MELÂNIA **D**IRCE **O**LIVEIRA **M**ARQUES

Aspectos anatômicos da via aérea superior para a personalização da terapia da apneia obstrutiva do sono

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Pneumologia
Orientador: Dr. Pedro Rodrigues Genta

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SUMÁRIO

LISTA DE ABREVIATURAS E UNIDADES

AASM	*American Academy of Sleep Medicine*
AOS	Apneia obstrutiva do sono
AIO	Aparelho intra-oral
cm	centímetros
cmH_2O	centímetros de água
CPAP	*Continuous positive airway pressure*
CAPPesq	Comissão de análise de projetos de pesquisa
DEN	Dependência ao esforço negativo
IAH	Índice de apneia-hipopneia
IAH NREM	Índice de apneia-hipopneia durante o sono não-REM
IAH REM	Índice de apneia-hipopneia durante o sono REM
IMC	Índice de massa corpórea
InCor	Instituto do Coração
Kg/m^2	quilogramas por metro quadrado
L/min	litros por minuto
min	minutos
mm^2	milímetros quadrados
n	número

NREM	*Non-rapid eye moviment*
NREM 1	Estágio 1 do sono NREM
NREM 2	Estágio 2 do sono NREM
NREM 3	Estágio 3 do sono NREM
$PaCO_2$	Pressão parcial de dióxido de carbono
Pcrit	Pressão crítica de fechamento da faringe
Pef	Pressão efetiva
Pn	Pressão nasal
Pt	Pressão traqueal
R	Resistência
REM	*Rapid eye movement*
SpO_2	Saturação periférica de oxigênio
TCLE	Termo de consentimento livre e esclarecido
USP	Universidade de São Paulo
VAS	Via aérea superior
V_imax	Pico de fluxo inspiratório

LISTA DE FIGURAS

RESUMO

Marques MDO. *Aspectos anatômicos da via aérea superior para a personalização da terapia da apneia obstrutiva do sono* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2018.

Introdução: A apneia obstrutiva do sono (AOS) é uma doença altamente prevalente, caracterizada pela obstrução recorrente da faringe durante o sono. Apesar do quadro clínico ser marcado por ronco e sonolência diurna excessiva e do maior risco cardiometabólico associado à AOS, uma grande parcela dos pacientes diagnosticados permanece sem nenhum tratamento. Dessa forma, são necessárias estratégias com o objetivo de otimizar as opções de tratamento para os pacientes com AOS. **Objetivos**: Esta tese é composta pela compilação de três artigos com o objetivo geral de avaliar os fatores fisiopatológicos anatômicos da AOS que podem influenciar na variabilidade individual de resposta ao tratamento. Os objetivos específicos de cada artigo são: *Artigo 1*) Avaliar se o padrão de obstrução da faringe influencia no efeito da mudança de decúbito de supino para lateral na patência da via aérea superior; *Artigo 2*) Avaliar as diferenças na complacência das regiões da faringe e sua associação com padrões de curva inspiratória; *Artigo 3*) Avaliar a influência da estrutura faríngea envolvida na obstrução e a colapsabilidade da via aérea superior na eficácia do aparelho intra-oral (AIO) no tratamento da AOS. **Métodos:** Foram recrutados pacientes com diagnóstico prévio de AOS com idade entre 21 a 70 anos. *Artigo 1*: Os indivíduos foram avaliados com sonoendoscopia e registro simultâneo do fluxo aéreo durante o sono natural em decúbito supino e lateral. *Artigo 2*: os indivíduos foram avaliados com sonoendoscopia e registro simultâneo da pressão faríngea durante o sono natural. *Artigo 3*: Os indivíduos foram avaliados na primeira noite com sonoendoscopia e, em duas noites adicionais, foram submetidos à polissonografia com e sem AIO para determinação do índice de apneia-hipopneia (IAH) e para a medida da pressão crítica de fechamento da faringe (Pcrit). **Resultados**: *Artigo 1*: Foram avaliados 24 pacientes (17 homens, idade: 53±6 anos,

IAH:48±28 eventos/hora). Em pacientes com obstrução associada a língua (n=10), não houve aumento significativo do pico de fluxo inspiratório e da ventilação minuto com a mudança de decúbito de supino para lateral. A posição lateral resultou em diminuição da ocorrência do colapso de epiglote e aumento de 45% na ventilação minuto entre os pacientes com obstrução da epiglote (n=6). *Artigo 2*: Foram avaliados 14 pacientes (9 homens, idade: 51±5 anos, IAH: 56±32 eventos/hora). Comparada à região retroglossal, a região retropalatal foi mais estreita (19,2 [23,9] mm^2 versus 55,0 [30,7]mm^2; p<0,001) e apresentou maior complacência (3,2 ± 2,1 mm^2/cmH_2O versus 2,1 ± 1,8 mm^2/cmH_2O; p <0,001). A dependência ao esforço negativo foi positivamente associada ao estreitamento da área retropalatal (r=0,47; p=0,001). *Artigo 3*: Foram avaliados 25 pacientes (17 homens, idade: 49±11 anos, IAH: 51±24 eventos/hora). O AIO reduziu a Pcrit em 3,9±2,4 cmH_2O e o IAH em 69%. A redução da Pcrit foi maior nos pacientes com a língua posteriorizada. A ppresença da língua posteriorizada (p=0,03) e menor colapsabilidade da faringe (Pcrit <1 cmH_2O) no momento inicial (p=0,04) foram determinantes de melhor resposta terapêutica demonstrada pela maior redução do IAH com o AIO (83% versus 48%; p<0,001). **Conclusões**: O padrão de obstrução e a colapsabilidade da faringe são fatores determinantes na resposta individual às modalidades terapêuticas alternativas para tratamento da AOS como terapia posicional e AIO. Pacientes com colapso de epiglote apresentaram melhora da patência da faringe com o decúbito lateral e assim podem se beneficiar da terapia posicional para AOS. A região retropalatal apresentou menor área e maior complacência comparada à região retroglossal nos pacientes com AOS. Finalmente, pacientes com língua posteriorizada e menor colapsabilidade da faringe são bons candidatos ao uso do AIO para tratamento da AOS.

Descritores: apneia do sono tipo obstrutiva; faringe/fisiopatologia; faringe/anatomia & histologia; obstrução das vias respiratórias; endoscopia; medicina de precisão.

ABSTRACT

Marques MDO. *Upper airway anatomy characteristics for obstructive sleep apnea personalized treatment* [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2018.

Introduction: Obstructive sleep apnea (OSA) is a highly prevalent disease characterized by recurrent pharyngeal obstruction during sleep. Despite symptoms such as snore and excessive daytime sleepiness and, the higher cardiometabolic risk related to OSA, a large proportion of patients do not receive any treatment for the disease. Therefore, strategies to improve management approaches for OSA are necessary. **Objectives:** This thesis consists of the compilation of three articles with a general aim of investigating the anatomic factors involved in OSA pathogenesis that could affect the individual variability of treatment responses. The specific aims of each article are: *Article 1:* To evaluate if the pattern of pharyngeal obstruction influences the effect of changing from supine to lateral position on upper airway patency; 2) To compare the compliance of each pharyngeal level and its association with inspiratory flow patterns; 3) To evaluate the effect of pharyngeal collapsibility and the pharyngeal structure causing collapse on the efficacy of oral appliance therapy for OSA. **Methods:** Patients previously diagnosed with OSA ranging from 21 to 70 years old were recruited for the studies. *Article 1*: Patients underwent upper airway endoscopy with simultaneous recordings of respiratory airflow in both supine and lateral position during natural sleep. *Article 2:* Patients underwent upper airway endoscopy with simultaneous recordings of pharyngeal pressure during natural sleep. *Article 3:* Patients underwent upper airway endoscopy on the first night. On two additional overnight studies, polysomnography was performed with and without an oral appliance to determine apnea-hypopnea index (AHI), and to measure the critical closing pressure (Pcrit). **Results:** *Article 1:* Twenty-four patients (17 men, 53±6 years old, AHI:48±28 events/hour) were studied. Patients with tongue-related obstruction (n=10) showed no improvement in airflow, and the tongue remained posteriorly located. Epiglottic obstruction was virtually abolished with lateral positioning and ventilation

increased by 45% compared to supine position. *Article 2*: Fourteen patients (9 men, 51±5 years old, AHI: 56±32 events/hour) were studied. Compared to the retroglossal airway, the retropalatal airway was smaller at end-expiration ($p < 0.001$), and had greater absolute and relative compliances ($p < 0.001$). NED was positively associated with retropalatal relative area change ($r=0.47$; $p < 0.001$). *Article 3*: Twenty-five patients (17 men, 49±11 years old, IAH: 51±24 events/hour) were studied. Oral appliance therapy reduced Pcrit by 3.9±2.4 cmH_2O and AHI by 69%. Oral appliance lowered Pcrit by 2.7±0.9 cmH_2O more in those with posteriorly-located tongue compared to those without ($p<0.008$). Posteriorly-located tongue ($p=0.03$) and lower baseline collapsibility ($p=0.04$) were significant determinants of a greater-than-average AHI response to therapy (83% versus 48%, $p<0.001$). **Conclusions:** The pattern of obstruction and pharyngeal collapsibility are determinants of the individual response to alternative OSA treatment such as positional therapy and oral appliance. Patients with epiglottic obstruction showed significant improvement with lateral sleeping position and, therefore may benefit from positional therapy for OSA. The retropalatal airway had a smaller area and a greater compliance compared to the retroglossal airway in OSA patients. Finally, patients with posteriorly located tongue plus less-severe collapsibility are good candidates for oral appliance therapy.

Descriptors: sleep apnea, obstructive; pharynx/physiopathology; pharynx/anatomy and histology; airway obstruction; endoscopy; precision medicine.

APRESENTAÇÃO

Esta tese é composta pela compilação dos três artigos a seguir que serão descritos e analisados: 1. Effect of sleeping position on upper airway patency in obstructive sleep apnea is determined by the pharyngeal structure causing collapse; 2. Retropalatal and retroglossal airway compliance in patients with obstructive sleep apnea; 3. Structure and severity of pharyngeal obstruction determine sleep apnea response to oral appliances.

1 Introdução

A apneia obstrutiva do sono (AOS) é um distúrbio respiratório caracterizado por obstrução recorrente da faringe durante o sono, resultando em hipóxia intermitente e fragmentação do sono [1]. Além do quadro clínico clássico representado por roncos, sono não reparador e sonolência diurna excessiva, a AOS está associada a comorbidades cardiovasculares e metabólicas em decorrência dos seus efeitos deletérios de ativação simpática, inflamação sistêmica, estresse oxidativo, disfunção endotelial e desregulação metabólica [2,3,4].

A prevalência crescente da AOS observada nas duas últimas décadas reflete a pandemia moderna de obesidade bem como o envelhecimento da população, dois dos principais fatores de risco para a doença[5]. O estudo EPISONO, realizado na cidade de São Paulo em 2010, mostrou que 30,5% das mulheres e 46,5% dos homens na população adulta apresentavam índice de apneia-hipopneia (IAH) maior ou igual a 5 eventos/hora de sono[6]. Mais recentemente, foram apresentadas estimativas para a prevalência global da AOS em adultos[7]. Quando considerado um IAH maior ou igual a 5 eventos/hora de sono, a prevalência global da AOS foi estimada em 1 bilhão de pessoas[7]. Desta forma, a AOS é um importante problema de saúde pública com consequências diretas na qualidade de vida e produtividade dos indivíduos, bem como no aumento da mortalidade[8].

