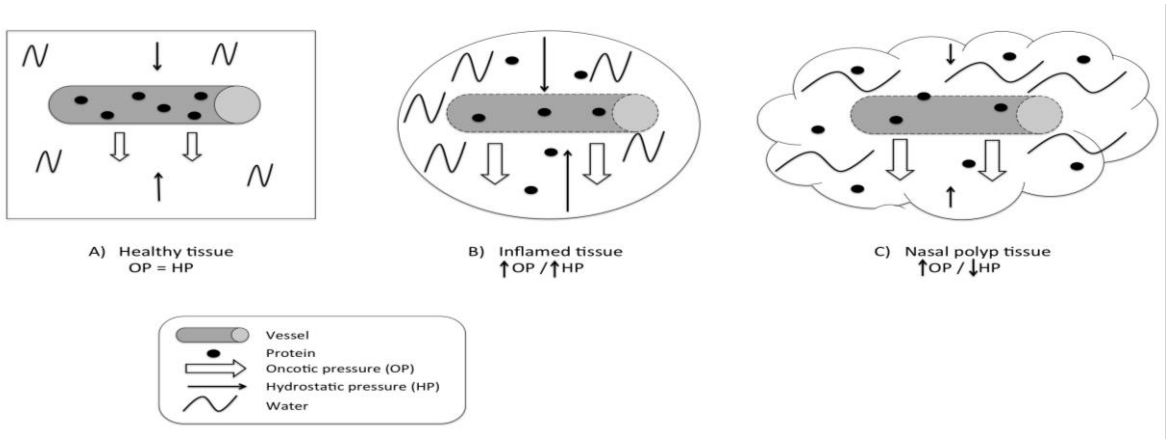

Figura 1: Ilustração demonstrando um aumento de permeabilidade capilar devido ao processo inflamatório com saída de proteína e aumento da pressão oncótica tecidual em B e C e consequentemente saída de água para o interstício e edema. Na figura B evidencia-se um aumento compensatório da pressão hidrostática intersticial em resposta ao aumento da pressão oncótica, limitando o edema. A figura C demonstra um aumento menos intenso da pressão hidrostática intersticial em resposta ao aumento da pressão oncótica, favorecendo maior saída de água do capilar para o tecido e maior edema tecidual.

- Avaliar o efeito da pressão positiva contínua na cavidade nasal;
- Avaliar o efeito do uso do corticosteroide tópico na patência nasal após a exposição aguda a pressão positiva contínua;
- Avaliar o efeito do aumento da pressão hidrostática intersticial no pólipo nasal com o emprego da transmissão da pressão positiva continua na via aérea superior.

3. MANUSCRITOS ORIGINAIS

3.1 Manuscrito Original 1

A literatura é bastante escassa sobre os efeitos da pressão positiva de ar na mucosa nasal. Os artigos mostram relatos de usuários de CPAP sobre os efeitos colaterais do uso deste dispositivo, sem avaliações precisas, objetivas ou experimentais.

Foi realizado um estudo com 27 indivíduos que foram expostos a pressão positiva nasal por 2 horas com CPAP e máscara nasal com pressão de 20cm/H_2O. Um questionário sobre sintomas alérgicos nasais foi aplicado e 2 grupos foram definidos – com e sem sintomas alérgicos nasais. Quatro métodos de avaliação da obstrução nasal foram aplicados imediatamente antes e após a exposição à pressão positiva, escala visual analógica (EVA), escala de sintomas da obstrução nasal (NOSE), pico de fluxo nasal inspiratório e rinometria acústica.

Observou-se aumento da obstrução nasal tanto com os métodos subjetivos (EVA e NOSE) quanto nas avaliações objetivas, mostrando redução da cavidade nasal na rinometria acústica e piora no pico de fluxo nasal inspiratório.

Observou-se, ainda, que indivíduos com queixas alérgicas nasais, apresentaram uma piora mais acentuada nos testes de permeabilidade nasal.

Concluiu-se, então, que a exposição aguda da cavidade nasal à pressão positiva, por CPAP, deteriora a patência nasal e que, em indivíduos com sintomas alérgicos nasais, essa piora é ainda mais acentuada.

ORIGINAL ARTICLE

Acute impact of continuous positive airway pressure on nasal patency

Leonardo Balsalobre, MD, Rogério Pezato, MD, PhD, Hiran Gasparini, BS, Fernanda Haddad, MD, PhD, Luis Carlos Gregório, MD, PhD and Reginaldo R Fujita, MD, PhD

Background: Continuous airflow in the upper airway can cause discomfort, leading to nasopharyngeal complaints. The aim of the present study is to evaluate the acute effects of continuous positive upper-airway pressure on nasal patency in awake normal subjects.

Methods: Twenty-seven adults (17 men; 10 women; age range, 18 to 43 years) were exposed to continuous airway pressure (20 cmH_2O) in the nasal cavity, delivered by a continuous positive airway pressure (CPAP) device through a nasal mask for 2 hours. Visual analogue scale (VAS) of nasal obstruction, Nasal Obstruction Symptom Evaluation (NOSE) modified scale, acoustic rhinometry (AR), and peak nasal inspiratory flow (PF) were measured before and after the use of CPAP.

Results: There was an increase in nasal obstruction scores both on the VAS ($p < 0.05$) and on the NOSE scale ($p < 0.05$), as well as a reduction in nasal cavity volume on AR ($p < 0.05$) and a decline in PF ($p < 0.05$). Subjects were stratified into 2 groups: with and without symptoms of allergic rhinitis. Nasal parameters were significantly worse in the rhinitis group, with higher nasal obstruction scores on the VAS ($p = 0.001$) and NOSE scale ($p < 0.001$) and decreased PF ($p < 0.001$).

Conclusion: Acute exposure to positive pressure via CPAP is associated with subjective and objective reductions in nasal patency. In individuals with allergic nasal symptoms, deterioration is even more severe than in patients without these symptoms.

Key Words:
nose; CPAP; positive pressure; nasal obstruction, allergic rhinitis

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The treatment of choice for patients with obstructive sleep apnea (OSA), especially in moderate and severe cases, is the use of continuous positive airway pressure (CPAP) devices. By delivering pressurized airflow through a nasal or oronasal mask, CPAP creates a pneumatic splint in the upper airway (UA). This positive air pressure is able to keep the UA patent, and thus prevent its collapse during sleep.[1] However, the main limiting factor of this therapy has been long-term adherence. It is estimated that between 25% to 50% of patients stop using the device at around 5 years.[2,3]

Possible causes for poor adherence to CPAP are mainly those related to the side effects of this treatment modality. Such effects are reported by 15% to 45% of patients; the most frequent include skin irritation, nasal congestion, and air leak.[4]

The continuous flow of air in the UA causes discomfort and leads to nasopharyngeal complaints, particularly nasal obstruction. It is worth noting that these symptoms are common in patients with OSA,[5–7] and are made worse by CPAP therapy.[8,9] However, controversy remains as to whether nasal side effects can actually predict poor adherence to these devices.[10,11] The majority of studies that assessed nasal complaints arising from the use of CPAP used only subjective methods, such as questionnaires, and yielded conflicting results.[12]

Within this context, the objective of the present study is to evaluate the acute effects of continuous positive upper-airway pressure on nasal patency, using objective and subjective methods of assessment.

Subjects and methods

This study was conducted to evaluate the effects of CPAP on nasal patency, from March to May 2016, at the Department of Otolaryngology–Head and Neck Surgery,

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Universidade Federal de São Paulo (UNIFESP). The project was approved by the UNIFESP Institutional Research Ethics Committee, with protocol number 897.279, on December 3, 2015. All individuals willingly agreed to take part in the study and provided written informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The study included healthy individuals, aged 18 to 60 years, without a diagnosis or history of treatment for breathing-related sleep disorders. All were recruited through advertisements posted throughout the UNIFESP campus. After screening, each participant was interviewed to exclude those with factors that might influence nasal patency:

- Use of medications such as antihistamines, antihypertensives, topical vasoconstrictors, systemic vasodilators, and topical and systemic corticosteroids in the last month;
- Sinonasal infection and/or inflammation in the preceding month;
- History of tumors and/or prior sinonasal surgery; and
- Smoking or illicit drug use.

Of the 33 individuals recruited through advertisements, 27 met the inclusion and exclusion criteria: 10 (37%) women and 17 (63%) men (age range, 18 to 43 years). The Score for Allergic Rhinitis (SFAR) was administered to assess for allergic rhinitis symptoms. Individuals with a score of 7 or higher were considered positive.[13]

Exposure to CPAP

All subjects were exposed to continuous airway pressure (20 cmH_2O) in the nasal cavity, delivered by a CPAP device through a nasal mask for 2 hours, while awake in the sitting position. No topical medications were placed in the nose before or after the intervention, and air leak through the mask was ruled out.

The following were performed and/or administered in all participants immediately before and after the use of CPAP:

- Visual analogue scale (VAS) of nasal obstruction;
- Nasal Obstruction Symptom Evaluation (NOSE) scale;
- Physical examination with anterior rhinoscopy and flexible fiber-optic nasopharyngolaryngoscopy;
- Acoustic rhinometry (AR) and peak nasal inspiratory flow (PF) measurement.

For comparison of nasal findings, participants were stratified into 2 groups: with and without symptoms of allergic rhinitis.

VAS

To evaluate nasal obstruction, each participant was asked to score their nasal obstruction at that point in time on a scale ranging from 0 to 10, with 0 = absence of nasal obstruction and 10 = complete nasal obstruction (Fig. 1).

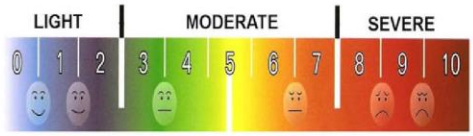

FIGURE 1. Visual analogue scale of nasal obstruction.

NOSE scale

We also administered the NOSE scale, in which the items referring to nasal obstruction during sleep and exercise had been removed, because individuals did not perform physical activity and did not sleep after the CPAP exposure. For each of the 3 questions, scores could range from 0 to 4, for a maximum score of 12 points (Table 1).

AR and PF

For objective evaluation of nasal patency, participants underwent AR and PF measurement.

AR was performed without administration of vasoconstrictor. The test was conducted in an acoustically treated room with all factors necessary to ensure the accuracy of the procedure, as standardized by the international Standardisation Committee on Objective Assessment of the Nasal Airway: each participant remained 30 minutes in an air-conditioned room (temperature set to 21°C before measurement), and ambient humidity was kept in the 50% to 60% range; the head of each participant was stabilized to ensure proper positioning of the pulse tube; petroleum jelly was used to prevent air leak; and participants were instructed to control their breathing. To ensure the accuracy of the test, at least 3 curves were plotted for each nostril. After each measurement, the nosepiece was removed from the naris, reconnected, and a new measurement was then obtained. The results were deemed adequate if the coefficient of variability was lower than 10%. The recorded curves were used to obtain a mean curve for each naris. The values of these mean curves were then analyzed. The same investigator performed all examinations. The cross-sectional area between the distances 0 and 5 cm, expressed in cm^2, was used for objective comparison of findings.

Measurement of PF was performed with an In-Check Nasal Inspiratory Flow Meter (ClementClarke International, Harlow, UK), equipped with an air-cushioned facemask. The device consists of a small facemask connected to a plastic cylinder through which air flows during a forced inspiration. PF was measured 3 consecutive times with a 1-minute interval between measurements, all obtained with the participant in the standing position. Results are obtained immediately, as with the peak expiratory flow meters used routinely in pulmonology practice to assess the expiratory capacity of the lungs.

TABLE 1. NOSE scale

	Not a problem	Very mild problem	Moderate problem	Very bad problem	Severe problem
1. Nasal congestion or stuffiness	0	1	2	3	4
2. Nasal blockage or obstruction	0	1	2	3	4
3. Trouble breathing through my nose	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Unable to get enough air through my nose during exercise or exertion	0	1	2	3	4

NOSE = Nasal Obstruction Symptom Evaluation.

Statistical analysis

The data were tabulated and analyzed in the SPSS v. 22 (IBM Corp., Armonk, NY) and Prism v. 7 (GraphPad Software Inc., La Jolla, CA) software packages. The nonparametric Wilcoxon test was used to assess within-group differences before and after exposure to CPAP. The Mann-Whitney *U* test was used to assess differences between 2 independent samples (individuals with and without allergic rhinitis). In all cases, p values < 0.05 were deemed statistically significant.

Results

Of the 27 patients assessed, 15 had allergic rhinitis symptoms (SFAR score of 7 or greater). There was no statistically significant difference in age on comparison between the allergic rhinitis symptoms and no allergic rhinitis symptoms groups ($p > 0.05$).