Entretanto, uma grande parcela dos pacientes diagnosticados com AOS permanece sem nenhum tratamento para a doença. Estudo recente que incluiu duas coortes prospectivas na China apontou que 67,8% dos indivíduos não havia recebido tratamento para a AOS após mais de 5 anos do diagnóstico realizado pela polissonografia [9]. Com relação ao tratamento

padrão-ouro com pressão positiva contínua em vias aéreas (continuous positive airway pressure [CPAP]), entre 20 a 30% dos pacientes diagnosticados recusa a terapia[10]. Além da manutenção dos sintomas diurnos e do maior risco cardiometabólico, estimativas indicam também o alto impacto econômico da AOS não tratada. A Academia Americana de Medicina do Sono (American Academy of Sleep Medicine [AASM]) reportou que os gastos anuais com diagnóstico e tratamento dos pacientes com AOS nos Estados Unidos em 2015 foram 67% menores do que aqueles com os pacientes não tratados[11]. Esses gastos adicionais decorrem de medicações e hospitalizações para comorbidades como hipertensão arterial e diabetes, acidentes automobilísticos e de trabalho, queda de produtividade e absenteísmo laboral relacionados à AOS. Desta forma, são necessárias estratégias com o objetivo de expandir e otimizar as opções de tratamento para os pacientes com AOS.

1.1 AOS e medicina personalizada

A medicina personalizada e de precisão considera a relevância da individualidade no contexto de saúde e doença. Esses conceitos se baseiam na estratégia de se aplicar uma medicina focada na prevenção e tratamento de doenças considerando a variabilidade da apresentação da doença e das respostas individuais ao tratamento[12]. Os conceitos de medicina personalizada têm se expandido para os distúrbios respiratórios do sono (Figura 1) englobando as quatro características da *P4 Medicine*: personalizada, preditiva, preventiva e participatória[13].

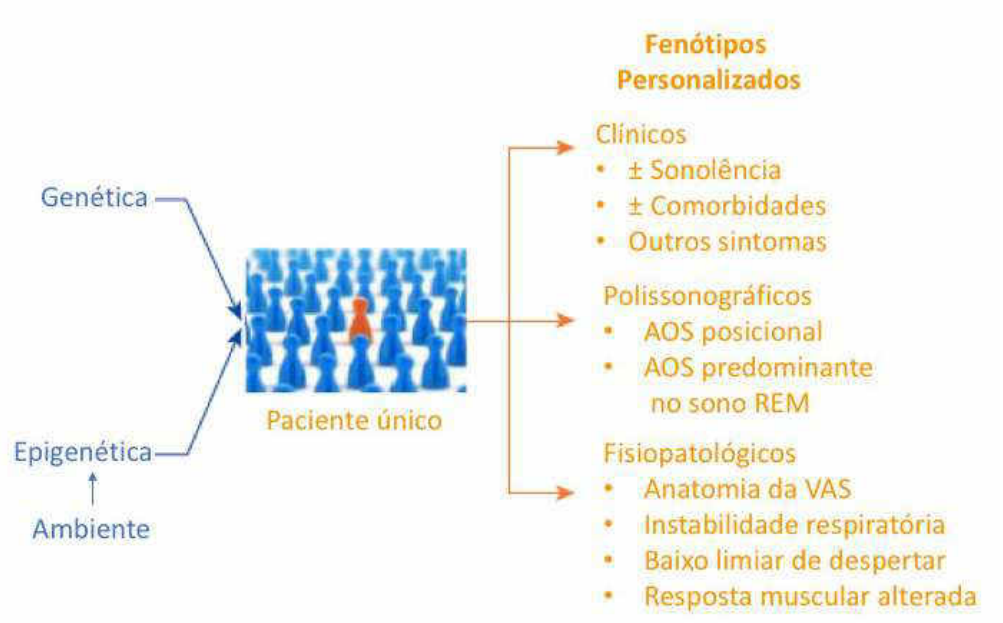

Figura 1 – Fenótipos personalizados da AOS
O conceito de medicina personalizada se fundamenta na noção que existem fatores individuais que determinam as características únicas de um paciente e que resultam em fenótipos personalizados que podem ser avaliados em domínios diferentes. AOS= apneia obstrutiva do sono; REM= *rapid eyes movement*; VAS=via aérea superior
FONTE: adaptado de Ann Am Thorac Soc 2016; 13: 1456-67.

O tratamento da AOS tem sido tradicionalmente baseado no IAH. Para pacientes com IAH <30 eventos por hora, são opções aceitáveis o aparelho intra-oral (AIO) e o CPAP. Para indivíduos com IAH>30 eventos por hora, o CPAP é geralmente a única opção recomendada. Dentro do conceito de personalização do tratamento, é fundamental explorar diferentes apresentações clínicas e características fisiopatológicas da doença a fim de oferecer alternativas ao CPAP. Em um mesmo grupo de pacientes com AOS grave, existem subgrupos específicos de pacientes que diferem na apresentação clínica da doença, sintomatologia e características fisiológicas. Nesses diferentes subgrupos, pode-se identificar determinantes fisiopatológicos com potencial para predizer resposta a diferentes modalidades de tratamento[14]. Dentre potenciais opções de tratamento como alternativa ao CPAP, se destacam

o AIO, a terapia posicional, medicações (sedativos, oxigênio, acetazolamida, etc) e terapia miofuncional[15].

A terapia posicional não é frequentemente prescrita no tratamento da AOS devido à inconsistência nos resultados de controle dos eventos obstrutivos[16]. Nos últimos anos, novos dispositivos de terapia posicional têm sido propostos[17,18]. São dispositivos pequenos e leves usados no pescoço ou no tórax capazes de detectar a posição corporal por meio de acelerômetros (Figura 2). Assim que o paciente assume a posição supina os dispositivos emitem vibrações estimulando o paciente a manter-se cada vez mais em decúbito lateral ao longo do tempo.

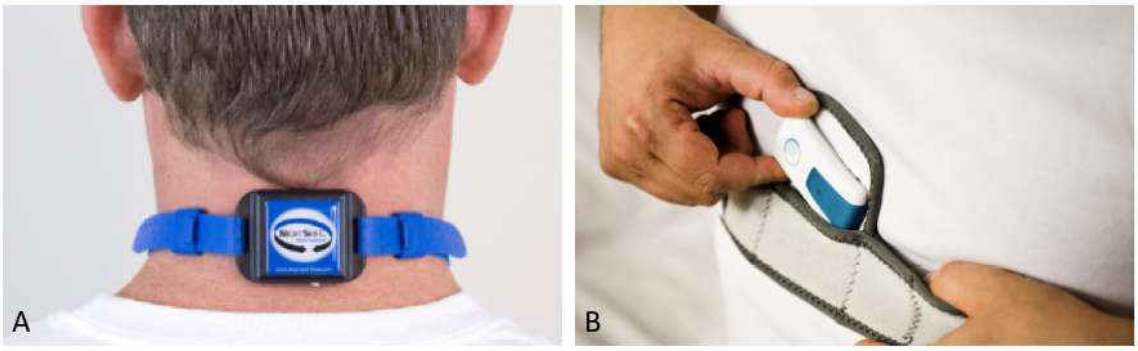

Figura 2 – Novos dispositivos de terapia posicional para AOS
A=Night shift positional therapy; B=Night balance sleep position trainer; AOS=apneia obstrutiva do sono

Os AIOs têm o objetivo de melhorar a configuração da via aérea superior e evitar a obstrução por meio de mudanças na posição da língua e protrusão da mandíbula[19]. Os dispositivos intra-orais de retenção lingual são menos utilizados e, por serem também menos estudados, não fazem parte do conjunto de evidências sobre os quais as recomendações para

os AIO se baseiam. Os AIOs de avanço mandibular são os mais estudados e empregados. Ao longo desta tese, AIO sempre se referirá ao AIO de avanço mandibular (Figura 3).

Figura 3 – Diferentes modelos de AIO para tratamento da AOS que promovem protrusão mandibular
A= SomnoDent Herbst; B=SomnoDent Classic; C=Resmed Narval; D=BlueSom BluePro
AIO= aparelho intra-oral; AOS=apneia obstrutiva do sono

Os AIOs são indicados para pacientes com AOS leve a moderada pela AASM[20]. Apesar disso, há evidências de que pacientes com AOS grave se beneficiam do AIO[21]. Devido a estas evidências, a AASM incluiu na sua última diretriz a indicação de AIO para pacientes intolerantes ao CPAP, independente do IAH. Uma opção de tratamento alternativo ao CPAP para pacientes com AOS grave é fundamental visto que muitos pacientes não aceitam o uso do CPAP. Permanece ainda não resolvida a predição de resposta ao AIO entre pacientes com AOS grave.

A presente tese é composta por três artigos que avaliaram os fatores fisiopatológicos anatômicos da AOS que podem influenciar a variabilidade individual de reposta ao tratamento, particularmente às modalidades terapêuticas alternativas ao CPAP. Dentre elas, destacamos a terapia posicional e o AIO por apresentarem boa tolerância pelos pacientes, porém eficácia variável.

1.2 Contribuição da anatomia da via aérea superior na gênese da AOS

A fisiopatologia da AOS é complexa e influenciada por diversos fatores (Figura 4). A anatomia da via aérea superior, resultante da interação entre a estrutura craniofacial e partes moles da faringe, é o fator mais importante na maioria dos indivíduos. As partes moles da faringe incluem a língua, a musculatura das paredes laterais da faringe e o palato mole. A obesidade pode provocar aumento do volume dos tecidos da faringe através da deposição de gordura entre as fibras musculares[22]. Dessa forma, tanto alterações da estrutura óssea (retrognatia por exemplo) quanto um aumento de partes moles associado à obesidade podem levar à redução do diâmetro da via aérea superior e consequente propensão à obstrução[23].

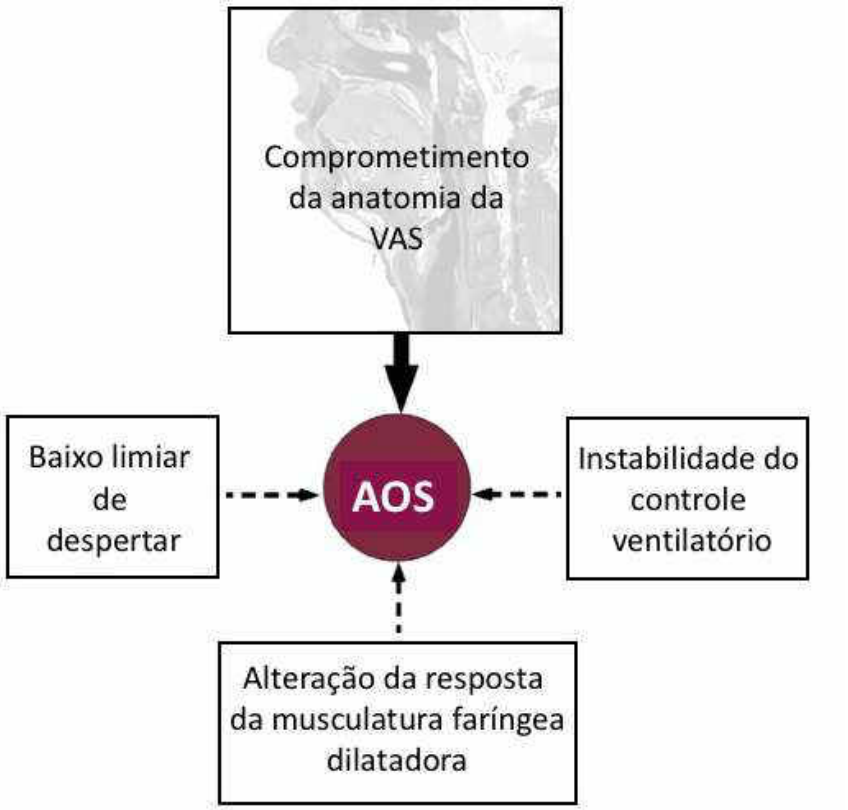

Figura 4 – Principais mecanismos fisiopatológicos envolvidos na AOS
Alteração da anatomia da VAS é um pré-requisito na gênese da AOS, combinada a graus variados de alterações não-anatômicas. AOS=apneia obstrutiva do sono; VAS=via aérea superior
FONTE: adaptado de Chest, 2017; 153:744-55

Além dos fatores anatômicos, pelo menos três outros mecanismos influenciam a gênese da apneia do sono: neuromodulação do tônus da faringe, limiar de despertar e controle da ventilação[24]. Durante o sono, há uma diminuição da atividade reflexa da musculatura dilatadora faríngea que responde à pressão negativa intraluminal, fazendo com que os indivíduos com anatomia desfavorável fiquem mais susceptíveis ao colapso[25]. O despertar precoce durante um evento respiratório obstrutivo impede o adequado recrutamento da musculatura dilatadora e pode promover instabilidade ventilatória [26]. A instabilidade respiratória decorre da resposta ventilatória exagerada após um evento respiratório. A hiperventilação resultante promove uma redução da $PaCO_2$ que por sua vez inibe o centro respiratório temporariamente[27]. A consequência é um novo evento respiratório, agora de origem central.

A contribuição de cada um desses fatores na gênese da AOS é variável em cada paciente indicando diferentes fenótipos fisiopatológicos[28]. O estudo aprofundado sobre esses fatores fisiopatológicos pode levar à melhor compreensão da ação de diferentes modalidades terapêuticas para tratamento da AOS, bem como a individualização e a geração de informações que podem ser preditoras de resposta aos tratamentos[15].

1.2.1 Anatomia da faringe

A faringe pode ser anatomicamente dividida em quatro regiões: nasofaringe (entre a margem posterior das conchas nasais e a margem posterior do palato duro), orofaringe retropalatal ou velofaringe (entre a margem posterior do palato duro e a margem caudal do palato mole), orofaringe retroglossal (entre a margem caudal do palato mole e a base da

epiglote) e hipofaringe (entre a epiglote e a laringe). A língua, o palato mole, as paredes laterais da faringe e a epiglote são as estruturas que estão mais envolvidas e podem determinar diferentes padrões de obstrução da via aérea superior (Figura 5).

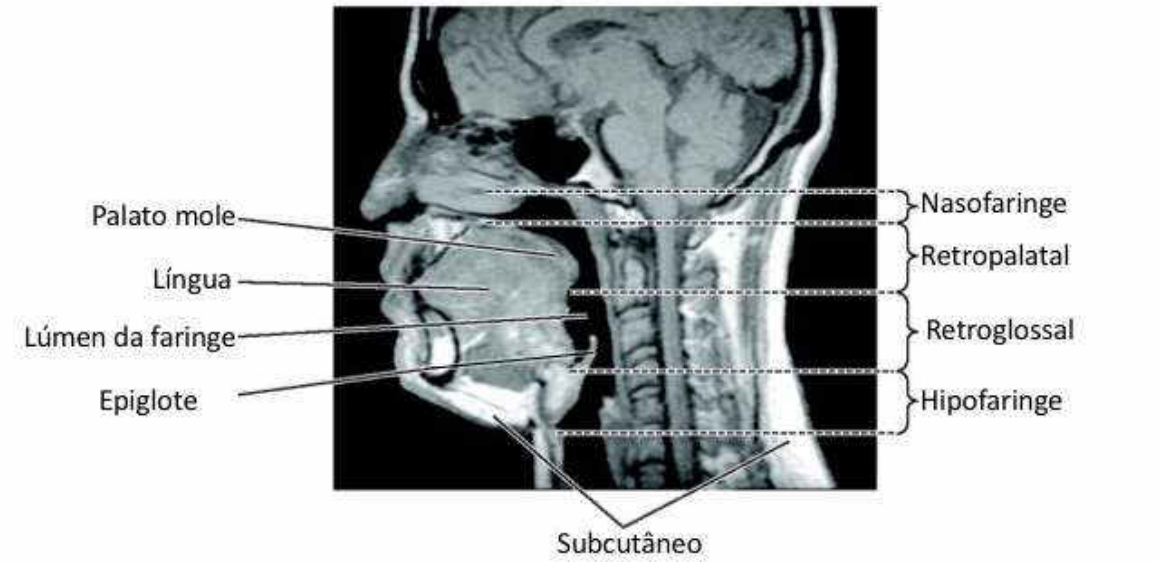

Figura 5 – Corte sagital de ressonância nuclear magnética da faringe
A imagem demonstra as regiões da faringe: nasofaringe, velofaringe, orofaringe e hipofaringe; e estruturas faríngeas envolvidas na obstrução da via aérea superior como o palato mole, a língua e a epiglote.
FONTE: adaptado de Am J Respir Crit Care Med 1995; 152:1673-89.

Dentre as estruturas faríngeas, a língua tem papel relevante tanto na fala e mastigação quanto na manutenção da patência da faringe[29]. A língua é composta por oito pares de músculos esqueléticos, parte deles sem nenhum ancoramento ósseo[29]. A infiltração de gordura observada na língua é consequência direta da obesidade e leva ao aumento do seu volume e consequente aumento do comprimento da faringe e da propensão ao colapso[30].

Os artigos apresentados nesta tese têm um enfoque particular no papel da língua nos padrões de obstrução da via aérea superior, que reflete características próprias no fluxo aéreo e que pode ser determinante em tratamentos alternativos para a AOS.

1.2.2 Sonoendoscopia

A avaliação da anatomia da faringe pode ser realizada por métodos de imagem como ressonância magnética e cefalometria, mas recentemente tem-se utilizado com grande frequência a sonoendoscopia para se avaliar de forma dinâmica a faringe durante o sono (Figura 6). A sonoendoscopia foi inicialmente realizada em dez pacientes com AOS durante o sono espontâneo em 1978 por Borowiecky e colegas. Em 1991, Croft e Pringle descreveram a sonoendoscopia realizada durante o sono induzido com midazolam[31].

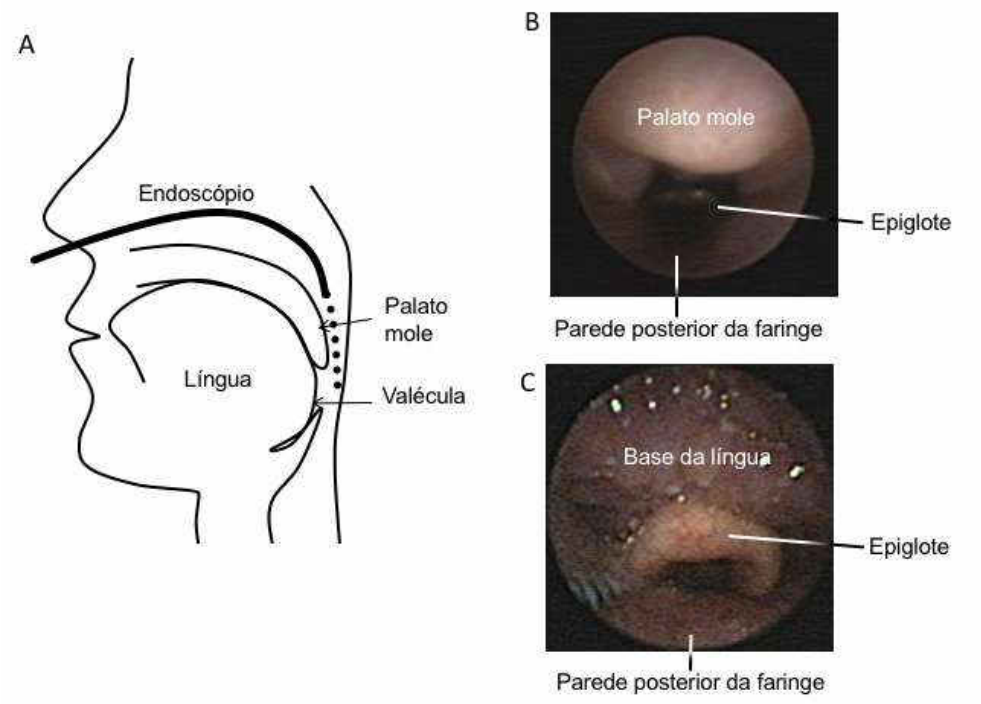

Figura 6 – Representação esquemática do posicionamento do endoscópio durante a sonoendoscopia (A) com visualização da velofaringe (B) e orofaringe (C)
FONTE: adaptado de Chest 2017; 152: 537-46.

Estudos que usaram a sonoendoscopia para avaliar o nível e as estruturas associadas ao colapso da faringe na AOS relatam a maior frequência de obstrução da velofaringe em

comparação com a orofaringe[32,33]. No segundo artigo desta tese nós avaliamos os possíveis mecanismos fisiopatológicos responsáveis pela maior ocorrência de colapso da região da velofaringe.

1.2.3 Pressão crítica de fechamento da faringe

A propensão anatômica para a gênese da AOS pode ser avaliada através da medida da colapsabilidade da faringe. A pressão crítica de fechamento da faringe (Pcrit) é definida pela pressão na qual ocorre o colapso da faringe.

A medida da Pcrit se baseia no principio do resistor de Starling. Trata-se de um modelo clássico utilizado para explicar os regimes de fluxo em um tubo colapsável[34]. No caso da via aérea superior, o modelo é composto por um tubo colapsável que tem extremidades rígidas (nariz e traqueia) e fica dentro de uma caixa selada (tecidos moles e estrutura craniofacial). Durante limitação de fluxo inspiratório, o modelo de Starling prevê que há estabilidade do fluxo após atingido pico inicial (achatamento do fluxo inspiratório). No modelo de Starling, a pressão à jusante (pressão inspiratória esofágica) não interfere no fluxo inspiratório durante limitação de fluxo inspiratório. (Figura 7, condição B). Durante limitação ao fluxo inspiratório, há relação linear entre pressão nasal e pico de fluxo inspiratório.

Para a determinação da Pcrit, o paciente utiliza um dispositivo de CPAP através de uma máscara nasal. Inicialmente a pressão de CPAP é titulada para abolir eventos respiratórios. A pressão de CPAP é então reduzida abruptamente enquanto o paciente dorme a fim de se induzir limitação ao fluxo inspiratório. A redução intermitente da pressão de

CPAP, de forma progressiva (pressões de CPAP progressivamente menores) promovem redução do pico de fluxo inspiratório. É gerado um gráfico de pico de fluxo inspiratório conforme pressão de CPAP. A Pcrit é igual a pressão de CPAP no fluxo zero[35].