Analysis of the effects of CPAP

When the group as a whole was assessed before and after CPAP exposure, the nasal parameters of interest demonstrated statistically significant deterioration. There was an increase in nasal obstruction scores both on the VAS ($p < 0.05$) and on the NOSE scale ($p < 0.05$), as well as a reduction in nasal cavity volume on AR ($p < 0.05$) and a decline in PF ($p < 0.05$) (Table 2).

Comparison between groups with and without allergic rhinitis symptoms

Nasal parameters were significantly worse in those that having allergic rhinitis symptoms, with higher nasal obstruction scores on the VAS ($p = 0.001$) and NOSE scale ($p < 0.001$) and decreased PF ($p < 0.001$) (Figs. 2 and 3, and 4).

AR

On AR, there was a greater reduction in nasal cavity volume after nasal exposure to CPAP in the allergic rhinitis symptoms group than in the non–allergic rhinitis symptoms group, although it did not reach statistical significance ($p = 0.15$).

Discussion

CPAP is considered the gold-standard treatment for patients with OSA. Its use is associated with substantial improvement in quality of life,[14] excessive daytime sleepiness, cognitive performance,[15,16] and sleep quality[17] in patients with this diagnosis. Recent studies have shown that the use of CPAP can modify cardiovascular risk factors, improving blood pressure control in hypertensive patients[18] and glycemic control in those with diabetes,[19] as well as provide secondary prevention against cardiovascular events[20] in patients with OSA.

Despite the benefits associated with the use of CPAP, adherence to this treatment modality is still the greatest challenge faced by sleep medicine specialists. There are several causes for poor adherence, such as claustrophobia caused by the mask, restriction of movement during sleep, and, not least, the nasal symptoms caused by CPAP itself, which can arise quickly, prompting premature removal of the mask.[9]

The present study showed that individuals who were exposed to continuous positive pressure in the nasal cavity via CPAP experienced a deterioration of nasal parameters, especially nasal obstruction. These results were confirmed by tests specific for assessment of nasal obstruction, such as PF and AR, with statistical significance.

When individuals were divided between those with and without allergic rhinitis symptoms, those in the former group exhibited deterioration of the nasal symptoms evaluated after exposure to positive pressure as compared with those in the non–allergic rhinitis symptoms group; differences were significant on VAS, NOSE, and PF. The reduction in nasal patency assessed by AR was also greater in the allergic rhinitis symptoms group than in the non–allergic rhinitis symptoms group, although the difference was not significant. The relatively small number of subjects studied may explain this result.

Nasal symptoms are common in patients with OSA,[6,7] and nasal obstruction is a risk factor for OSA.[21] Nasal congestion secondary to allergic rhinitis promotes

TABLE 2. Descriptive statistics in 27 subjects (pre-exposure vs postexposure to positive pressure)*

	Pre-exposure	Postexposure	p^a
Visual analog scale	2.66 ± 1.8 (0–7)	4.55 ± 2.6 (0–9)	0.009
Peak inspiratory flow	127.15 ± 50.2 (60–313)	112.37 ± 54.8 (46–306)	0.008
Acoustic rhinometry	11.98 ± 3.6 (7.03–24.75)	10.08 ± 2.4 (5.08–15.35)	0.006
NOSE	2.74 ± 1.85 (0–6)	5.00 ± 3 (0–10)	0.006

*Values are mean ± SD (minimum–maximum).
[a]Wilcoxon test.
NOSE = Nasal Obstruction Symptom Evaluation; SD = standard deviation.

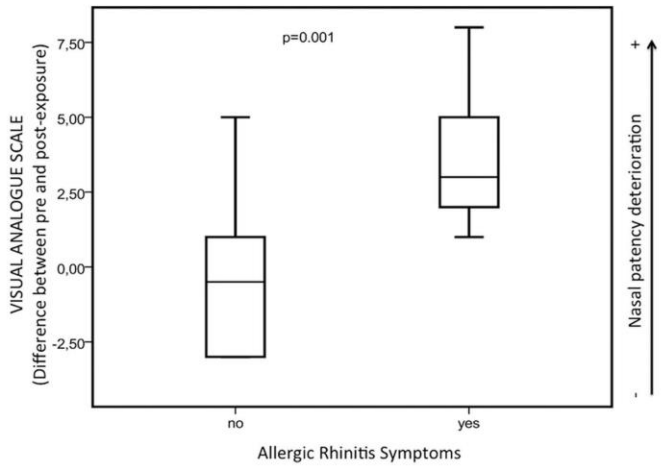

FIGURE 2. Comparison the difference between the values of the VAS before and after exposure to positive pressure in the groups with and without nasal allergic symptoms. VAS = visual analogue scale.

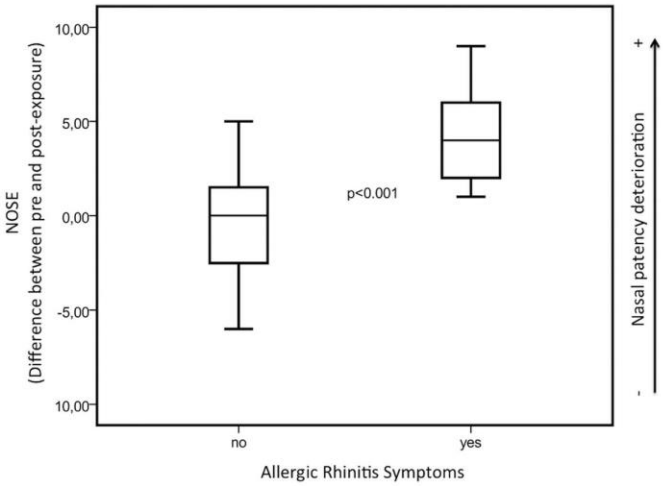

FIGURE 3. Comparison the difference between the values of the NOSE before and after exposure to positive pressure in the groups with and without nasal allergic symptoms. NOSE = Nasal Obstruction Symptom Evaluation.

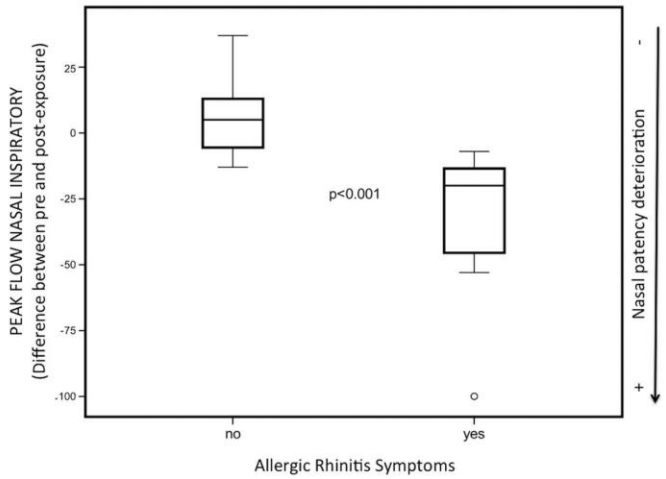

FIGURE 4. Comparison the difference between the values of the PF before and after exposure to positive pressure in the groups with and without nasal allergic symptoms. PF = peak nasal inspiratory flow.

sleep-disordered breathing in individuals with rhinitis; this, in turn, is associated with increased risk of moderate to severe OSA.[21,22]

Many studies have tried to improve the adherence of apneic patients to CPAP by proposing measures such as use of humidifiers, warmers, and even more comfortable masks.[23] However, one must bear in mind that the patient's own breathing pattern is a very important factor in adherence. The results of the present study provide further evidence of the need for prior nasal assessment in patients before starting CPAP use, especially in those with allergic nasal symptoms, which, if improperly treated, can be worsened by positive pressure, thus leading to poor treatment adherence.

Willing et al.[24] have conducted a similar study in normal individuals, and found different results. They have shown that CPAP use for 6 hours decreased nasal resistance. However, important methodological differences were noted between the present study and the study by Willing et al.[24] Of note, AR was employed in the present study and posterior rhinomanometry in the cited study. The posture adopted by the studied subjects was also different: seated orthostatic in the present study and recumbent in the other. It is known that this can influence nasal resistance.[25] Furthermore, special attention was given to symptoms of allergic rhinitis in the present study, a different feature when compared to the study by Willing et al.[24] All these methodological differences preclude further and deeper comparisons of results.

We decided to administer the SFAR questionnaire instead of classic allergy tests such as radioallergosorbent test (RAST) or the skin-prick test. Hence, one could argue this is a study limitation. Actually, we were seeking to divide subjects into those with and those without nasal symptoms of allergy, rather than merely determining whether participants reacted positively to 1 or more allergens. The small sample size, the fact that participants did not have sleep apnea, and were involved a 2-hour exposure to CPAP in an awake, upright position that differed from an 8-hour exposure in a sleeping, supine patient may be considered a limitation of this study. Moreover, with the idea of creating a study group with the least possible nasal changes that could influence the effect of positive pressure, many factors were used as exclusion criteria. For this reason, individuals may differ from the real life population; however, the chance of bias was minimized. On the other hand, the methodology adopted in this study was chosen in an attempt to increase the accuracy of results by using not only subjective methods, such as questionnaires, but also objective ones (namely, PF and AR).

Further studies involving individuals with OSA and assessing the influence of heated humidification through the present methods are necessary to clarify this issue.

Conclusion

Acute exposure to positive pressure via CPAP is associated with subjective and objective reductions in nasal patency. In individuals with allergic nasal symptoms, deterioration is even more severe than in patients without these symptoms.

H.G. applied the methods. L.B. and R.P. wrote the manuscript. F.H., L.C.G., and R.F. helped with general support.

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3.2 Manuscrito Original 2

Nosso estudo prévio (Balsalobre et al. 2017) mostrou que a pressão positiva aguda na cavidade nasal leva a uma piora da patência nasal, e que a piora é ainda mais acentuada em indivíduos com sintomas alérgicos nasais. A partir destes achados, um outro estudo foi desenvolvido com o objetivo de avaliar o efeito do corticosteroide tópico na patência nasal após exposição aguda a pressão positiva.

Dez indivíduos com sintomas alérgicos nasais e com teste de punctura positivo para aeroalérgenos foram expostos a pressão positiva nasal por 1 hora com o uso de CPAP e máscara nasal com pressão de 15 cm/H_2O. Os mesmos métodos de mensuração da obstrução nasal foram aplicados imediatamente antes e após a exposição a pressão positiva, escala visual analógica (EVA), escala de sintomas da obstrução nasal (NOSE), pico de fluxo nasal inspiratório e rinometria acústica. Tratamento com budesonida tópica nasal na dose de 400mcg/dia foi instituído por 4 semanas e novamente os testes foram realizados antes e após a exposição à pressão positiva.

A comparação entre EVA, NOSE, PFNI e RmA antes e após o uso da budesonida tópica e após a exposição à pressão positiva mostrou uma melhora nos escores de obstrução nasal e patência nasal, estatisticamente significante.

Concluiu-se, que o uso do corticoide tópico foi capaz de reduzir os efeitos irritativos na mucosa nasal à pressão positiva, levando a uma melhora dos parâmetros da patência nasal.

Título: Effect of topical corticosteroids on nasal patency after acute positive airway pressure exposure

Revista: Brazilian Journal of Otorhinolaryngology (submetido)

Autores: Leonardo Balsalobre, Aline Bruno Figueiredo, Rogério Pezato, Reginaldo R. Fujita

ABSTRACT

Background: Nasal congestion and obstruction are reported in the majority of continuous positive airway pressure (CPAP) users and are frequently cited as reasons for noncompliance. Baseline inflammation due to allergic rhinitis (AR) could increase or exacerbate the inflammatory effect of high airflow in the nasal cavity as the result of CPAP and lead to greater CPAP intolerance. In this setting, intranasal steroids would be expected to counteract the nasal inflammation caused by AR and/or CPAP. The objective of the present study is to evaluate the effects of topical corticosteroid use on nasal patency after acute exposure to positive pressure. **Methods:** Ten individuals with allergic rhinitis were exposed to 1 hour of continuous airway pressure (15 cm/H_2O) in the nasal cavity, delivered by a CPAP device. Visual analog scale (VAS), Nasal Obstruction Symptom Evaluation (NOSE) scale, acoustic rhinometry (AcRh) and peak nasal inspiratory flow (PNIF) were performed before and after the intervention. After 4-weeks topical nasal steroid (budesonide) application, positive pressure exposure was repeated as well as the first assessments. **Results:** Patients reported a statistically significant improvement both on the VAS ($p=0.013$) and NOSE ($p < 0.01$). Furthermore, objective measurements were improved as well, with increased nasal cavity volume on AcRh ($p=0.02$) and increased PNIF ($p=0.012$), after corticosteroid treatment. **Conclusion:** In patients with allergic rhinitis, intranasal corticosteroid therapy improved objective and subjective parameters of nasal patency after acute exposure of the nasal cavity to positive pressure.