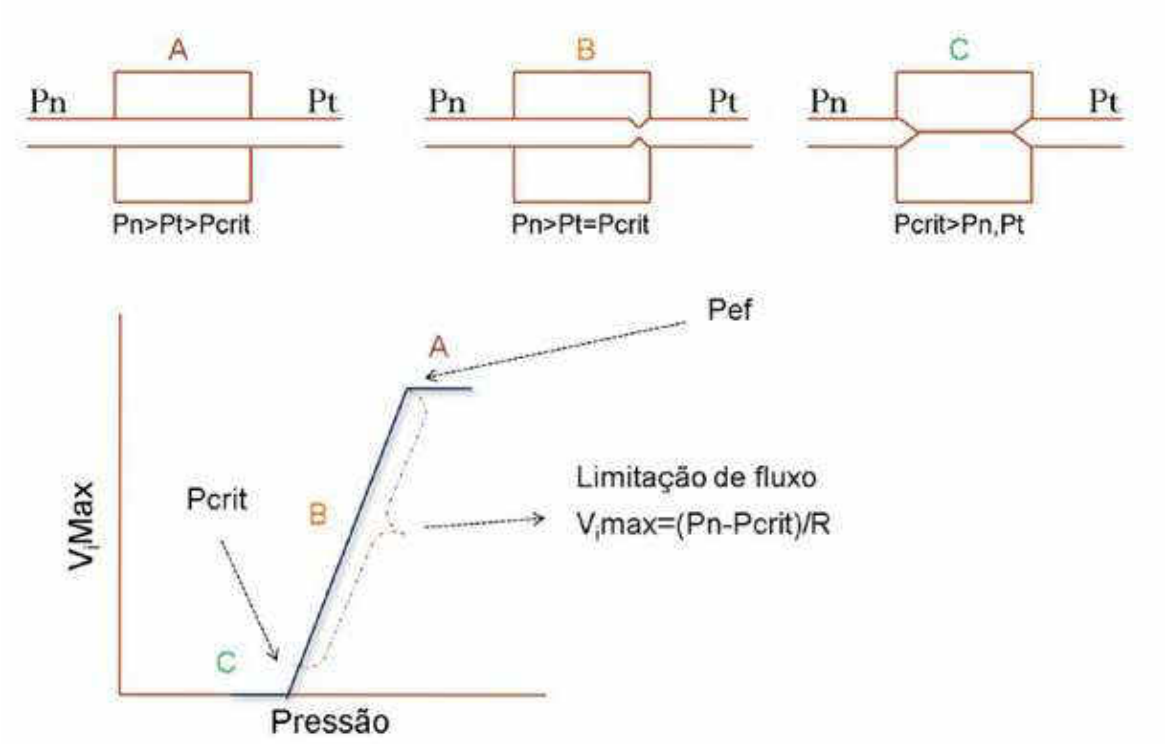

Figura 7 – Representação do modelo do resistor de Starling
O resistor de Starling é composto por um tubo colapsável interposto por extremidades rígidas (nariz e traqueia). O segmento fica dentro de uma caixa selada (tecidos moles e estrutura cranio facial ao redor da faringe). Na condição A a faringe está patente Na condição B há um gradiente de pressão decrescente em direção à extremidade traqueal devido à resistência à montante, onde a pressão traqueal se aproxima da Pcrit. A faringe está parcialmente colabada na condição B e o pico de fluxo inspiratório ($V_i max$) não depende da pressão traqueal, havendo relação linear entre $V_i max$ e pressão nasal. A condição B caracteriza a limitação ao fluxo inspiratório onde o fluxo inspiratório é constante (curva achatada) após pico de fluxo inspiratório. Na condição C ocorre o colapso e a Pcrit é maior que a pressão nasal. $V_i max$=pico de fluxo inspiratório; Pcrit= pressão crítica de fechamento da faringe; Pn=pressão nasal; Pt=pressão traqueal; R=resistência; Pef=pressão efetiva (ausência de limitação ao fluxo inspiratório)
FONTE: adaptado de Am Rev Respir 1991; 143: 1300-3

A Pcrit é capaz de diferenciar o espectro a AOS (Figura 8), com valores mais positivos de Pcrit indicando maior colapsabilidade da via aérea e se associando a maior gravidade da AOS[36].

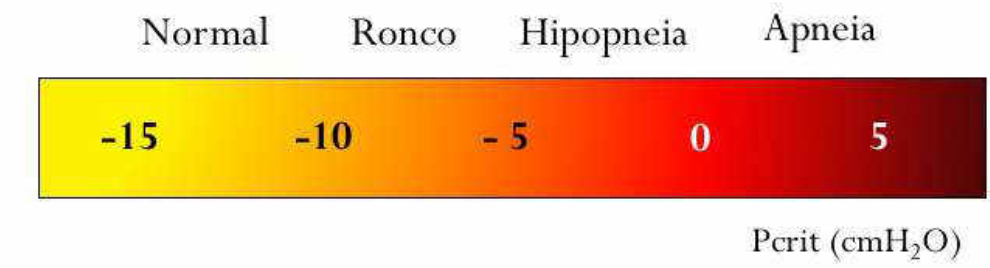

Figura 8 – As medidas da Pcrit refletem um *continuum* de colapsabilidade da via aérea superior
FONTE: adaptado de J Appl Physiol 2007; 102: 547–56

1.3 Justificativa

Apesar das consequências da AOS na qualidade de vida e sua associação com comorbidades cardiometabólicas, uma grande parte dos pacientes diagnosticados permanece sem nenhum tratamento[9]. A presente tese explorou fatores anatômicos envolvidos na gênese da AOS que podem ser determinantes em terapias alternativas ao CPAP. Nos artigos que serão apresentados na próxima seção realizamos avaliações fisiológicas da anatomia e colapsabilidade da via aérea superior por meio de sonoendoscopia e medidas de Pcrit em pacientes com AOS.

O artigo 1 é intitulado “Effect of sleeping position on upper airway patency in obstructive sleep apnea is determined by the pharyngeal structure causing collapse”. A nossa hipótese neste estudo era de que pacientes com obstrução faríngea associada à língua e à

epiglote apresentariam melhora significativa da patência faríngea na posição lateral considerando o efeito gravitacional sobre essas estruturas.

O artigo 2 é intitulado “Retropalatal and retroglossal airway compliance in patients with obstructive sleep apnea”. Neste estudo nós investigamos os mecanismos para a predominância do colapso palatal observado nos pacientes com AOS.

O artigo 3 é intitulado “Structure and severity of pharyngeal obstruction determine sleep apnea response to oral appliances”. Nossa hipótese neste estudo era de que os dois maiores determinantes para o sucesso terapêutico do AIO para o tratamento da AOS seriam a estrutura faríngea envolvida na obstrução e a colapsabilidade da via aérea superior medida pela Pcrit.

Os resultados encontrados têm potenciais implicações para personalização das diferentes modalidades terapêuticas alternativas ao CPAP para tratamento da AOS.

2 Artigos

2.1 Artigo 1: Citação Completa

Marques M, Genta PR, Sands SA, Azarbarzin A, Taranto-Montemurro L, de Melo C, White DP, Wellman A. Effect of Sleeping Position on Upper Airway Patency in Obstructive Sleep Apnea Is Determined by the Pharyngeal Structure Causing Collapse. *Sleep* 2016; 40 (3):zsx005.

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ORIGINAL ARTICLE

Effect of Sleeping Position on Upper Airway Patency in Obstructive Sleep Apnea Is Determined by the Pharyngeal Structure Causing Collapse

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Objectives: In some patients, obstructive sleep apnea (OSA) can be resolved with improvement in pharyngeal patency by sleeping lateral rather than supine, possibly as gravitational effects on the tongue are relieved. Here we tested the hypothesis that the improvement in pharyngeal patency depends on the anatomical structure causing collapse, with patients with tongue-related obstruction and epiglottic collapse exhibiting preferential improvements.

Methods: Twenty-four OSA patients underwent upper airway endoscopy during natural sleep to determine the pharyngeal structure associated with obstruction, with simultaneous recordings of airflow and pharyngeal pressure. Patients were grouped into three categories based on supine endoscopy: Tongue-related obstruction (posteriorly located tongue, $N = 10$), non-tongue related obstruction (collapse due to the palate or lateral walls, $N = 8$), and epiglottic collapse ($N = 6$). Improvement in pharyngeal obstruction was quantified using the change in peak inspiratory airflow and minute ventilation lateral versus supine.

Results: Contrary to our hypothesis, patients with tongue-related obstruction showed no improvement in airflow, and the tongue remained posteriorly located while lateral. Patients without tongue involvement showed modest improvement in airflow (peak flow increased 0.07 L/s and ventilation increased 1.5 L/min). Epiglottic collapse was virtually abolished with lateral positioning and ventilation increased by 45% compared to supine position.

Conclusions: Improvement in pharyngeal patency with sleeping position is structure specific, with profound improvements seen in patients with epiglottic collapse, modest effects in those without tongue involvement and—unexpectedly—no effect in those with tongue-related obstruction. Our data refute the notion that the tongue falls back into the airway during sleep via gravitational influences.

Keywords: Supine position, airway obstruction, epiglottis, sleep apnea.

Statement of Significance

Sleeping lateral rather than supine can have a profound impact on obstructive sleep apnea (OSA) but the improvement in upper airway patency varies from patient to patient for reasons that remain unclear. We show that the improvement in airway patency with lateral positioning depends on the pharyngeal structure impeding airflow: Patients with epiglottic collapse improved markedly and those without tongue-related obstruction (soft-palate/lateral walls) showed modest improvements. Most surprisingly, relief from gravitational effects on the tongue with lateral positioning had no effect on airway patency in patients with tongue-related obstruction.

INTRODUCTION

Obstructive Sleep Apnea (OSA) is characterized by recurrent upper airway collapse[1] and is often aggravated by sleeping in the supine position.[2] However, there is wide variability between patients in the response to positional changes. The reason for this variability is poorly understood. Some studies suggest that sleeping supine could affect the collapse of particular structures within the airway, such as the tongue base or epiglottis.[3–5] However, these studies lacked quantitative measurements of airway size and flow in the different sleeping positions, making it difficult to determine the effect size of positional changes.

In recent years, the large number of drug-induced sleep endoscopy (DISE) studies performed in OSA patients has shown that upper airway obstruction results from the collapse of one or more pharyngeal structures: the soft palate, the lateral pharyngeal walls, the tongue base, and the epiglottis.[6,7] Furthermore, imaging studies have shown that gravity can affect upper airway soft tissue structures and their relationship with bony enclosures.[8,9] However, the positional effect on pharyngeal structures such as the tongue base and epiglottis was not reported in these studies. It is unknown how lateral sleep affects the tongue position and airway patency when compared to the supine position. Likewise, changes in epiglottic closure due to sleep position have also not been well characterized.

We hypothesized that the improvement in upper airway patency from supine to lateral sleep would be dependent on the structure causing pharyngeal collapse. Specifically, we hypothesized that patients with tongue-related obstruction or epiglottic collapse might be the most amenable to positional changes. This hypothesis was based on the theoretical notion that gravity may have a greater effect on these structures. To test this hypothesis, we evaluated OSA patients in lateral and supine sleep with upper airway endoscopy and concurrent measurements of airflow and epiglottic pressure.