Key words: nose; CPAP; positive pressure; nasal obstruction; allergic rhinitis; topical corticosteroid

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disorder. In a large epidemiologic study conducted in a major Brazilian metropolis, it was found to affect 32.8% of the adult population[1]. OSA is characterized by recurrent episodes of upper-airway obstruction occurring during sleep[2], combined with recurrent cycles of desaturation and reoxygenation, sympathetic overactivity and intrathoracic pressure changes, sleep fragmentation, decreased quality of life (QoL), significant functional impairment, increased risk of road traffic accidents, and medical comorbidities (particularly cardiovascular). The first-line treatment of OSA is continuous positive airway pressure (CPAP), which has been shown to reduce the risks of the aforementioned complications, improve QoL, and lower the rate of motor vehicle accidents[3]. Variable adherence to therapy, however, limits its overall effectiveness; 46% to 83% of patients are nonadherent[4]. The user–mask interface, discomfort from the air pressure required, nasal obstruction and dryness, and psychological and social factors lead to poor acceptance and nonadherence[5].

Allergic rhinitis (AR) is a chronic mucosal inflammation with a prevalence of up to 25% in European countries[6] and could be one of the factors responsible for CPAP-related discomfort in patients with OSA. Although allergic rhinitis and OSA are closely associated, and each condition can be detrimental to the other[7], there is still no consensus on the actual effects of CPAP on the nasal cavity of patients with AR. A recently published article compared individuals with and without rhinitis and demonstrated a difference in physiological and biological changes in the nasal mucosa of those with OSA, but found no exacerbation of nasal symptoms[8]. On the other hand, in a previous study, our group showed that individuals exposed to continuous positive pressure in the nasal cavity via CPAP experienced a deterioration of nasal parameters, especially nasal obstruction. Furthermore, in individuals with allergic nasal symptoms, said deterioration is more severe than in patients without these symptoms[9]. Thus, it is worth considering that baseline inflammation due to AR could increase or exacerbate

the inflammatory effect of high airflow in the nasal cavity as the result of CPAP and lead to greater CPAP intolerance.

Treatment with intranasal corticosteroids is strongly recommended for patients with a clinical diagnosis of AR and symptoms that interfere with their daily life[10]. As nasal complaints are a significant problem in patients with OSA who use CPAP, evaluating and treating such complaints is critical for the proper management of these patients[8]. In this setting, intranasal steroids would be expected to counteract the nasal inflammation caused by AR and/or CPAP.

Within this context, the objective of the present study is to evaluate the effects of topical corticosteroid use on nasal patency after acute exposure to positive pressure.

MATERIAL AND METHODS

This study was from January to March 2018 at the Department of Otolaryngology and Head and Neck Surgery, Federal University of São Paulo (UNIFESP), Brazil. The UNIFESP institutional Research Ethics Committee approved the project with protocol number 897.279 on 3 December 2015. All participants volunteered to take part in the study and provided written informed consent.

The sample included healthy individuals, aged 18 to 30 years, with no diagnosis or history of treatment for breathing-related sleep disorders. All were recruited through ads posted throughout the UNIFESP campus. After screening, each participant was interviewed to exclude those with factors that might influence nasal patency:

- Use of medications such as antihistamines, antihypertensives, topical vasoconstrictors, systemic vasodilators, and topical and systemic corticosteroids in the preceding month;

- Sinonasal infection and/or inflammation in the preceding month;
- History of tumors and/or prior sinonasal surgery;
- Smoking or illicit drug use; and

Participants were also asked whether they experienced any nasal allergy symptoms, such as itching, sneezing, or nasal discharge. Those who replied positively underwent a skin prick test. Participants with a negative prick test were excluded from further analysis.

Skin prick test

Prick tests were performed by inoculation of the right forearm in the morning and reading after 15 minutes. One needle was used for each antigen in each patient.

All allergen extracts had the same provenance (standardized) and the following allergies were tested:

1. Histamine
2. *Dermatophagoides pteronyssinus*
3. *Dermatophagoides farinae*
4. *Blomia tropicalis*
5. *Penicillium notatum*
6. *Alternaria alternata*
7. *Aspergillus fumigatus*
8. Dog
9. Cat
10. *Blattella germanica*

11. *Periplaneta americana*

Histamine served as a positive control. The test was considered positive when an allergen raises a wheal 3 mm or larger; the reaction is greater than or equal to that caused by histamine; and the patient has no reaction to the saline solution.

Exposure to continuous positive airway pressure

All subjects were exposed to 1 hour of continuous airway pressure (15 cm/H_2O) in the nasal cavity, delivered by a CPAP device (F&P Icon, Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) attached to a nasal mask (Meridian Nasal Mask, ResMed Ltd., Bella Vista, Australia), while awake in the sitting position. No topical medications were placed in the nose before or after the intervention, and air leak through the mask was ruled out.

The following were performed and/or administered in all participants immediately before and after the use of CPAP:

1. Visual analogue scale (VAS) of nasal obstruction
2. Nasal Obstruction Symptom Evaluation (NOSE) scale;
3. Acoustic rhinometry (AcRh); and
4. Peak nasal inspiratory flow (PNIF) measurement.

Visual analogue scale (VAS)

To evaluate nasal obstruction, each participant was asked to score their nasal obstruction at that point in time on a scale ranging from 0 to 10, with 0 = absence of nasal obstruction and 10 = complete nasal obstruction (Figure 1).

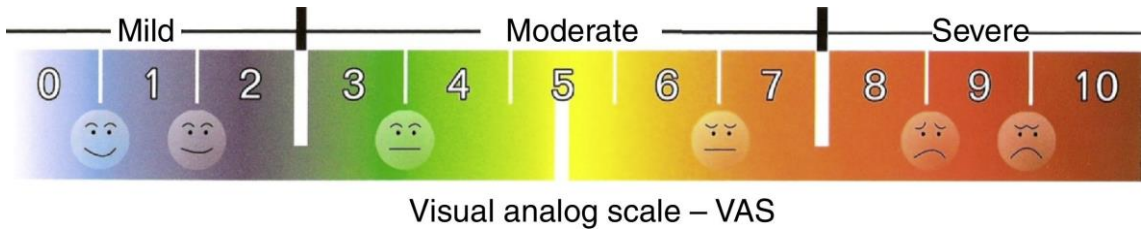

Figure 1: Visual analogue scale (VAS) of nasal obstruction.

Nasal Obstruction Symptom Evaluation (NOSE) scale

We also administered an adapted version of the NOSE scale, in which the items referring to nasal obstruction during sleep and exercise had been removed, as individuals did not perform physical activity and did not sleep after CPAP exposure. For each of the three questions, scores could range from 0 to 4, for a maximum score of 12 points (Table 1).

Table 1. Adapted Nasal Obstruction Symptom Evaluation (NOSE) scale used in the study.

	Not a problem	Very mild problem	Moderate problem	Fairly bad problem	Severe problem
1. Nasal congestion or stuffiness	0	1	2	3	4
2. Nasal blockage or obstruction	0	1	2	3	4
3. Trouble breathing through my nose	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Unable to get enough air through my nose during exercise or exertion	0	1	2	3	4

For objective evaluation of nasal patency, participants underwent AcRh and PNIF measurement.

Acoustic rhinometry (AcRh)

AcRh was performed without administration of vasoconstrictor. The test was conducted in an acoustically treated room with all factors necessary to ensure the accuracy of the procedure, as standardized by the international Standardisation Committee on Objective Assessment of the Nasal Airway: each participant remained 30 minutes in an air-conditioned room (temperature set to 21°C before measurement), and ambient humidity was kept in the 50–60% range; the head of each participant was stabilized to ensure proper positioning of the pulse tube; petroleum jelly was used to prevent air leak; and participants were instructed to control their breathing. To ensure the accuracy of the test, at least three curves were plotted for each nostril. After each measurement, the nosepiece was removed from the naris, reconnected, and a new measurement was then obtained. The results were deemed adequate if the coefficient of variability was lower than 10%. The recorded curves were used to obtain a mean curve for each naris. The values of these mean curves were then analyzed. The same investigator performed all examinations. The cross-sectional area between the distances 0 and 5 cm, expressed in cm^2, was used for objective comparison of findings.

Peak nasal inspiratory flow (PNIF)

Measurement of PNIF was performed with an In-Check Nasal Inspiratory Flow Meter (ClementClarke International, Harlow, UK), equipped with an air-cushioned facemask. The device consists of a small facemask connected to a plastic cylinder through which air flows during a forced inspiration. PNIF was measured three consecutive times with a 1-minute interval between measurements, all acquired with the participant in the standing position. Results are obtained immediately, as with the peak expiratory flow meters used routinely in Pulmonology practice to assess the expiratory capacity of the lungs. The largest measure obtained was used for analysis.

Use of intranasal corticosteroids

Once all baseline assessments had been completed, all patients received four bottles of budesonide 100 mcg and instructed to administer 1 spray into each nostril in the morning and evening. All participants were taught how to apply the spray properly.

After 28 days of budesonide administration, participants were re-exposed to CPAP. Before and after this exposure, the VAS and NOSE scales were re-administered and AcRh and PNIF measurement were performed again, exactly as before.

The study design is demonstrated in Figure 2.

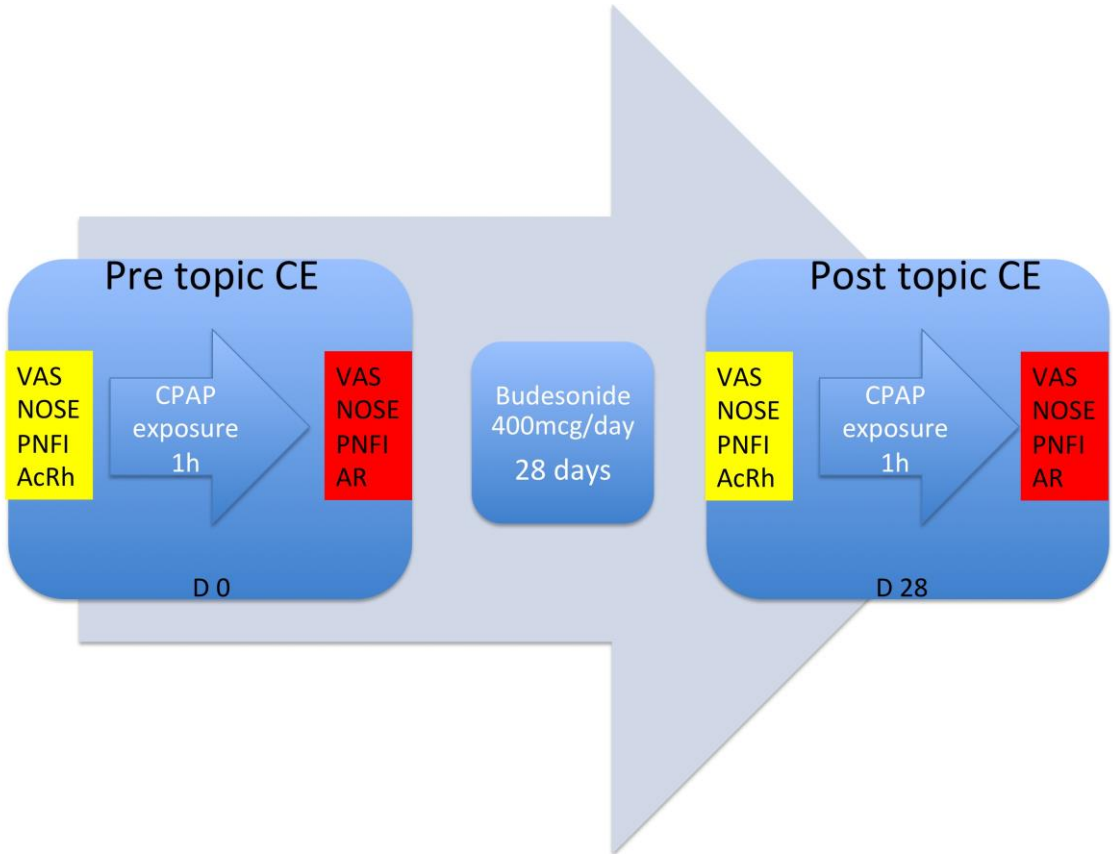

Figure 2: Study design. Legends: CE – corticosteroid; VAS – visual analogue scale; NOSE – Nasal Obstruction Symptom Evaluation scale; PNFI – peak nasal inspiratory flow; AcRh – acoustic rhinometry.

Statistical analysis

Data were tabulated and analyzed in SPSS v. 22 (IBM Corp., New York, NY, USA) and Prism v. 7 (GraphPad Software Inc., La Jolla, CA, USA). The nonparametric Wilcoxon test was used to assess within-group differences before and after exposure to CPAP. In all cases, p-values < 0.05 were deemed statistically significant.

RESULTS

The original sample comprised 20 subjects; 10 were excluded because they did not meet the inclusion and exclusion criteria. Thus, the final sample comprised 10 subjects. The mean age was 23.5 years, with 7 male and three female patients.

Effect of topical corticosteroid before positive pressure exposure

VAS, NOSE, PNIF, and AcRh findings before and after the course of topical corticosteroids, all before CPAP exposure (yellow in Figure 2), were compared.

On subjective evaluation of nasal symptoms (VAS and NOSE), participants reported significant improvement after 28 days of topical corticosteroid use (p=0.02 and p=0.016 respectively). Conversely, there was no improvement in objective parameters (PNIF and AcRh) after corticosteroid therapy.

Effect of topical corticosteroid after positive pressure exposure

Separate comparisons of VAS, NOSE, PNIF, and AcRh findings before and after topical corticosteroid use, but after CPAP exposure (red in Figure 2), were performed.

After four weeks of topical corticosteroid therapy, patients reported improvement both on the VAS (Figure 3) and NOSE (Figure 4). Furthermore, objective measurements were improved as well, with increased nasal cavity volume on AcRh (Figure 6) and increased PNIF (Figure 5).

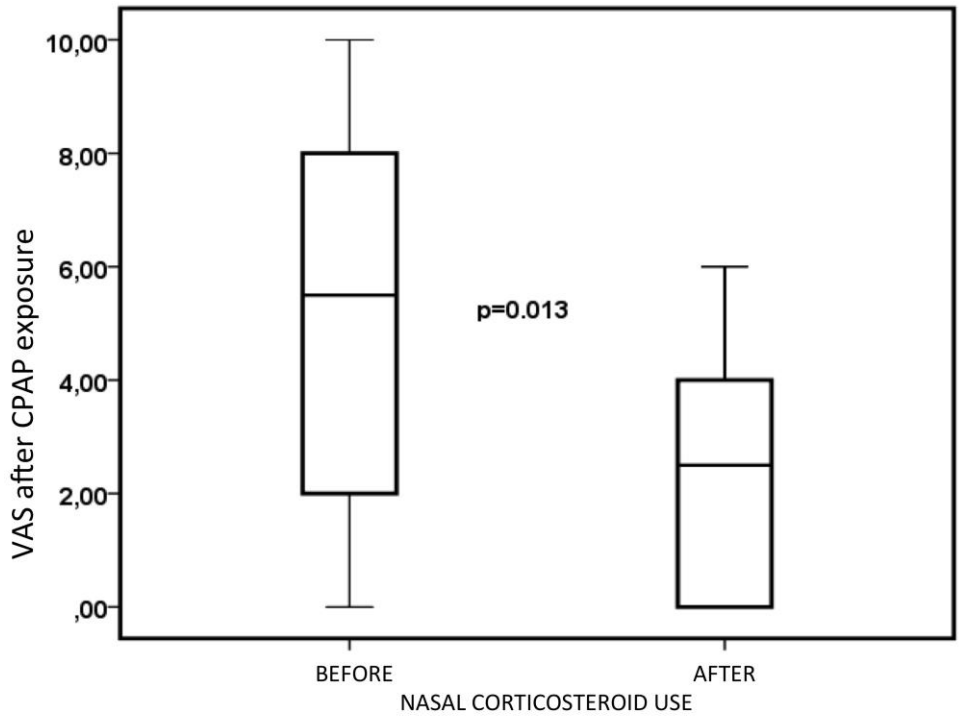

Figure 3: Comparison between visual analogue scale (VAS) scores before and after nasal corticosteroid use, after positive pressure exposure.

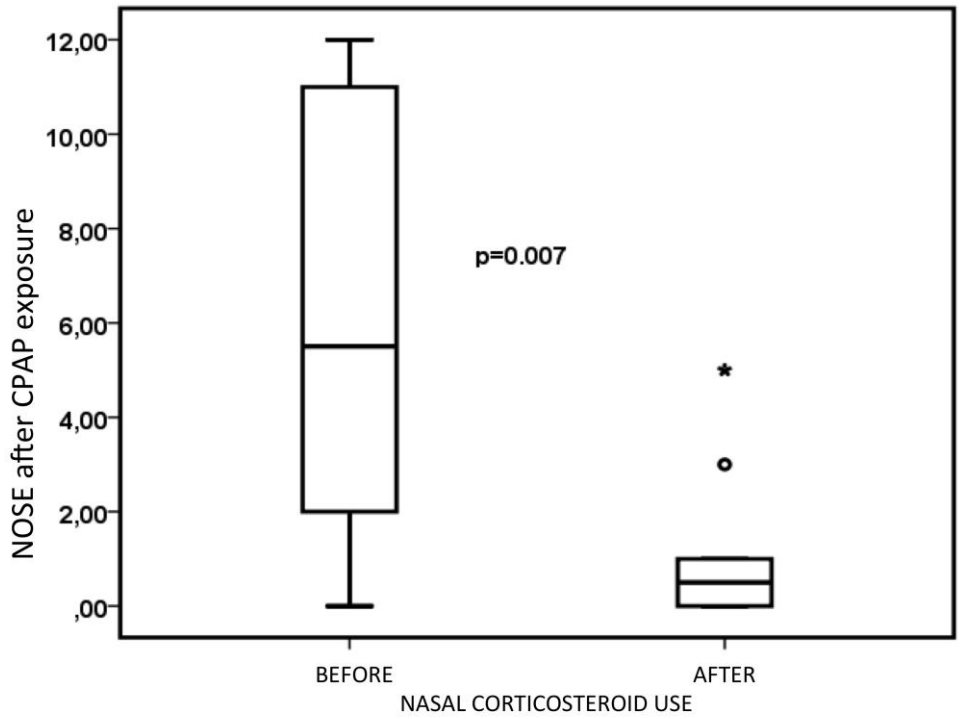

Figure 4: Comparison between NOSE scores before and after nasal corticosteroid use, after positive pressure exposure.

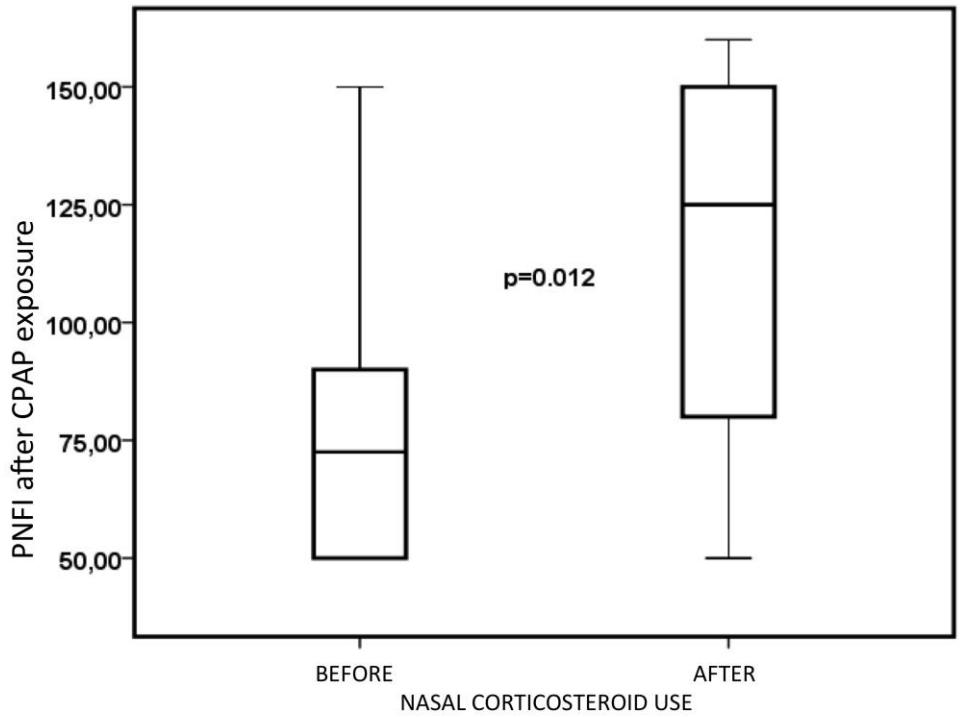

Figure 5: Comparison between PNIF findings before and after nasal corticosteroid use, after positive pressure exposure.

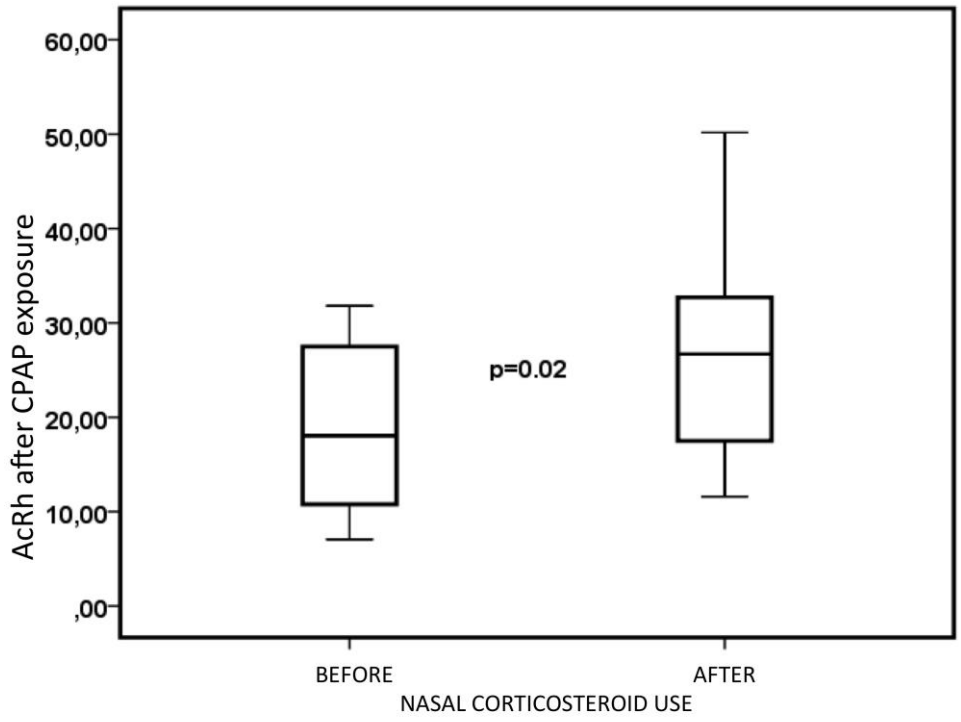

Figure 6: Comparison between AcRh values before and after nasal corticosteroid use, after positive pressure exposure.

DISCUSSION

The present study demonstrated that the use of topical corticosteroids by individuals with AR led to an improvement in nasal patency (both objectively and subjectively measured) after acute exposure to positive pressure in the nasal cavity.

AR is a chronic inflammatory condition of the nasal mucosa. Studies have shown that exposure of the nasal mucosa of allergic and non-allergic patients to CPAP leads to an increase in nasal neutrophil levels[8,11]. A recent study by our group showed that exposure of the nasal cavity to CPAP led to deterioration of nasal parameters, especially nasal patency. This deterioration was even worse in individuals with nasal allergic symptoms[9]. This leads us to believe that CPAP may exacerbate a baseline inflammatory state of the nasal mucosa in patients with AR, which in turn may potentiate the usual side effects of CPAP

therapy. Some studies, however, maintain that CPAP itself produces a subclinical nasal inflammation because, despite a detected increase in neutrophils in the nasal cytology of CPAP users, there was no worsening of nasal symptoms in patients with AR[8]. It is worth noting that these contradictory results may be attributable to differences in methodology. Both the present study and the previous study by our group[9] assessed nasal parameters immediately before and after CPAP exposure, while the aforementioned cytology study[8] evaluated specific physiological and biological changes in the nasal mucosa of patients with OSA after chronic CPAP use rather than immediately after CPAP exposure. It can be hypothesized that the potential irritative effect of continuous pressure on the nasal mucosa, especially in individuals with AR, is more intense during CPAP therapy and, consequently, immediately after its use, and may become less symptomatic a few hours after exposure.