METHODS

Subjects

Patients with OSA as defined by an apnea-hypopnea index (AHI) > 10 events/h were invited to participate in the study. The age range was 21–70 years. Subjects were excluded if they had heart failure, diabetes, or renal insufficiency, or if they were taking medications that could affect upper airway muscle function. The study was approved by the Institutional Review Board at Brigham and Women's Hospital. Written informed consent was obtained before participation in the study.

Instrumentation

Subjects were instrumented with electrodes for electroencephalography (C4-A1, O2-A1), left and right electrooculography, and submental electromyography for sleep staging. After

topical application of a decongestant (oxymetazoline 0.05%) and anesthetic (lidocaine 4%), a 5-French pressure catheter (Millar Instruments, Houston, TX) and a 2.8 mm-diameter pediatric bronchoscope (model BFXP-160F, Olympus, Tokyo, Japan) were inserted through the left and right nostrils, respectively. The pressure catheter was placed at the level of the epiglottis. Subjects breathed via a nasal mask that was connected to a pneumotachometer (Hans-Rudolph, Kansas City, MO) and a differential pressure transducer (Validyne, Northridge, CA) to measure airflow. A modified continuous positive airway pressure (CPAP) device (Pcrit 3000, Philips Respironics, Monroeville, PA) was attached to the mask to hold the airway open when needed to enable visualization of all airway structures. To standardize observations, the position of the airway structures and airflow rates were quantified at the same CPAP levels during supine and lateral sleep. Spike 2 software (Cambridge Electronic Design, Cambridge, England) was used to acquire the physiologic signals and endoscopic images. All signals were captured at a sampling frequency of 500 Hz, and the images were sampled at 30 frames/s.

Protocol

The subjects were asked to sleep in the supine position on a thin pillow with the chin forward. For the lateral position, they were asked to lie in the right lateral decubitus position with the head in a lateral neutral position. The body position was monitored directly by the investigator who stayed inside the room during the study and assured that both postures were constant during data collection. In order to evaluate the different pharyngeal structures causing collapse, the bronchoscope's tip was initially placed in the nasopharynx above the palate. Several sequences of flow-limited breaths (lack of increase in flow despite decreasing epiglottic pressure) were recorded with the scope in the nasopharynx. The tip was then advanced to the oropharynx to observe the oropharyngeal and hypopharyngeal structures. Once the bronchoscope was placed at each one of the pharyngeal levels, minimal movement was then performed to prevent the subjects from awakening. This process was then repeated in the alternate sleeping position. As many breaths were observed in both sleeping positions and at both pharyngeal levels as possible during the night of study.

Data Analysis

Patients were categorized into two groups according to the position of the tongue base: tongue-related obstruction and non-tongue related obstruction. Tongue-related obstruction was defined when the tongue base was touching or covering the anterior aspect of the epiglottis and thus obliterating the vallecula. The cardinal feature of this group was a posteriorly located tongue during expiration and inspiration. Non-tongue related obstruction was defined when collapse occurred due to the palate or lateral walls without tongue base involvement (the vallecula was clearly visible and the tongue base was not touching the epiglottis). The occurrence of epiglottic collapse was associated with severe airflow obstruction regardless of the location of the tongue base (see description of epiglottic collapse below), and for this reason the presence of epiglottic collapse received its own category. The epiglottis could obstruct the pharynx by either anteroposterior or lateral (folding) movement. This classification was based on the video images of the velopharynx and oropharynx recorded during the natural sleep in both supine and lateral positions. Each patient was classified independently by two investigators blinded to the sleeping position after the recording of the full study. Any discrepancies were resolved by a third investigator.

In order to assess changes in the functional size of the airway due to positional changes, inspiratory peak airflow and minute ventilation from all eligible flow-limited breaths during non-rapid eyes movement (NREM) sleep were analyzed. Pharyngeal pressure was monitored to determine flow-limitation defined by the lack of increase in flow despite decreasing epiglottic pressure. Eligible breaths included those that were free of artifacts and arousals and where the endoscope was in the nasopharynx (above the palate and not touching the airway structures of interest). Particular attention was paid to peak flow during flow limitation because previous studies have suggested that it is a good surrogate measurement of upper airway size and collapsibility.[10,11] This concept is derived from the observation that, during flow limitation, peak inspiratory flow is correlated with pharyngeal cross-sectional area at end-expiration of the previous breath.

Statistical Analysis

Descriptive values are presented as the mean ± standard deviation or the median (1st, 3rd quartile) for continuous variables. Demographic variables were compared with a one-way analysis of variance and Chi-square test. A McNemar Chi Square statistic was used to test for changes in the collapse category with changes in position. Because collapse of the epiglottis is intermittent, as described below, the proportion of breaths with epiglottic collapse between the supine and lateral positions were compared using a Wilcoxon signed-rank test. A Wilcoxon signed-rank test was used for comparisons between the inspiratory peak flow and ventilation in different positions. Data analysis was performed using SPSS statistical software (version 17, SPSS Inc., Chicago, IL), and statistical significance was considered when the p value was $< .05$.

RESULTS

Twenty-four OSA patients (age 53 ± 6 years; 17 men and 7 women) were studied. The subjects' characteristics are presented in Table 1. We analyzed a total of 886 flow-limited breaths during supine NREM sleep (37 ± 45 breaths per subject) and 1026 flow- limited breaths (43 ± 43 breaths per subject) during lateral NREM sleep. The pharyngeal pressure swings for the breaths in the supine position were −10.7 ± 7.1 cmH_2O, and the pharyngeal pressure swings for the breaths in the lateral position were −8.5 ± 4.7 cmH_2O. Four subjects required CPAP to hold the airway open enough to visualize the structures involved in collapse. The CPAP used in these patients were 2, 5, 6, and 8 cmH_2O. At atmospheric pressure, these four patients exhibited continuously cycling apneas with frequent arousals, which made observation of the collapsing structures difficult. In order to make equal comparisons between supine and lateral sleep, care was taken to study these patients at the same level of CPAP in both positions. Inspiratory peak flow across all patients was 0.22 (0.14–0.35) L/s in supine position, and 0.24 (0.16–0.33) L/s in lateral sleeping position ($p < .001$). Minute ventilation across all patients was 4.75 (3.19–6.58) L/min in the supine position, and 5.85 (3.95–7.42) L/min in the lateral position ($p < .001$).

Table 1—Subjects Characteristics.

	All subjects (*n* = 24)	Tongue-related obstruction (*n* = 10)	Non-tongue related obstruction(*n* = 8)	Epiglottic collapse (*n* = 6)	*p*
Age (years)	53.3 ± 6.6	54.8 ± 5.9	49.9 ± 6.2	56.3 ± 7.2	.14
Sex (M/F)	17/7	5/5	6/2	6/0	.09
Neck circumference (cm)	41.1 ± 3.2[a]	40.5 ± 3.2[a]	41.2 ± 3.6[a]	40.7 ± 3.0	.61
BMI (kg/m^2)	32.0 ± 5.9	33.3 ± 7.3	31.3 ± 2.8	31.0 ± 6.9	.69
AHI (events/hour)	48 ± 28	41.5 ± 27.0	58.0 ± 33.1	45.3 ± 21.7	.46

AHI = apnea-hypopnea index; BMI = body mass index. Data are presented as mean ± standard deviation.
[a]data not reported for one subject in tongue-related obstruction group and one subject in the non-tongue related obstruction group.

Tongue-Related Obstruction (*n* = 10)

We hypothesized that the tongue base would be affected by gravity and, if posteriorly located in the supine position, would move anteriorly during lateral sleep and be associated with improved airflow. To test this hypothesis, we assessed the position of the tongue endoscopically and airflow parameters in supine and lateral sleep. Contrary to our original hypothesis, we found that in the ten patients with a posteriorly located tongue during supine sleep, the tongue remained posteriorly located in seven patients in lateral sleep (p = 1.0). Note the lack of tongue movement in three representative patients in Figure 1. In two patients in this group, the endoscopic oropharyngeal views during lateral sleep were not adequate for evaluation of the tongue position. Therefore, we did not have adequate information in these two individuals to draw conclusions about the location of the tongue base during lateral sleep. In another patient, we observed an anterior movement of the tongue in the lateral sleeping position compared to supine, allowing clear visualization of the vallecula in the lateral position. None exhibited isolated palatal or lateral walls collapse upon moving to the lateral position (while some patients appeared to narrow in the lateral dimension, the lateral walls never actually touched). In addition to no change in tongue position, there was no improvement in inspiratory peak flow or ventilation. As shown in Figure 2, the inspiratory peak flow increased negligibly (lateral minus supine: 0.03 L/s), and the ventilation did not change (lateral minus supine: 0 L/min). These data demonstrate that neither the tongue position nor the functional size of the airway changes with a change in body position in patients with predominantly tongue related obstruction.

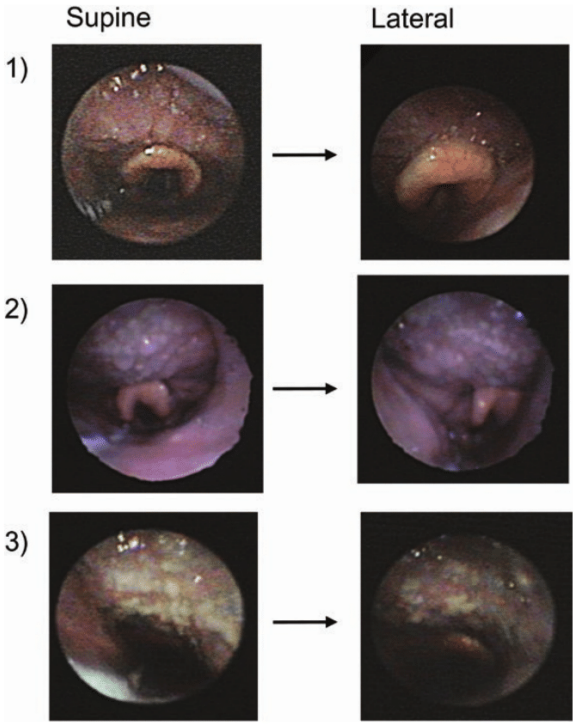

Figure 1—Endoscopic oropharyngeal views of tongue-related obstruction in three representative subjects. Supine sleep is shown in the left panel and lateral sleep is shown in the right panel. Note that the tongue is touching the epiglottis and obliterating the vallecula in both supine and lateral sleep.

Non-Tongue Related Obstruction (*n* = 8)

We originally hypothesized that patients without tongue base obstruction, that is, collapse due to the palate and/or lateral walls, would exhibit no improvement (and possibly worsening in the case of lateral walls collapse) in the lateral position. We found that in these patients, the tongue base remained in an "anterior" location during lateral sleep (Figure 3), and the structure causing collapse did not change. All eight patients in this group had non-tongue obstruction during both supine and lateral sleep (p = 1.0). Contrary to our original hypothesis, we found a slight increase in inspiratory peak flow and an even larger increase in ventilation (Figure 4). The inspiratory peak flow increased 0.07 L/s (p = .04), and the ventilation increased 1.5 L/min (p = .01). Hence, in these patients without tongue related obstruction, airway patency tended to increase.

Epiglottic Collapse (*n* = 6)

Epiglottic collapse (Figure 5) was placed in a separate category because it is often associated with severe and abrupt changes in flow that, when present, predominate as the mechanism of collapse. This behavior is illustrated in Figure 6, which shows a raw tracing of epiglottic collapse. In the supine position at end-expiration in this patient, the epiglottis is low-hanging and

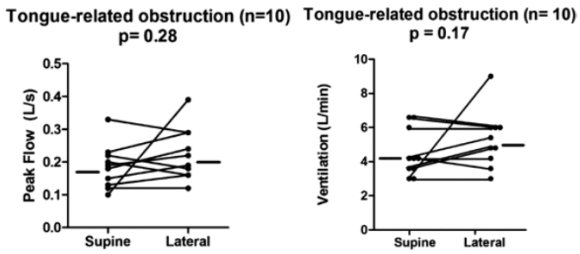

Figure 2—Peak flow and ventilation did not increase from supine to lateral sleep in patients with tongue-related obstruction. Data presented as individual median values for each patient in both sleeping positions.

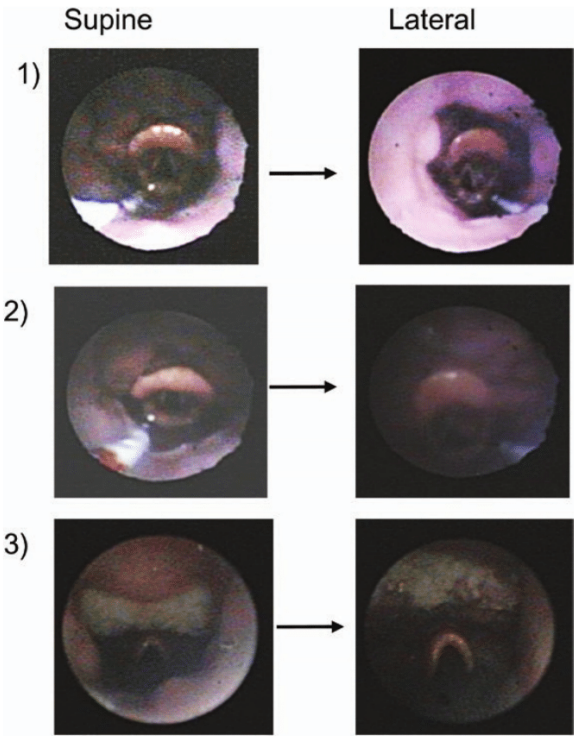

Figure 3—Endoscopic oropharyngeal views of non-tongue related obstruction in three patients. The tongue is not touching the epiglottis and the vallecula is visible in both positions.

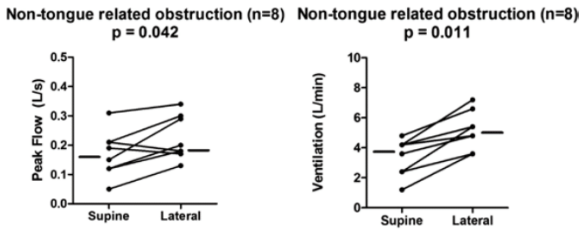

Figure 4—Peak flow and ventilation increased in lateral sleep among patients without tongue-related obstruction. Data presented as individual median values for each patient in both sleeping positions.

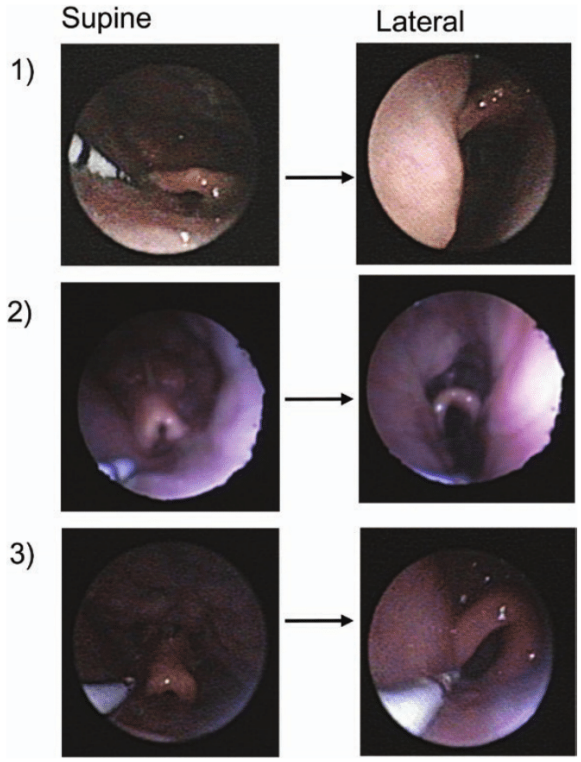

Figure 5—Endoscopic views of epiglottic collapse in three subjects. The epiglottis appeared more posterior and closer to laryngeal inlet during supine sleep than in the lateral position.

partially covers the laryngeal inlet. During inspiration, the epiglottis closes rapidly and completely. Note also how the epiglottic collapse occurs immediately after a non-flow limited breath; this is a cardinal feature of epiglottic collapse, that is, it is intermittent. To deal with this intermittency, we counted the percentage of breaths exhibiting epiglottic collapse in the supine position and compared it to the percentage of breaths with epiglottic collapse in the lateral position. We found that epiglottic collapse decreased markedly in most patients (from 66.5% ± 25.3% to 12.3% ± 19.2%, see Figure 7). This was supported by objective measurements of ventilation, which increased from 3.3 (2.7–5.8) L/min while supine to 6.3 (4.2–7.9) L/min while lateral (Figure 8). The inspiratory peak flow, on the other hand, did not increase, possibly because epiglottic collapse often occurs abruptly during mid-inspiration and thus does not alter inspiratory peak flow (note in Figure 6 that peak flow is "normal"). Also because of the intermittent nature of the epiglottic collapse, other potential sites of collapse (ie, soft palate, lateral walls) were observed on the breaths when epiglottic collapse did not occur. Two patients with epiglottic collapse also exhibited collapse of the lateral walls without tongue base involvement.

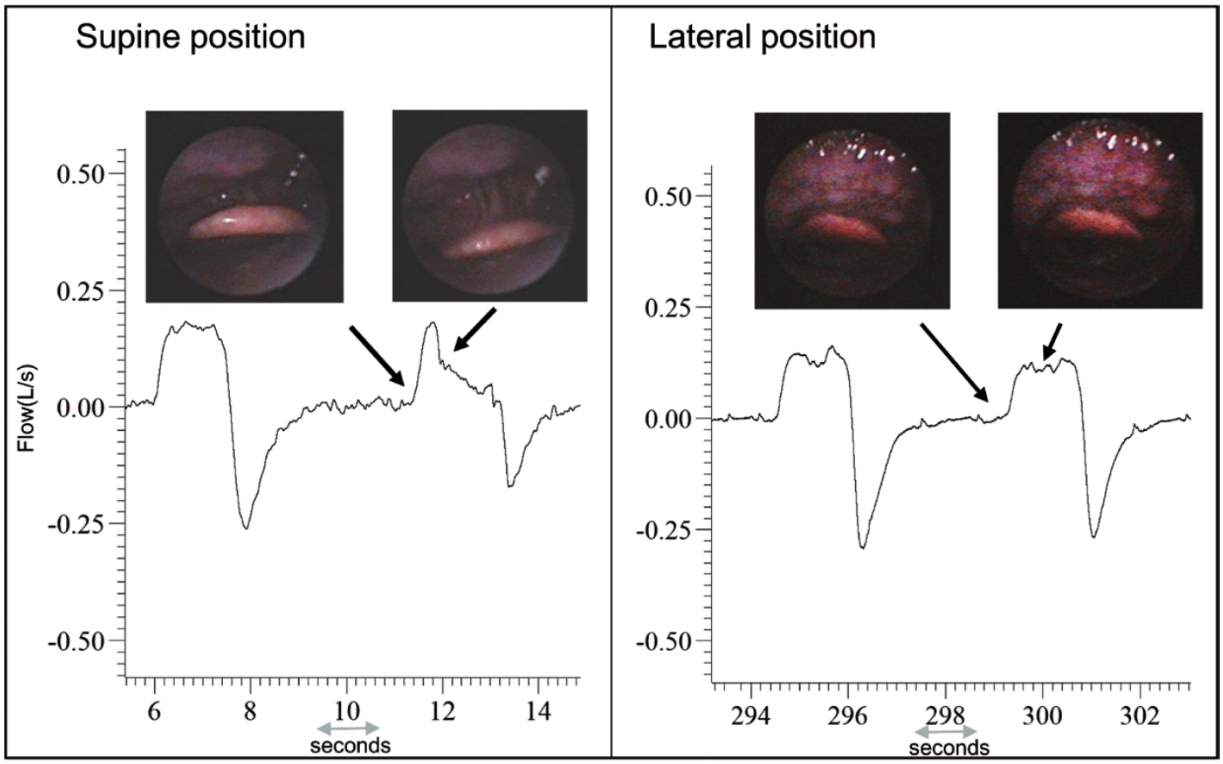

Figure 6—Raw data of a representative subject showing the retrodisplacement of the epiglottis in supine sleep, and inspiratory airflow reduction concomitant to the epiglottic collapse. The epiglottis is less close to the laryngeal inlet, and it is not collapsing in the lateral position. The arrows indicate the epiglottis position at the end-expiration and initial inspiration.

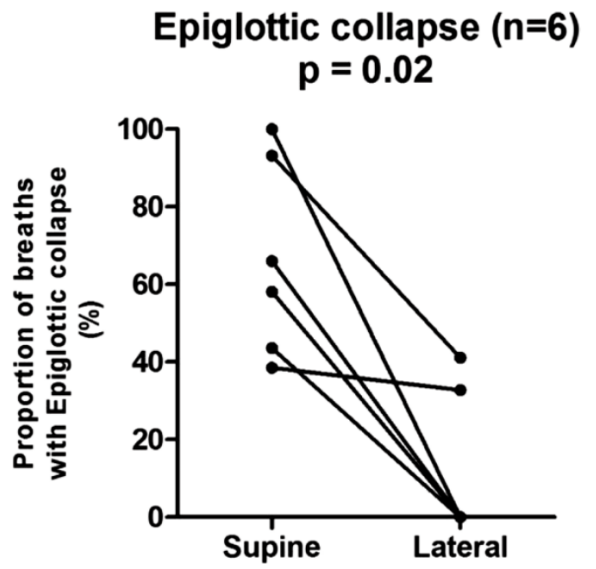

Figure 7—Reduction in the proportion of breaths exhibiting epiglottic collapse from supine to lateral sleep.

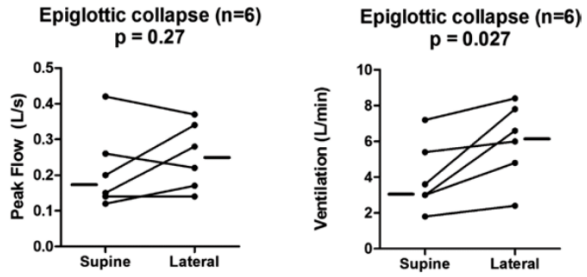

Figure 8—Ventilation improved from supine to lateral sleep in patients with epiglottic collapse. Data presented as individual median values for each patient in both sleeping positions. .

DISCUSSION

The major findings of the current study were:

1. Patients with tongue related obstruction did not exhibit a change in tongue position or airflow upon moving onto their side.
2. Airway patency improves slightly with lateral positioning in patients "without" tongue related obstruction.