Topical corticosteroids are the first-line therapy of choice for AR. These drugs act locally on the nasal mucosa, primarily by regulating protein synthesis, leading to inhibition of various pro-inflammatory cytokine productions[12] and, consequently, reduced nasal congestion. A recent randomized placebo-controlled study showed a significant improvement in nasal obstruction and AHI in patients with OSA following a 1-month course of intranasal fluticasone[13]. Although our study did not include patients diagnosed with OSA, only subjects with AR, our initial evaluation of the effect of a 28-day course of intranasal budesonide showed a significant improvement in subjective nasal obstruction (VAS and NOSE), corroborating these findings. It is worth noting that there was no statistically significant improvement on post-treatment and pre-treatment comparison of these individuals through objective parameters (AcRh and PNIF).

However, when comparing nasal obstruction scores – both subjective (VAS and NOSE) and objective (AcRh and PNIF) – before and after the use of topical corticosteroids, but after exposure to acute positive pressure via CPAP, statistically significant improvement was observed in all these parameters. This leads us to believe that acute positive pressure exposure actually potentiates

chronic irritation of the nasal mucosa, which in turn has been mitigated by topical corticosteroid therapy; this may even account for the improvement in objective measures of nasal patency, which was not observed in the previous comparison without exposure to CPAP.

Two randomized, placebo-controlled clinical trials[14,15] assessed the effects of topical nasal corticosteroid therapy (fluticasone) on CPAP compliance. Fluticasone was associated with some benefit on average duration of CPAP use per night, but statistical significance was not reached. Both studies recruited unselected groups of patients with OSA, with no specific focus on preexisting rhinitis or nasal symptoms. It is well known that the clinical response to nasal steroids is better in patients with AR than in those without AR[16]. Accordingly, a systematic review and meta-analysis of this subject suggested that nasal steroids may improve adherence to CPAP use to a greater extent in patients with AR than in those with non-allergic rhinitis[17]. The present study showed that topical nasal corticosteroids were effective in mitigating the acute effects of positive pressure on the nasal cavity of individuals with AR, especially nasal obstruction. It is important to note that the two studies cited above[14,15] evaluated the effect of topical nasal steroids on adherence to CPAP, while the present study consisted of objective and subjective evaluations of the effects of acute positive pressure exposure on the nasal cavity before and after use of topical budesonide.

One of the limitations of this study was the small number of patients. Nevertheless, it should be considered that allergic rhinitis affects 10–25% of the general population; therefore, we had to recruit volunteers who were willing to undergo an exhaustive battery of questionnaires and tests, had a positive skin prick test result, and were then subjected to two trials of CPAP. This constitutes another limitation: participants did not have sleep apnea, and their exposure to CPAP (for 1 hour only, while awake, in the upright position) differed substantially from the typical exposure of an OSA patient (positive pressure for up to 8 hours while sleeping and supine). Finally, the duration of intranasal steroid therapy (4

weeks) could be considered another potential weakness of this study. Nevertheless, we obtained significant results.

CONCLUSION

In patients with allergic rhinitis, intranasal corticosteroid therapy improved objective and subjective parameters of nasal patency after acute exposure of the nasal cavity to positive pressure.

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3.3 Manuscrito Original 3

Estudos recentes têm mostrado que, além da inflamação crônica da mucosa nasal, um desequilíbrio entre as pressões oncóticas e hidrostáticas parece fazer também parte da fisiopatologia da formação do pólipo nasal.

No intuito de confirmar esta teoria, foi feita a hipótese de que o aumento da pressão hidrostática intersticial no pólipo nasal pudesse diminuir o volume do pólipo nasal.

O método escolhido para aumentar a pressão hidrostática intersticial foi o fornecimento de pressão positiva na cavidade nasal de pacientes portadores de RSCcPN, através do uso de CPAP por um período de 2 horas. A pressão se transmitiria para o pólipo, aumentando assim a pressão hidrostática intersticial.

A possível diminuição do tamanho pólipo nasal poderia resultar num aumento da patência nasal, e por essa razão, foram também utilizados testes que avaliassem a patência nasal, tanto subjetivos – EVA e NOSE, quanto objetivos – PFNI e RA, além da endoscopia nasal para avaliação direta do grau dos pólipos nasais.

Vale a pena ressaltar que o presente estudo não teve como objetivo sugerir ou indicar o uso clinico do CPAP como tratamento da RSCcPN, tendo o mesmo sido utilizado apenas como um meio de confirmar uma nova teoria que vem surgindo sobre a fisiopatologia desta doença.

Os resultados mostraram uma diminuição do tamanho dos pólipos, porém não houve uma melhora dos parâmetros da patência nasal. Isso pode ser explicado pela deterioração dos mesmos parâmetros ocorrida também nos indivíduos normais do grupo controle, consequente a exposição à pressão positiva aguda

Título: What is the impact of positive airway pressure in nasal polyposis? An experimental study.

Revista: International Archives of Otorhinolaryngology (aceito para publicação)

Autores: Leonardo Balsalobre, Rogério Pezato, João Mangussi-Gomes, Luciano Lobato Gregório, Fernanda Haddad, Luis Carlos Gregório, Reginaldo R. Fujita

ABSTRACT

Introduction: It has been hypothesized that increasing the interstitial hydrostatic pressure within the sinonasal mucosa of patients with nasal polyposis (NP) might decrease the size of nasal polyps. **Objectives**: To evaluate the effects of positive airway pressure, delivered by a continuous positive airway pressure (CPAP) device, in patients with NP and in control subjects. **Methods**: Twelve patients with NP and 27 healthy subjects were exposed to CPAP (20 cm/H_2O) for 2 hours. Visual analog scale (VAS), Nasal Obstruction Symptom Evaluation (NOSE) scale, acoustic rhinometry (AR), peak nasal inspiratory flow (PNIF) and nasal endoscopy (NE – Meltzer's polyp grading system) were performed before and after the intervention, for all patients. **Results:** The control group showed a significant worsening in nasal obstruction symptoms, as measured by VAS and NOSE ($p < 0.01$), and a significant decrease in nasal patency, as measured by the PNIF and AR ($p < 0.01$). For the NP group, VAS, NOSE, and AR did not differ significantly ($p = 0.72$, $p = 0.73$, and $p=0.17$, respectively), but PNIF values worsened ($p = 0.04$) after exposure to CPAP. There was a statistically significant reduction in the nasal polyps' size ($p = 0.04$). **Conclusions**: Positive pressure worsened the nasal obstruction symptoms and decreased objective parameters of nasal patency in control subjects. In patients with NP, exposure to CPAP reduced the nasal polyps' size, and the nasal patency, as measured by PNIF. However, it had no significant effects in AR and in nasal obstruction symptoms.

Key words: Chronic Rhinosinusitis, Endoscopy, Extracellular Matrix, Nasal Airflow Dynamics, Rhinosinusitis.

1. INTRODUCTION

Recent studies have shown that nasal polyposis (NP) is characterized not only by chronic inflammation of the sinonasal mucosa, but also by a biomechanical disequilibrium between oncotic and hydrostatic pressures within the vessels and interstitial space. In normal subjects, and in the context of an inflammatory process, the equilibrium between these factors is responsible for limiting to a certain extent the extravasation of fluid to the interstitial space. In NP, however, there is a partial dysfunction of these equilibrium mechanisms, which facilitates the development of edema and alters the tissue remodeling process (**Figure 1**)[1–3].

In this sense, we have hypothesized that increasing the interstitial hydrostatic pressure might counteract the increased oncotic pressure and further mitigate the development NP. Besides decreasing the size of nasal polyps, the increased interstitial hydrostatic pressure could also improve the nasal patency and reduce symptoms of nasal obstruction in patients with NP [4]. A rational way to test this theory is to deliver continuous positive airway pressure (CPAP) to the nasal cavities of NP patients.

The objective of this study was to evaluate the effects of positive pressure, delivered by a continuous positive airway pressure (CPAP) device, on patients with NP and in control subjects, with special interest in nasal obstruction symptoms, objective nasal patency parameters, and nasal polyps' size.

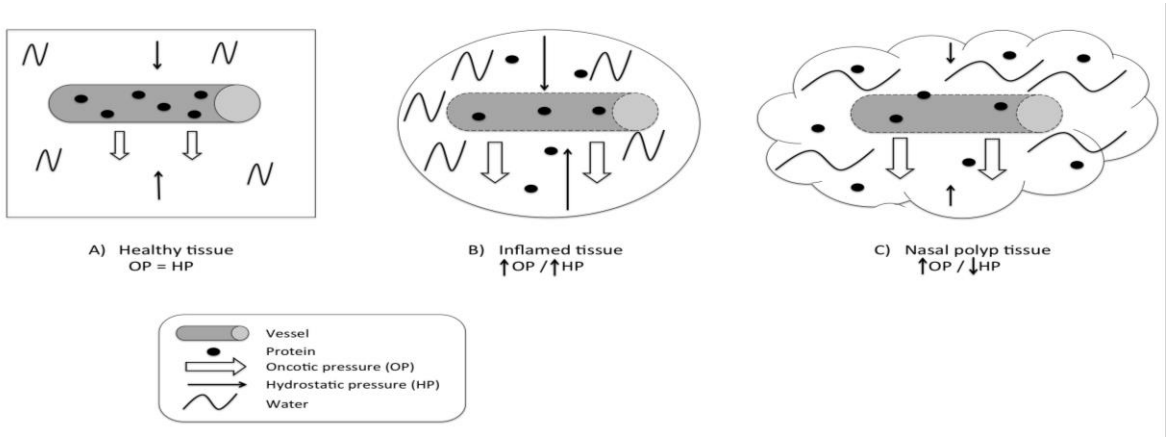

Figure 1. Illustration showing an increase in capillary permeability due to inflammation, with protein loss and increasing tissue oncotic pressure (B and C), and, consequently, extravasation of water to the interstitial space and edema. B) Compensatory increase in interstitial hydrostatic pressure in response to increasing oncotic pressure, thus limiting edema. C) Less marked increase in interstitial hydrostatic pressure in response to increasing oncotic pressure, facilitating the greater loss of water from the capillary lumen into the tissues and, consequently, increased edema.

2. METHODS

2.1. Design, Setting, and Study Population

An analytic, observational, and cross-sectional study was conducted at a tertiary otorhinolaryngology referral center, from January 2016 to August 2016. Participants were divided in two groups. The NP group included only those individuals with a recent diagnosis of NP, according to the EPOS 2012 Guidelines[5], and with polyps graded ≥ 1 according to Meltzer's polyp grading system[6]. The control group included only healthy individuals. For both groups, participants should be older than 18 years-old and younger than 65 years-old, and the following were excluded:

- Those using or who had recently used (< 4 weeks) antihistaminic or antihypertensive drugs, topical vasoconstrictors, systemic vasodilators, or systemic/topic corticosteroids;

- Those with severe septal deviation precluding nasal endoscopy or the use of nasal cannulas for acoustic rhinometry;
- Those with a present or past history of tumors, prior sinonasal surgery, known diagnosis of obstructive sleep apnea, and/or use of CPAP;
- Those with a present or past history of smoking or illicit drug use.

For the control group, those who had a present or recent past (< 4 weeks) history of sinonasal infections and/or inflammation were also excluded.

After application of inclusion and exclusion criteria, 13 and 27 subjects were included in the NP and control groups, respectively. Of these, 12 and 27 subjects were considered for the final analysis, respectively, because one patient from the NP group did not tolerate the intervention (CPAP). In the NP group, 5 (41.6%) participants were women and 7 (58.4%) were men, with age ranging from 34 to 65 years. Of the 27 individuals in the control group, 10 (37.0%) were women and 17 (63.0%) were men, with age ranging from 18 to 43 years.

This study conforms to recognized ethical standards and the Declaration of Helsinki and was approved by the local institutional review board (n. 897.279, 12/2015). Written informed consent was obtained from every participant included in the study.

2.2. Exposure to positive pressure – continuous positive airway pressure (CPAP)

All subjects were exposed to CPAP, delivered by a mechanical device (F&P Icon, Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) attached to a nasal mask (Meridian Nasal Mask, ResMed Ltd., Bella Vista, Australia) for 2 hours, at a pressure of 20 cm/H_2O. All patients were in a comfortable sitting

position during the whole procedure, and air leak through the mask was ruled out for all cases. No topical medications were used before or after the intervention.

2.3. Analyzed Variables

The following parameters were measured for all participants, immediately before and after exposure to the CPAP:

- Visual analog scale (VAS) for nasal obstruction symptoms;
- Nasal Obstruction Symptom Evaluation (NOSE) scale;
- Nasal endoscopy (NE);
- Acoustic rhinometry (AR);
- Peak nasal inspiratory flow (PNIF).