3. Epiglottic collapse improves substantially with a change to the lateral body position during sleep.

The postural differences observed in OSA patients are likely due to some combination of unfavorable upper airway geometry, decreased lung volume, and failure of the dilator muscles to compensate.[12] The effect of sleeping position on upper airway soft tissue structures and their relation to bony enclosures has also been investigated with different imaging methods. Walsh et al. performed optical coherence tomography in 11 OSA patients and 11 control subjects during wakefulness.[13] The pharyngeal cross sectional area did not change when moving from the supine to the lateral position in both groups. On the other hand, Isono et al. used endoscopy during general anesthesia and reported a larger cross sectional area in the lateral posture in eight OSA patients.[14] However, neither of these studies attempted to identify reasons for inter individual differences in response to positional changes. Differences in upper airway shape have also been shown to participate in the genesis of positional airway obstruction.[15] For instance, a more elliptical airway shape with reduced anteroposterior diameter in supine posture increases the susceptibility for pharyngeal collapse.[13,16] More recently, DISE has been used to evaluate the influence of head position on upper airway obstruction and has shown a decreased frequency of complete anteroposterior collapse at the velum, tongue base, and epiglottis level with lateral rotation of the head.[5] Lee et al. performed DISE in 85 patients and reported a decrease in the prevalence of tongue base obstruction when moving from supine (71.1%) to lateral sleep (7.1%).[3] However, there are some methodological differences between this paper and our study. First, as a condition for tongue base obstruction, Lee and colleagues used the criteria of a 50% displacement compared to wakefulness. This is problematic because visual estimates of percent collapse are highly subjective. To reduce the subjectivity, we adopted a categorization for airway collapse that considered the position of the tongue base relative to the vallecula and epiglottis during end-expiration. The use of such anatomical landmarks, we believe, makes the categorization criteria more objective. Additionally, we observed the relation between the structures during end-expiration, which could minimize the fact that the airway structures are heavily influenced by the pressure in the pharynx during inspiration. For instance, if the palate collapses in the supine position then this would make the downstream oropharyngeal pressure much more negative during inspiration, which could then pull the tongue into the airway. Had the palate not collapsed (and the negative oropharyngeal pressure not been created), then the tongue may not have collapsed. Thus, one future research direction is to evaluate the relationship between the tongue position and epiglottic pressure.

Our finding that patients who exhibit tongue related obstruction do not show improved airway patency when moving from supine to lateral has several pathophysiological implications. First, it is now unlikely—in patients with oropharyngeal narrowing—that the reason for upper airway collapse while supine is that the tongue simply falls back into the airway during sleep, since the tongue "falls" into the airway during supine sleep to the same exact extent in the lateral position, which is not attributable to gravitational influences. Thus an alternative mechanism is needed for these patients. The muscular hydrostat argument[17,18] may provide insight into this phenomenon, whereby the tongue maintains a constant volume (regardless of the forces acting on it ie, gravity, muscle activation). In this case, our data lead us to speculate that an enlarged tongue (thereby posteriorly located) has little space to move into (with position changes/muscle activation) regardless of whether supine or lateral. If the tongue was anteriorly located, it still could be sucked into the airway—but this only happened when the palate collapsed first causing the epiglottic pressure to become very negative (−10 to −15 cmH_2O). In one patient, the tongue did seem to "creep" backwards over time (several breaths), but this was difficult to quantify and in the overwhelming majority of the breaths the tongue appeared "anteriorly located." Additionally, the tongue does not fall back when these patients with non-tongue obstruction move from the lateral to the supine position possibly because the muscles activate to move the tongue forward resisting the collapsing force (as opposed to a large tongue which has little space to move when activated).

Regarding epiglottic collapse, a recent systematic review in adult OSA patients indicated that this occurs more often than previously described from studies performed during wakefulness or with CT imaging, which provides poor visualization of the epiglottis.[19] Before the use of DISE to evaluate upper airway obstruction, the prevalence of epiglottic collapse was estimated to be 12% of OSA patients. However, studies performed during (drug-induced) sleep have demonstrated a much higher prevalence. Lan and colleagues studied 64 OSA patients with DISE and found that 30% exhibited complete collapse of the epiglottis.[20] Cavaliere et al found that 23% of the 66 patients studied had epiglottis involvement.[21] A similar prevalence of 24% was found in Ravesloot's study of 100 consecutive OSA patients.[22] Finally, Golz and colleagues noted that 26% of the 187 patients they studied had epiglottic collapse.[23] Similarly, we found epiglottic collapse in 25% of the 24 patients included in our study. Therefore, epiglottic collapse is more common than previously thought.

Research also indicates that epiglottic collapse is difficult to treat. Some studies demonstrate that CPAP may be ineffective in patients who have a severely floppy epiglottis because the pressure may further push the epiglottis into the laryngeal inlet.[24–26] The extent to which epiglottic collapse contributes to CPAP failure or non-adherence is not known and is an area of interest for future study. Although surgical resection or trimming of the epiglottis may be an option, no controlled studies have reported the efficacy of this approach, and the potential for side effects such as aspiration are not trivial.[27,28] Epiglottic collapse may also be difficult to treat with oral appliances. In the presence of hypopharyngeal obstruction (mainly epiglottic collapse) during DISE, simulation of jaw advancement for prediction of oral appliance therapy outcome showed a tendency towards less successful treatment.[29] Furthermore, Kent et al performed DISE in thirty-five consecutive patients with incomplete resolution of OSA following oral appliance therapy. Eleven patients (31.4%) had complete epiglottic obstruction at baseline, and with the oral appliance seven of them (64%) had persistent collapse of the epiglottis.[30] Therefore, conventional therapies may not be effective to treat OSA associated with epiglottic collapse.

The results of the current study suggest that epiglottic collapse responds well to positional therapy. Consistent with this finding, two previous studies have suggested that positional therapy is an effective treatment for patients with epiglottic collapse. In a study that compared patients with positional and non-positional OSA, Victores et al. demonstrated that epiglottic collapse in the supine position was twice as frequent among the positional (64%) as compared with the non-positional patients (36%).[4] In that study, epiglottic collapse in positional OSA patients improved with lateral positioning. Safiruddin et al. also showed that lateral head rotation was associated with improvement in epiglottic collapse as compared to supine sleep.[5] However, both studies were based on qualitative DISE findings. Our study measured airflow and thus adds objective evidence of airway anatomical changes. From these data, we speculate that the epiglottis is affected by gravity and is therefore influenced by position changes.

Although positional therapy is an inexpensive therapeutic choice, it is rarely prescribed for OSA.[31] There may be several reasons for this. First, for a long time, techniques such as the "tennis-ball method" were the only available procedures for avoiding supine sleep. Oksenberg et al. tested the tennis ball technique in 12 positional OSA patients and showed a reduction of supine sleep duration from 79% to 12% with a concomitant reduction of the AHI from 47 to 18 events/h.[32] However, a subsequent study compared a modified tennis ball technique to CPAP in 20 positional OSA patients and found that CPAP was more effective at reducing the AHI.[33] The discomfort related to this method was a barrier for its use and resulted in poor long-term compliance, with less than 10% of patients reporting continued use 2.5 years after prescription.[34] However, new devices specifically designed to prevent supine sleep have been developed. Bignold et al. tested a position monitoring and supine alarm device. It recorded sleep position accurately and reduced both the supine time (from 19% to 0.4%) and AHI (25 events/h to 13 events/h).[35] Another device which is worn around the chest and vibrates when the patient lies supine was associated with good compliance (64% using more than 4 h/night) over 6 months.[36,37] Finally, a neck-worn device designed to restrict supine sleep showed benefits by improving the AHI (average reduction of 69%) and sleep architecture (decreased number of arousals and increased N2).[38] Therefore, more comfortable and effective devices may be used for positional therapy.

This study has several limitations. First, due to the invasiveness of the study, the sample size was fairly small. Nevertheless, the different collapsing groups were equally well represented and clear changes in the outcome variables were observed during natural sleep endoscopies. Second, a complete set of polysomnographic parameters, including the AHI could not be obtained for all patients due to the complexity of the protocol instrumentation. However, airflow and ventilation measurements were obtained under both study conditions, allowing comparison of changes in the functional size of the airway. Third, the instruments themselves could have affected the site of collapse and the flow rates. However, we believe this is unlikely because when the scope is in the velopharynx, it is not touching any of the airway structures. In addition, while the scope was touching the palate when it was placed in the oropharynx, the flow rates from these breaths were excluded from analysis. Finally, we note that a previous study has found that the upper airway is not altered by the presence of a catheter in the airway.[39]

In conclusion, improvement in pharyngeal patency with sleeping position is structure specific. Our findings suggest that the tongue may not play as important a role as previously thought. In particular, this study shows that lateral positioning for epiglottic collapse is quite effective. Therefore, if CPAP alternatives are being considered for these patients, then positional therapy is a potential option.

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DISCLOSURE STATEMENT

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2.2 Artigo 2: Citação Completa

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Retropalatal and retroglossal airway compliance in patients with obstructive sleep apnea

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ABSTRACT

Objectives: We hypothesized that preferential retropalatal as compared to retroglossal collapse in patients with obstructive sleep apnea was due to a narrower retropalatal area and a higher retropalatal compliance. Patients with a greater retropalatal compliance would exhibit a recognizable increase in negative effort dependence (NED).

Methods: Fourteen patients underwent upper airway endoscopy with simultaneous recordings of airflow and pharyngeal pressure during natural sleep. Airway areas were obtained by manually outlining the lumen. Compliance was calculated by the change of airway area from end-expiration to a pressure swing of -5 cm H_2O. NED was quantified for each breath as [peak inspiratory flow minus flow at -5 cm H_2O]/[peak flow] $\times$ 100.

Results: Compared to the retroglossal airway, the retropalatal airway was smaller at end-expiration ($p < 0.001$), and had greater absolute and relative compliances ($p < 0.001$). NED was positively associated with retropalatal relative area change ($r = 0.47$; $p < 0.001$).

Conclusions: Retropalatal airway is narrower and more collapsible than retroglossal airway. Retropalatal compliance is reflected in the clinically-available NED value.

1. Introduction

Obstructive sleep apnea (OSA) is caused by pharyngeal collapse during sleep and is associated with adverse health outcomes (Grandner et al., 2016; Reutrakul and Mokhlesi, 2017). Pharyngeal collapse can occur at the retropalatal level (soft palate), retroglossal level (tongue base), oropharyngeal lateral walls, and/or hypopharynx (epiglottis). Retropalatal collapse occurs more commonly (80–95%) than retroglossal collapse (40–55%) among OSA patients (Ravesloot and De Vries, 2011; Vroegop et al., 2014, 2013). The reasons for the preferential collapse of the retropalatal airway are not totally understood.

Previous imaging studies in OSA patients using optical coherence tomography during wakefulness have shown that the retropalatal airway is narrower than the retroglossal airway (Walsh et al., 2008). Additionally, endoscopic imaging during general anesthesia, in which airway collapse was produced by a gradual reduction in CPAP, has shown that the retropalatal space is narrower and collapses completely at a higher pressure than the retroglossal space (Isono et al., 1997). However, retropalatal and retroglossal within-breath compliances during phasic breathing in sleeping OSA patients have not been compared.