2.3.1. Visual analog scale (VAS) and Nasal Obstruction Symptom Evaluation (NOSE) scale

For the evaluation of nasal obstruction symptoms, all participants were asked to score their nasal obstruction severity in a 10-cm VAS, ranging from “zero” to “10”, with “zero” meaning “complete absence of nasal obstruction”, and “10” meaning “complete nasal obstruction”.

The NOSE scale, previously adapted to Brazilian Portuguese[7], was also administered and calculated for all participants, with scores ranging from 0 to 12. Because of the characteristics of this study, the assessment of nasal obstruction during sleep and exercise was not considered.

2.3.2. Nasal Endoscopy (NE)

NE was performed in all patients. An 18-cm, 4-mm, zero-degree rigid endoscope (Hopkins II, Karl Storz Ltd., Tuttlingen, Germany) attached to a video camera system (IK-M51H / IK-CU51 Imaging System, Toshiba America Inc., Irvine-CA, USA), monitor (OEV 141, Olympus Optical Ltd., Barlett-TN, USA), and a light source (Innova Light & Image FX 300R, Innova Technik, Cajamar-SP, Brazil) were used. Images were digitally recorded with a video capture device (HD PVR Rocket, Hauppauge Inc., Hauppauge-NY, USA).

Two blinded evaluators, both of whom were experienced rhinologists, watched every NE recorded, and together classified the severity of NP for every nasal cavity, according to Meltzer's polyp grading system[6] (**Table 1**).

Table 1: Meltzer's polyp grading system

Endoscopic appearance	Score
No visible nasal polyps	0
Small amount of polypoid disease confined within the middle meatus	1
Multiple polyps occupying the middle meatus	2
Polyps extending beyond the middle meatus	3
Polyps completely obstructing the nasal cavity	4

2.3.3. Acoustic rhinometry (AR) and peak nasal inspiratory flow (PNIF)

For the objective evaluation of nasal patency, all patients underwent acoustic rhinometry (AR) and peak nasal inspiratory flow (PNIF), before and after exposition to CPAP.

AR was performed without administration of vasoconstrictors, with a calibrated acoustic rhinometer and a specific software (A1 Acoustic Rhinometer, GM Instruments Ltd., Kilwinning, UK). The test was conducted as standardized by

the International Standardization Committee on Objective Assessment of the Nasal Airway[8]. Each participant remained for 30 minutes in an air-conditioned room (temperature set to 21°C before measurement, and ambient humidity kept in the 50–60% range); the head of each participant was stabilized to ensure proper positioning of the pulse tube; petroleum jelly was used to prevent air leak; all participants were instructed to control their breathing.

At least three curves were obtained for each nostril – after each measurement, the nosepiece was removed, reconnected, and a new measurement was then obtained; the results were considered adequate if the coefficient of variability was lower than 10%; the recorded curves were used to obtain a mean curve for each nostril; the values of these mean curves were then analyzed. All examinations were performed by the same investigator, experienced in AR. The cross-sectional area between the distances of 0 and 5 cm, expressed in cm^2, was used for objective comparison of findings.

The measurement of PNIF was performed with a portable device (In-Check Nasal Inspiratory Flow Meter, Clement Clarke International Ltd., Essex, UK), equipped with an air-cushioned facemask. PNIF was measured with the participant in the standing position, in three consecutive times with a 1-minute interval between measurements. Results were obtained immediately, and the average of the measures was considered for the final analysis.

2.4. Statistical analysis

Data was plotted and analyzed in the SPSS *v.* 22 (IBM Corp., New York-NY, USA) and Prism *v.*7 (GraphPad Software Inc., La Jolla-CA, USA) software environments. The Wilcoxon, Mann-Whitney U, and Fisher's exact tests were used to assess differences within and between groups. The binomial sign test was used for estimation of statistical significance for the Meltzer score before and after exposure to CPAP for the NP group. In all cases, p values < 0.05 were considered statistically significant.

3. RESULTS

There was no statistically significant difference in gender distribution between groups (p = 1.00). Participants in the control group were significantly younger than patients in NP group (p < 0.01) (**Table 2**).

Table 2: Demographic characteristics for the Control Group and the NP Group.

		Control Group	NP Group	p
Gender	Female (%)	10 (37.0%)	5 (41.6%)	1.00
	Male (%)	17 (63.0%)	7 (58.4%)	
Age	Age average (±SD)	24.03 ± 4.17	48.17 ± 10.94	< 0.01

NP: nasal polyposis; SD: standard deviation.

3.1. Effects of positive pressure on symptoms of nasal obstruction (VAS and NOSE)

For the control group, there was a significant deterioration in nasal obstructive symptoms, as measured by the VAS and NOSE, after exposure to CPAP (p < 0.01). In the NP group, VAS and NOSE did not differ significantly after exposure to CPAP (p = 0.72 and p = 0.73, respectively).

3.2. Effects of positive pressure on nasal patency (AR and PNIF)

Anterior nasal cavity volume and PNIF decreased significantly in the control group after CPAP use (p < 0.01). For the NP group, the values of PNIF worsened (p = 0.04), but there was no significant alteration in AR after the intervention (p=0.17).

3.3. Effects of positive pressure on nasal endoscopy (NE)

There was a statistically significant reduction in nasal polyps' size for the NP group, as measured by NE the Meltzer score (p = 0.04) (**Video 1** – supplementary material). Results for both groups are summarized in **Table 3**.

Table 3: Effects of CPAP in patients with nasal polyposis and in control subjects.

Variables (average ± SD)		Control Group			NP Group		
		Pre-CPAP	Post-CPAP	p*	Pre-CPAP	Post-CPAP	p*
Symptoms of nasal obstruction	VAS	2.66 ± 1.8	4.55 ± 2.6	< 0.01	4.75 ± 2.43	5.25 ± 3.06	0.72
	NOSE	2.74 ± 1.85	5.00 ± 3.00	< 0.01	6.62 ± 2.97	6.13 ± 2.59	0.73
Nasal patency	AR	11.98 ± 3.6	10.08 ± 2.4	< 0.01	5.06 ± 2.83	4.36 ± 1.78	0.17
	PNIF	127.15 ± 50.2	112.37 ± 54.8	< 0.01	117.5 ± 53.92	92.5 ± 43.99	0.04
Nasal endoscopic evaluation	Meltzer Score	---	---	---	6.08 ± 1.68 †	5.42 ± 1.88 †	0.04 ∫

SD: standard deviation; CPAP: continuous positive airway pressure; NP: nasal polyposis; VAS: visual analog scale; NOSE: nasal obstruction symptoms evaluation; PNIF: peak nasal inspiratory flow; * p-values for comparisons within-group; † Meltzer score for both nasal cavities. ∫ Binomial sign test.

4. DISCUSSION

4.1. Synopsis of Key Findings

Positive pressure significantly worsened the nasal obstruction symptoms and decreased the objective parameters of nasal patency in control subjects. In patients with NP, exposure to CPAP reduced the nasal polyps' size, and the nasal patency, as measured by PNIF. However, it had no significant effects on AR and on nasal obstruction symptoms.

4.2. Strengths and Limitations of this Study

This study presents some limitations, being arguably its small sample size the most important one. For instance, increasing the number of participants could yield statistically significant results for nasal patency parameters in the NP group, for example. It could be also questioned whether the exposure to CPAP for longer periods of time, set at different pressures, or with the patients in different positions, could yield different results. Indeed, patients with OSA use CPAP for 8 sleeping-hours and in the horizontal position. These factors affect the lymphatic and venous drainage of the nasal mucosa and could also have influenced the results of this study[9].

Moreover, the long-term effects of CPAP on NP were not evaluated. Considering that oncotic pressure does not change with time, but hydrostatic pressure decreases after CPAP exposure is ended, the polyps could have returned to their pre-exposure size after some hours/days. A secondary evaluation would be ideal to assess what are the real permanent effects of CPAP on the interstitial hydrostatic pressure and the polyps' volume.

Nonetheless, this study has the great advantage of experimentally determining the effects of positive pressure on NP, which, to the best of our knowledge, had never been done before. It was also possible to compare these effects in healthy individuals. The results presented are worthy to be taken into consideration in the understanding of the NP pathophysiology.

4.3. Interpretation of Findings and Comparison with other Studies

Previous studies have disclosed differences in the extracellular matrix composition and the remodeling process that takes place in the sinonasal mucosa of patients with NP, mainly due to differences in TGF-beta and metalloproteinases expression[10, 11]. This has raised the suspicion for a biomechanical disequilibrium in NP pathogenesis[11–14], which would facilitate

mucosal growth excess in the presence of chronic inflammation[3]. Subsequent studies showed that immune regulatory cells, such as dendritic cells and mesenchymal stem cells, could also be involved in the maintenance of chronic inflammation, abnormal remodeling, and biomechanical imbalance, typically found in patients with NP[15–18].

Recently, these biomechanical differences were experimentally demonstrated in the sinonasal mucosa of patients with NP[1–3]. The biomechanical dysfunction found in NP is characterized by a deficiency in the ability to properly raise interstitial hydrostatic pressure in response to fluid extravasation during the inflammatory process, a mechanism that is crucial to limit the development of edema, and is closely related to the extracellular matrix composition[1–3].

In this context, it has been shown that synechial tissues exhibit biomechanical properties similar to those of the healthy nasal mucosa. Thus, fibrosis could be a possible remodeling mechanism that would enhance the interstitial hydrostatic pressure in NP[4]. In the present study, the interstitial hydrostatic pressure in NP was indirectly increased through the acute and transient delivery of CPAP to the nasal cavity. It was observed a significant reduction in the nasal polyps' size in patients with NP after exposure to CPAP. This suggests that, in fact, increasing interstitial hydrostatic pressure in nasal polyps, even if indirectly, acutely and transiently, can possibly affect the pathophysiology of NP.

In patients with obstructive sleep apnea syndrome (OSA), the use of CPAP (especially at high titers, e.g., 20 cm/H_2O) causes nasal obstruction and local irritation symptoms, ultimately leading to treatment intolerance and nonadherence. In this study, the control group showed marked nasal obstruction worsening both in subjective (VAS, NOSE) and objective measurements (AR and PNIF), which is in line with previous studies[19].

In the NP group, although PNIF values worsened after exposure to CPAP, there was no significant worsening of nasal obstruction symptoms or in AR measurements. CPAP also determined a decrease in the nasal polyps' size in the NP group. The reason for these observations is still unclear and admits at least two interpretations:

1) The reduction in the nasal polyps' size prevented significant worsening of nasal patency parameters and nasal obstruction symptoms in patients with NP, in spite of the worsening PNIF;

2) Or, although CPAP determined a decrease in the nasal polyps' size, no improvement in nasal obstruction symptoms and nasal patency parameters were observed. This could be explained by the fact that patients with NP already have significantly decreased nasal patency and obstructive nasal symptoms at baseline and this would prevent further deterioration in obstructive parameters after exposure to CPAP.

4.4. Clinical Applicability

Although it was not the primary objective of this study, CPAP could be used as a therapeutic option, especially in patients with OSA and NP, prior or not to endoscopic endonasal surgery. Future studies could address such possibilities.

5. CONCLUSION

Positive pressure significantly worsened the nasal obstruction symptoms and decreased the objective parameters of nasal patency in control subjects. In patients with NP, exposure to CPAP reduced the nasal polyps' size, and the nasal patency, as measured by PNIF. However, it had no significant effects on AR and on nasal obstruction symptoms.

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4. CONCLUSÕES

A exposição aguda à pressão positiva via CPAP está associada a reduções subjetivas e objetivas da permeabilidade nasal. Em indivíduos com sintomas nasais alérgicos, a deterioração é ainda mais grave do que em pacientes sem esses sintomas.

O uso do corticosteroide intranasal levou a uma melhora dos parâmetros da patência nasal (tanto objetivos quanto subjetivos) após a exposição à pressão positiva aguda da cavidade nasal de pacientes com rinite alérgica.

A pressão positiva piorou significativamente os sintomas de obstrução nasal e diminuiu os parâmetros objetivos da permeabilidade nasal nos controles. Em pacientes com RSCcPN, a exposição ao CPAP reduziu o tamanho dos pólipos nasais e a patência nasal, medida pelo pico de fluxo nasal inspiratório. No entanto, não teve efeitos significativos na rinometria acústica e nos sintomas de obstrução nasal.

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Anexo 1. Termo de Consentimento Livre e Esclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado a participar de um estudo intitulado: **"Avaliação dos efeitos da pressão positiva continua no pólipo nasal"**.

As informações abaixo estão sendo fornecidas para esclarecê-lo sobre sua possível participação voluntária neste estudo, que tem como objetivo "avaliar os efeitos do uso de uma pressão maior a do ar que respiramos no pólipo nasal, esta pressão positiva será aplicada através de uma máscara como a de inalação". Este estudo será feito da seguinte maneira:

"Os pacientes com polipose nasal respirarão através de uma máscara parecida de inalação que estará enviando o ar com uma pressão maior que a habitual através do aparelho CPAP que é utilizado para exame de polissonografia, após duas horas de uso da máscara o paciente terá seu pólipo avaliado através de exames não invasivos como rinometria acústica e nasofibroscopia" e a sua participação consiste em autorizar o uso do CPAP, não havendo nenhuma modificação do tratamento devido a participação no estudo. O uso do CPAP terá o benefício adicional de avaliar a aderência do paciente ao uso deste aparelho nos pacientes que por ventura tenham Apneia do Sono e necessitem terapia com CPAP.

O Sr. tem toda a liberdade de retirar o seu consentimento e deixar de participar do estudo a qualquer momento sem penalização alguma. Neste caso o Sr. poderá continuar seu tratamento na Instituição sem problemas.

Todas as informações obtidas a seu respeito neste estudo, serão analisadas em conjunto com as de outros voluntários, não sendo divulgado a sua identificação ou de outros pacientes em nenhum momento.

O Sr. tem a garantia de que todos os dados obtidos a seu respeito, assim como qualquer material coletado só serão utilizados neste estudo.

Caso seja necessário, o Sr. terá assistência permanente durante o estudo, ou mesmo após o término ou interrupção do estudo.

Se ocorrer qualquer problema ou dano pessoal comprovadamente decorrente dos procedimentos ou tratamentos aos quais o Sr. será submetido, lhe será garantido o direito a tratamento gratuito na Instituição e o Sr. terá direito a indenização determinada por lei. ”

O Sr. não receberá nenhuma compensação financeira relacionada à sua participação neste estudo. Da mesma forma, o Sr. não terá nenhuma despesa pessoal em qualquer fase do estudo, incluindo exames e consultas. Durante o período de sua participação, se houver qualquer despesa adicional de sua parte em relação à condução ou alimentação, Sr. será reembolsado. ”

A qualquer momento, se for de seu interesse, o Sr. poderá ter acesso a todas as informações obtidas a seu respeito neste estudo, ou a respeito dos resultados gerais do estudo. ”

Em qualquer etapa do estudo, o Sr. terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O principal investigador é o Dr. Leonardo Balsalobre que pode ser encontrado no endereço Pedro de Toledo 950 Telefone 98966.7132. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Botucatu, 572 – 1º andar – cj 14, 5571-1062, FAX: 5539-7162 – E-mail: cepunifesp@unifesp.br.

Quando o estudo for finalizado, o Sr. será informado sobre os principais resultados e conclusões obtidas no estudo.

Esse termo foi elaborado em duas vias devidamente assinadas, sendo que uma ficará com o Sr. e a outra conosco.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo **”Avaliação dos efeitos da pressão positiva continua no pólipo nasal”**. Eu discuti com o Dr. Leonardo Balsalobre sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e

riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Data: _____/_____/_____

_____

Nome do participante da pesquisa assinatura

Declaro que obtive de forma apropriada e voluntária, o Consentimentos Livre e Esclarecido deste paciente (ou representante legal) para a participação neste estudo. Declaro ainda que me comprometo a cumprir todos os termos aqui descritos. ”

Data: _____/_____/_____

_____

Leonardo Balsalobre

Anexo 2. Parecer do Comitê de Ética em Pesquisa

MINISTÉRIO DA SAÚDE - Conselho Nacional de Saúde - Comissão Nacional de Ética em Pesquisa – CONEP

PROJETO DE PESQUISA ENVOLVENDO SERES HUMANOS

Projeto de Pesquisa:	avaliação dos efeitos da pressao positiva continua no polipo nasal

Informações Preliminares

Responsável Principal

CPF: 18222065882	Nome: rogério pezato
Telefone: (11) 5343-6534	E-mail: pezatobau@ig.com.br

Instituição Proponente

CNPJ:	Nome da Instituição: Universidade Federal de São Paulo - UNIFESP/EPM

É um estudo internacional? Não

Equipe de Pesquisa

CPF	Nome
26010424860	FERNANDA LOUISE MARTINHO HADDAD
29407661857	Leonardo Lopes Balsolobre Filho
96025077800	Luiz Carlos Gregório
00383501814	Reginaldo Raimundo Fujita

Área de Estudo

Grandes Áreas do Conhecimento (CNPq)

- Grande Área 2. Ciências Biológicas

Título Público da Pesquisa: avaliação dos efeitos da pressao positiva continua no polipo nasal

Contato Público

CPF	Nome	Telefone	E-mail
18222065882	rogério pezato	(11) 5343-6534	pezatobau@ig.com.br

Contato Leonardo Lopes Balsolobre Filho

Desenho de Estudo / Apoio Financeiro

Desenho:

20 paciente com mais de 18 anos e menos que 65 anos sem doença sistemica com diagnostico de polipose nasal segundo a EPOS 2012 estagio 3 a 4 de Hadley, e um periodo de 1 mês de washout para uso de vasoconstritores nasais, serao submetidos a exposição de pressao continua (acima de 15 mmH20) atraves do CPAP por um período mínimo de 2h, onde sera avaliado os efeitos deste sobre o polipo atraves de nasofibroscopia com captura de imagem para avaliação da area do polipo atraves de programa de computação, rinometria, rinomanometria e peak flow tudo sendo realizado antes e imediatamente após a exposição do polipo nasal ao cpap.Os pacientes nao receberao nenhuma sedação previamente ao procedimento.Para analise estatistico sera utilizado o teste de wilcoxon

Apoio Financeiro

CNPJ	Nome	E-mail	Telefone	Tipo
	Universidade Federal de São Paulo - UNIFESP/EPM	cepunifesp@epm.br;arpmeleti@unifesp.br		Institucional Principal

Palavra Chave

Palavra-chave
polipose nasal

Detalhamento do Estudo

Resumo:

Atraves de estudos realizados por nosso grupo demonstramos que existem diferenças na composiçao da matrix extra-celular da mucosa nasal de pacientes sem sintomatologia da via aerea comparado com tecido polipoide nasal de pacientes com polipose nasal (Balsalobre L, Pezato R, Perez-Novo C, Alves MT, Santos RP, Bachert C, Weckx LL. Epithelium and stroma from nasal polyp mucosa exhibits inverse expression of TGF-1 as compared with healthy nasal mucosa. J Otolaryngol Head Neck Surg. 2013 Apr 15;42:29. Pezato R, Balsalobre L, Lima M, Bezerra TF, Voegels RL, Gregório LC, Stamm AC,van Zele T. Convergence of two major pathophysiologic mechanisms in nasal polyposis: immune response to Staphylococcus aureus and airway remodeling. J Otolaryngol Head Neck Surg. 2013 Mar 28;42:27.). Estas diferenças nos levaram a criação de um conceito que a mucosa polipoide seria mais sujeita a formação de edema devido as suas propriedades mecanicas, sendo um tecido frouxo com baixa matrix extra-celular (Pezato R, Voegels RL. Why do we not find polyps in the lungs? Bronchial mucosa as a model in the treatment of polyposis. Med Hypotheses. 2012 Apr;78(4):468-70.). Para comprovar a veracidade deste conceito demonstramos que a pressao hidrostatica instersticial no tecido polipoide apresenta um menor aumento apos infusao de soro fisiologica quando comparado com o tecido nasal normal, demonstrando assim uma maior complacencia deste tecido para formação de edema, devido a alteraçao de um dos principais mecanismos para o retorno do fluido extravasado do capilar durante o processo inflamatorio, a pressao intersticial hidrostatica (Pezato R, Voegels RL, Pinto Bezerra TF, Perez-Novo C, Stamm AC, Gregorio LC. Mechanical disfunction in the mucosal oedema formation of patients with nasal polyps. Rhinology. 2014 Jun;52(2):162-6.). Seguindo nossa linha de pesquisa gostariamos de avaliar se o aumento da pressao intersticial reduziria o edema e consequentemente o polipo e seus sintomas.Neste estudo propomos avaliar os efeitos da pressao positiva sobre o tecido nasal polipoide.Materail e método:20 paciente com mais de 18 anos e menos que 65 anos sem doença sistemica com diagnostico de polipose nasal segundo a EPOS 2012 grau 3 a 4 de Hadley, e um periodo de 1 mês de washout para uso de vasoconstritores nasais, serao submetidos a exposição de pressao continua (acima de 15 mmH20) atraves do CPAP por um período mínimo de 2h, onde sera avaliado os efeitos deste sobre o polipo atraves de nasofibroscopia com captura de imagem para avaliação da area do polipo atraves de programa de computação, rinometria, rinomanometria e peak flow tudo sendo realizado antes e imediatamente após a exposição do polipo nasal ao cpap.Os pacientes nao receberao nenhuma sedação previamente ao procedimento. Para analise estatistico sera utilizado o teste de wilcoxon

Introdução:

Atraves de estudos realizados por nosso grupo demonstramos que existem diferenças na composiçao da matrix extra-celular da mucosa nasal de pacientes sem sintomatologia da via aerea comparado com tecido polipoide nasal de pacientes com polipose nasal (Balsalobre L, Pezato R, Perez-Novo C, Alves MT, Santos RP, Bachert C, Weckx LL. Epithelium and stroma from nasal polyp mucosa exhibits inverse expression of TGF-1 as compared with healthy nasal mucosa. J Otolaryngol Head Neck Surg. 2013 Apr 15;42:29. Pezato R, Balsalobre L, Lima M, Bezerra TF, Voegels RL, Gregório LC, Stamm AC,van Zele T. Convergence of two major pathophysiologic mechanisms in nasal polyposis: immune response to Staphylococcus aureus and airway remodeling. J Otolaryngol Head Neck Surg. 2013 Mar 28;42:27.). Estas diferenças nos levaram a criação de um conceito que a mucosa polipoide seria mais sujeita a formação de edema devido as suas propriedades mecanicas, sendo um tecido frouxo com baixa matrix extra-celular (Pezato R, Voegels RL. Why do we not find polyps in the lungs? Bronchial mucosa as a model in the treatment of polyposis. Med Hypotheses. 2012 Apr;78(4):468-70.). Para comprovar a veracidade deste conceito demonstramos que a pressao hidrostatica instersticial no tecido polipoide apresenta um menor aumento apos infusao de soro fisiologica quando comparado com o tecido nasal normal, demonstrando assim uma maior complacencia deste tecido para formação de edema, devido a alteraçao de um dos principais mecanismos para o retorno do fluido extravasado do capilar durante o processo inflamatorio, a pressao intersticial hidrostatica (Pezato R, Voegels RL, Pinto Bezerra TF, Perez-Novo C, Stamm AC, Gregorio LC. Mechanical disfunction in the mucosal oedema formation of patients with nasal polyps. Rhinology. 2014 Jun;52(2):162-6.). Seguindo nossa linha de pesquisa gostariamos de avaliar se o aumento da pressao intersticial reduziria o edema e consequentemente o polipo e seus sintomas.Neste estudo propomos avaliar os efeitos da pressao positiva sobre o tecido nasal polipoide.

Hipótese:

Poderia o aumento da pressao intersticial hidrostatica diminuir o edema no tecido polipóide em pacientes com Sinusite Crônica com Polipose Nasal?

Objetivo Primário:

Avaliar o efeito da exposição do tecido polipoide nasal a pressao positiva

Objetivo Secundário:

Avaliar se a pressao positiva aplicada ao tecido polipoide altera a pressao intersticial

Metodologia Proposta:

Materail e método:20 paciente com mais de 18 anos e menos que 65 anos sem doença sistemica com diagnostico de polipose nasal segundo a EPOS 2012 grau 3 a 4, e um periodo de 1 mês de washout para uso de vasoconstritores nasais, serao submetidos a exposição de pressao continua (acima de 15 mmH20) atraves do CPAP por um período mínimo de 2h, onde sera avaliado os efeitos deste sobre o polipo atraves de nasofibroscopia com captura de imagem para avaliação da area do polipo atraves de programa de computação, rinometria, rinomanometria e peak flow tudo sendo realizado antes e imediatamente após a exposição do polipo nasal ao cpap.Os pacientes nao receberao nenhuma sedação previamente ao procedimento. Para analise estatistico sera utilizado o teste de

wilcoxon.Para avaliar a transmissao da pressao positiva aplicada por CPAP, 10 pacientes com indicação de polipectomia, terao a pressao intersticial aferida pelo CDS, tecnica descrita em Pezato R, Voegels RL, Pinto Bezerra TF, Perez-Novo C, Stamm AC, Gregorio LC. Mechanical disfunction in the mucosal oedema formation of patients with nasal polyps. Rhinology. 2014 Jun;52(2):162-6., onde uma agulha com sensor para variaçao de pressao sera colocada no polipo após a anestesia geral e previamente a sua exerese cirurgica.

Critério de Inclusão:

Maiores de 18 anos e menores de 65 anos, ausência de doença sistemica, não uso de vasoconstritor nasal nos últimos 30 dias ao recrutamento.Apresentar diagnóstico de Polipose Nasal de acordo com o EPOS 2012, e estar classificado como Polipose Nasal grau 3-4 de Hadley.

Riscos:

O procdimento nao aumentara risco ao paciente, sendo que o uso da pressao positiva com o CPAP tera o beneficio adicional de avaliar a complacencia do paciente ao uso deste aparelho nos pacientes que por ventura tenham Apneia do sono e necessitem terapia com CPAP. Os pacientes que tiverem a pressao intersticial monitorizada durante o uso do CPAP, nao terao prejuizo, pois estarao sob anestesia geral devido ao procedimento cirurgico que serao submetidos por indicação prévia de polipectomia, sera acrescentado apenas dois minutos de monitorização do polipo no ato cirurgico, e o polipo nao sofrera maiores danos pois este sera removido durante a cirurgia. Os pacientes contaram com o beneficio de possuírem um CPAP na sala cirurgica sendo util na recuperação pós anestesica em caso de hipoventilação.

Benefícios:

O uso do CPAP tera o beneficio adicional de avaliar a complacencia do paciente ao uso deste aparelho nos pacientes que por ventura tenham Apneia do sono e necessitem terapia com CPAP.Os pacientes que tiverem a pressao intersticial monitorizadas com o CPAP imediatemente previo a polipectomia contaram com o beneficio de possuírem um CPAP na sala cirurgica sendo util na recuperação pós anestesica em caso de hipoventilação.

Metodologia de Análise de Dados:

Utilizara o programa SPSS aplicando o teste nao paramétrico de Wilcoxon

Desfecho Primário:

Demonstrar o efeito da pressao positiva em diminuir o edema no pólipo nasal e consequentemente a diminuição volumetrica do pólipo nasal

Desfecho Secundário:

Demonstrar que a pressao positiva aplicada no pólipoé refletida para a regiao intersticial do tecido polipoide

Tamanho da Amostra no Brasil: 30

Data do Primeiro 15/10/14 00:00

Países de Recrutamento

País de Origem do Estudo	País	Nº de participantes da pesquisa
Sim	BRASIL	30

Outras Informações

Haverá uso de fontes secundárias de dados (prontuários, dados demográficos, etc)?

Não

Informe o número de indivíduos abordados pessoalmente, recrutados, ou que sofrerão algum tipo de intervenção neste centro de pesquisa:

30

Grupos em que serão divididos os participantes da pesquisa neste centro

ID Grupo	Nº de Indivíduos	Intervenções a serem relizadas
polipo nasal e pressao intersticial	10	avaliação simultanea da pressao intersticial do polipo em uso de cpap
polipose nasal e cpap	20	apos cpap sera avaliado rinometria, rinomanometria, peak flow nasal e nasofibroscopia

O Estudo é Multicêntrico no Brasil?

Não

Propõe dispensa do TCLE?

Não

Haverá retenção de amostras para armazenamento em banco?

Não

Cronograma de Execução

Identificação da Etapa	Início (DD/MM/AAAA)	Término (DD/MM/AAAA)
recrutamento	15/10/2014	14/11/2014
efeitos do cpap no polipo nasal	17/11/2014	18/03/2015
avaliação dos dados coletados	19/03/2015	13/05/2015
escrito e divulgação do estudo	28/07/2015	29/10/2015

Orçamento Financeiro

Identificação de Orçamento	Tipo	Valor em Reais (R$)
doutorado	Bolsas	R$ 24.000,00
uso e materiais descartaveis do CDS	Custeio	R$ 5.000,00
Total em R$		R$ 29.000,00

Bibliografia:

Balsalobre L, Pezato R, Perez-Novo C, Alves MT, Santos RP, Bachert C, Weckx LL. Epithelium and stroma from nasal polyp mucosa exhibits inverse expression of TGF-1 as compared with healthy nasal mucosa. J Otolaryngol Head Neck Surg. 2013 Apr 15;42:29. Pezato R, Balsalobre L, Lima M, Bezerra TF, Voegels RL, Gregório LC, Stamm AC,van Zele T. Convergence of two major pathophysiologic mechanisms in nasal polyposis: immune response to Staphylococcus aureus and airway remodeling. J Otolaryngol Head Neck Surg. 2013 Mar 28;42:27. Pezato R, Voegels RL. Why do we not find polyps in the lungs? Bronchial mucosa as a model in the treatment of polyposis. Med Hypotheses. 2012 Apr;78(4):468-70. Pezato R, Voegels RL, Pinto Bezerra TF, Perez-Novo C, Stamm AC, Gregorio LC. Mechanical disfunction in the mucosal oedema formation of patients with nasal polyps. Rhinology. 2014 Jun;52(2):162-6.

Upload de Documentos

Arquivo Anexos:

Tipo	Arquivo
Folha de Rosto	comite etica.pdf
TCLE - Modelo de Termo de Consentimento Livre e Esclarecido	TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO.doc
Projeto Detalhado	estudo detalhado.docx

Finalizar

Manter sigilo da integra do projeto de pesquisa: Sim

Prazo: Até a publicação dos resultados

UNIVERSIDADE FEDERAL DE SÃO PAULO - UNIFESP/ HOSPITAL SÃO PAULO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: avaliação dos efeitos da pressao positiva continua no polipo nasal
Pesquisador: rogério pezato
Área Temática:
Versão: 2
CAAE: 39340614.2.0000.5505
Instituição Proponente: Universidade Federal de São Paulo - UNIFESP/EPM
Patrocinador Principal: Universidade Federal de São Paulo - UNIFESP/EPM

DADOS DO PARECER

Número do Parecer: 945.319
Data da Relatoria: 03/02/2015

Apresentação do Projeto:
Conforme parecer CEP. 897.279 de 3/12/2015

Objetivo da Pesquisa:
Conforme parecer CEP. 897.279 de 3/12/2015

Avaliação dos Riscos e Benefícios:
Conforme parecer CEP. 897.279 de 3/12/2015

Comentários e Considerações sobre a Pesquisa:
Conforme parecer CEP. 897.279 de 3/12/2015

Considerações sobre os Termos de apresentação obrigatória:
Trata-se de resposta de pendencia apontada no parecer inicial.

Recomendações:
A pesquisa será realizada no Hospital Universitário/Hospital São Paulo (HU/HSP)ou em seus ambulatórios, será necessário enviar carta de autorização da Coordenadoria de Ensino e Pesquisa do HU/HSP (que pode ser conseguida na Diretoria Clínica do HSP, no 1° andar do Hospital São Paulo). Esta, é uma solicitação da Diretoria Clínica do HSP/HU. Apresentar essa carta como NOTIFICAÇÃO ao CEP_Unifesp

Endereço: Rua Botucatu, 572 1° Andar Conj. 14
Bairro: VILA CLEMENTINO **CEP:** 04.023-061
UF: SP **Município:** SAO PAULO
Telefone: (11)5539-7162 **Fax:** (11)5571-1062 **E-mail:** cepunifesp@unifesp.br

UNIVERSIDADE FEDERAL DE SÃO PAULO - UNIFESP/ HOSPITAL SÃO PAULO

Continuação do Parecer: 945.319

Conclusões ou Pendências e Lista de Inadequações:

Sem inadequações - aprovado com recomendação

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

O CEP informa que a partir desta data de aprovação, é necessário o envio de relatórios semestrais (no caso de estudos pertencentes à área temática especial) e anuais (em todas as outras situações). É também obrigatória, a apresentação do relatório final, quando do término do estudo.

SAO PAULO, 04 de Fevereiro de 2015

Assinado por:
Miguel Roberto Jorge
(Coordenador)

Endereço: Rua Botucatu, 572 1° Andar Conj. 14
Bairro: VILA CLEMENTINO **CEP:** 04.023-061
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Anexo 3. Termo de Consentimento Livre e Esclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado a participar de um estudo intitulado: **"Efeito do corticoide tópico na patencia nasal após exposição à pressão positiva continua"**

As informações abaixo estão sendo fornecidas para esclarecê-lo sobre sua possível participação voluntária neste estudo, que tem como objetivo "avaliar os efeitos do uso de uma pressão maior do que respiramos na patência nasal de pacientes com rinite alérgica e o efeito do uso do corticoide intranasal, esta pressão positiva será aplicada através de uma máscara como de inalação". Este estudo será feito da seguinte maneira "os pacientes diagnosticados com rinite alérgica serão submetidos ao *prick-test* e respirarão através de uma máscara parecida de inalação que estará enviando o ar com uma pressão maior que a habitual através do aparelho CPAP que é utilizado para exame de polissonografia, antes e após uma hora de uso da máscara o paciente será avaliado através de exames não invasivos como rinometria acústica, nasofibroscopia e questionários. Após 1 mês de uso de corticoide tópico nasal, a exposição ao CPAP e os testes antes e depois serão repetidos. A sua participação consiste em autorizar o uso do CPAP e a realização do *prick test* não havendo nenhuma modificação do tratamento devido a participação no estudo. O uso do CPAP terá o beneficio adicional de avaliar a complacência do paciente ao uso deste aparelho nos pacientes que por ventura tenham Apneia do Sono e necessitem terapia com CPAP.

O Sr. tem toda a liberdade de retirar o seu consentimento e deixar de participar do estudo a qualquer momento sem penalização alguma. Neste caso o Sr. poderá continuar seu tratamento na Instituição sem problemas.

Todas as informações obtidas a seu respeito neste estudo, serão analisadas em conjunto com as de outros voluntários, não sendo divulgado a sua identificação ou de outros pacientes em nenhum momento.

O Sr. tem a garantia de que todos os dados obtidos a seu respeito, assim como qualquer material coletado só serão utilizados neste estudo.

Caso seja necessário, o Sr. terá assistência permanente durante o estudo, ou mesmo após o término ou interrupção do estudo.

Se ocorrer qualquer problema ou dano pessoal comprovadamente decorrente dos procedimentos ou tratamentos aos quais o Sr. será submetido, lhe será garantido o direito a tratamento gratuito na Instituição e o Sr. terá direito a indenização determinada por lei."

O Sr. não receberá nenhuma compensação financeira relacionada à sua participação neste estudo. Da mesma forma, o Sr. não terá nenhuma despesa pessoal em qualquer fase do estudo, incluindo exames e consultas. Durante o período de sua participação, se houver qualquer despesa adicional de sua parte em relação a condução ou alimentação, Sr. Não será reembolsado"

A qualquer momento, se for de seu interesse, o Sr. poderá ter acesso a todas as informações obtidas a seu respeito neste estudo,ou a respeito dos resultados gerais do estudo."

Em qualquer etapa do estudo, o Sr. terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O principal investigador é o Dr. Leonardo Balsalobre que pode ser encontrado no endereço Pedro de Toledo 950 Telefone 98966 7132. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Botucatu, 572 – 1º andar – cj 14, 5571-1062, FAX: 5539-7162 – E-mail: cepunifesp@unifesp.br.

Quando o estudo for finalizado, o Sr. será informado sobre os principais resultados e conclusões obtidas no estudo.

Esse termo foi elaborado em duas vias devidamente assinadas, sendo que uma ficará com o Sr. e a outra conosco.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo "Diferenças entre células tronco mesenquimas de pólipos nasais com células tronco de tecido nasal saudável". Eu discuti com a pesquisadora Aline Bruno Figueiredo sobre a minha decisão em participar nesse estudo.

Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Data: _____/_____/_____

_____

Nome do participante da pesquisa assinatura

Declaro que obtive de forma apropriada e voluntária, o Consentimentos Livre e Esclarecido deste paciente (ou representante legal) para a participação neste estudo. Declaro ainda que me comprometo a cumprir todos os termos aqui descritos. ”

Data: _____/_____/_____

_____

Leonardo Balsalobre

Normas para teses e dissertações [Internet]. 2ª ed. rev. e corrigida. São Paulo: Universidade Federal de São Paulo, Biblioteca Antônio Rubino de Azevedo, Coordenação de Cursos; 2015 [2017 Dec 7]. Available from: http://www.bibliotecasp.unifesp.br/Documentos-Apostila/normas-para-teses-e-dissertacoes

Rother ET, Braga MER. Como elaborar sua tese: estrutura e referências. 2ª ed. São Paulo: BC Gráfica, 2005.