In addition to a lack of information about phasic airway narrowing in OSA, it is not known how much airway compliance (measured endoscopically) translates into the within-breath airflow changes that are a hallmark of flow-limited inspiration in OSA (Genta et al., 2014; Owens et al., 2014; Pamidi et al., 2017). The reduction from peak to mid-inspiratory airflow during inspiratory flow limitation is commonly known as "scooping" or more formally "negative effort dependence (NED)", and is easily recognized from inspection of the airflow shape during polysomnography. Given the association between cross-sectional area and airflow, we hypothesized that NED would reflect the compliance of the airway. To test these concepts, OSA patients were evaluated with upper airway endoscopy and simultaneous measurements of airflow and pharyngeal pressure during natural sleep.

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2. Methods

2.1. Subjects

Patients with a previous diagnosis of OSA were invited to participate in the study. The age range was 21 to 70 years. Subjects were excluded if they had heart failure, diabetes, or renal insufficiency, or if they were taking medications that could affect upper airway muscle function. The study was approved by the Institutional Review Board at Brigham and Women's Hospital. Written informed consent was obtained from all patients before participation in the study.

2.2. Instrumentation

The participants were instrumented with electrodes for sleep staging: electroencephalography (C4-A1, O2-A1), left and right electrooculography, and submental electromyography. After topical application of a decongestant (oxymetazoline 0.05%) and anesthetic (lidocaine 4%), a 5-French pressure catheter (Millar Instruments, Houston, TX) and a 2.8 mm-diameter pediatric bronchoscope (model BFXP-160F, Olympus, Tokyo, Japan) were passed through 2 sealed ports in a nasal mask. The catheter and the bronchoscope were then inserted through the left and right nostrils, respectively. The tip of the pressure catheter was placed at the level of the epiglottis. Subjects breathed via the nasal mask that was connected to a pneumotachometer (Hans-Rudolph, Kansas City, MO) and differential pressure transducer (Validyne, Northridge, CA) to measure airflow. Physiological signals and endoscopic videos were synchronized and saved using Spike 2 software (Cambridge Electronic Design, Cambridge, England). Electroencephalography, electrooculography, and electromyography data were sampled at 125 Hz. Pressure and flow data were captured at a sampling frequency of 500 Hz. Endoscopic images were sampled at 30 frames/second.

2.3. Protocol

The subjects were asked to sleep supine with the neck in a neutral position. The bronchoscope´s tip was initially placed in the velopharynx above the palate. In this position, several sequences of flow-limited breaths (lack of increase in flow despite decreasing pharyngeal pressure) were recorded. The endoscope was then advanced to the oropharynx to observe the oropharyngeal and hypopharyngeal structures (Fig. 1) under the same conditions. The position of the scope was adjusted if necessary to provide a clear view of both pharyngeal levels and to keep the entire lumen in the field of view.

2.4. Data analysis

Periods of NREM sleep during stable flow limitation at atmospheric pressure without arousals were considered for analysis (Azarbarzin et al., 2017). Sequences were discarded if the endoscopic image quality was not satisfactory (e.g. presence of secretions or insufficient view of the airway circumference).

Retropalatal and retroglossal images at three time points were captured for luminal area determination: 1) at the end of expiration, 2) at a pharyngeal pressure swing of -5 cm H_2O, 3) and at the peak negative inspiratory pressure. Retropalatal and retroglossal luminal areas were obtained by manually outlining the airway lumen using computer software (Image Processing Toolbox, Matlab, Natick, MA). Image distortion caused by the wide-angle endoscopic lens was digitally corrected before analysis. For each image, the software provided an area in pixels (Fig. 2). The pharyngeal pressure catheter was used as a reference to convert pixel number to absolute area, as previously described (Isono et al. (1993)). Briefly, the catheter diameter in each endoscopic image was manually measured in number of pixels at the level of the airway luminal outline (Fig. 2). Area in pixels was then converted to mm^2 using

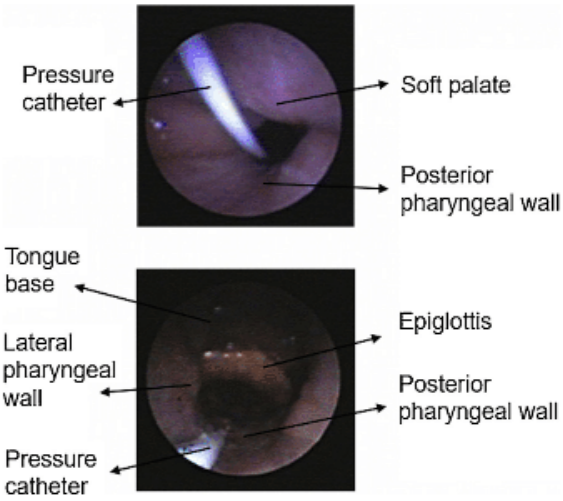

Fig. 1. Example of endoscopic views of retropalatal and retroglossal airway with anatomic landmarks identified.

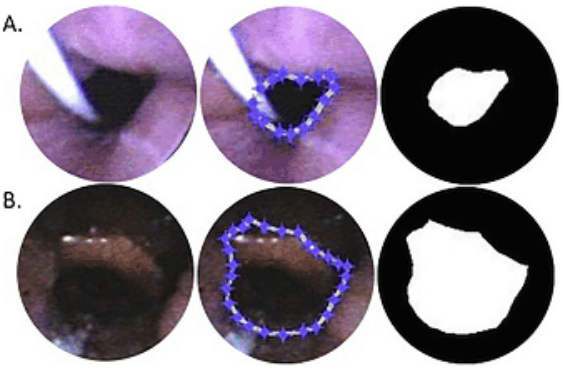

Fig. 2. Examples of retropalatal (A) and retroglossal (B) images showing the airway luminal outline. The catheter diameter was measured at the same plane of the luminal outline. The white images on the right highlight the airway lumen from which the number of pixels were counted. Luminal areas were calculated by converting the area in pixels to mm^2 using the conversion factor obtained with the known catheter diameter.

the conversion factor obtained with the known catheter diameter. Retropalatal and retroglossal airway absolute compliance was calculated as the change in luminal area/luminal pressure swing using the formula: ([luminal area at end-expiration] – [luminal area at a pharyngeal pressure swing of –5 cm H_2O]/5 cm H_2O). Relative compliance was calculated as the percent change in luminal area/luminal pressure swing. The same pressure swing of –5 cm H_2O was used for all calculations to control for the driving pressure through the airway. Minus 5 cm H_2O was chosen to guarantee that a minimum comparable pressure swing was achieved at both pharyngeal levels during flow limitation. NED was calculated for each breath included in the analysis using the formula: ([peak inspiratory flow] – [flow at a pharyngeal pressure swing of –5 cm H_2O]/peak inspiratory flow) × 100.

2.5. Definition of compliance

The strictest definition of compliance of a structure (upper airway) is the change in volume per change in extraluminal minus intraluminal pressure. We consider three factors in our definition: First, we note that

we use the term "compliance" in reference to the *cross-sectional compliance*; conceptually, the cross-sectional area dominates the effect on airflow obstruction. Second, we inherently take the extraluminal pressure to be equal to zero (i.e. atmospheric pressure outside the body) in our calculations; however, we acknowledge that opposing pharyngeal dilator muscle forces act during inspiration to partially maintain area for any given intraluminal pressure (theoretically, by achieving negative local extraluminal pressure). Thus, our measure of compliance, which is based on intraluminal pressure alone, is not a pure measure of pharyngeal tissue properties (e.g. under hypotonic conditions), but rather a reflection of the *effective compliance* observed during spontaneous breathing in sleep; it is this effective compliance that we consider is most relevant to the manifest pharyngeal obstruction. Our approach here is congruent with approaches to measure arterial compliance (Gamble et al., 1994; Wiinberg, 2000). Third, our measure is intentionally a dynamic measure, intended to capture effects on the time scale of the respiratory cycle, and may therefore be different to steady-state values. Rather than use the term *dynamic effective cross-sectional compliance*, we use the term *compliance* for ease of communication.

2.6. Statistical analysis

Descriptive values are presented as the mean ± standard deviation (SD) or the median [interquartile range] for continuous variables. Normal distribution was tested using the Shapiro-Wilk test. A Mann-Whitney U test was used for comparisons between peak inspiratory flow, the change in luminal areas and compliances at each pharyngeal level. Inspiratory time and peak negative pressure of retropalatal and retroglossal breaths were compared using a t-test. A Spearman rank order test was performed for correlation analyses between retropalatal and retroglossal luminal area changes and NED. Data analysis was performed using SPSS statistical software (version 20, SPSS Inc., Chicago, IL), and statistical significance was considered when the p value was < 0.05.

3. Results

Fourteen OSA patients (age 51 ± 5 years; 9 men and 5 women) were studied. Subjects' characteristics are presented in Table 1. We analyzed a total of 228 flow-limited breaths at the retropalatal level (16 ± 8 breaths per subject) and 142 flow-limited breaths (10 ± 6 breaths per subject) at the retroglossal level all during supine NREM sleep (Table 2).

3.1. Retropalatal and retroglossal luminal area and compliance

We assessed the luminal area of both pharyngeal levels at the end of expiration, at a pharyngeal pressure of –5 cm H_2O, and at the peak negative inspiratory pressure. An example of airflow, pharyngeal pressure, and both retropalatal and retroglossal endoscopic views from a representative subject are shown in Fig. 3. With a progressive reduction in pharyngeal pressure— from end-expiration (0 cm H_2O), to –5 cm H_2O, and then peak negative pressure (−11.4 ± 6 cm H_2O) — retropalatal luminal area fell markedly from 19.2 [23.9] mm^2 to 5.1 [9.1]mm^2, and finally 1.6 [2.2] mm^2. By contrast, the retroglossal luminal started from 55.0 [30.7] mm^2 and fell modestly to 43.5 [25.9] mm^2, and finally 33.2 [27.3] mm^2. On average, we found that the retropalatal luminal area was significantly smaller than the retroglossal luminal area at all three time points analyzed ($p < 0.001$) (Fig. 4).

Table 1
Subjects' characteristics.

Parameters	Values
Age (years)	51 ± 5
Sex (% men)	64
Body mass index, BMI (kg/m^2)	35 ± 6
Neck circumference (cm)	42 ± 4
Apnea-hypopnea index, AHI (events/hour)	56 ± 32
Supine apnea-hypopnea index, AHI (events/hour)	61 ± 31

Data presented as mean ± standard deviation.

Table 2
Comparisons of breaths selected for analysis at the retropalatal and retroglossal levels.

	Retropalatal breaths (n = 228)	Retroglossal breaths (n = 142)	p value
Peak inspiratory flow, L/s	0.25 [0.14]	0.26 [0.21]	0.265
Inspiratory time, sec	1.7 ± 0.3	1.6 ± 0.4	0.100
Peak negative pressure, cm H_2O	−11.9 ± 6	−10.5 ± 5	0.050
End-expiratory area, mm^2	19.2 [23.9]	55.0 [30.7]	< 0.001
Pressure swing of −5 cm H_2O area, mm^2	5.1 [9.1	43.5 [25.9]	< 0.001
Peak negative pressure area, mm^2	1.6 [2.2]	33.2 [27.3]	< 0.001
Absolute compliance, mm^2/cm H_2O	3.2 ± 2.1	2.1 ± 1.8	< 0.001
Relative compliance, %/ cm H_2O	11.9 ± 3.3	3.2 ± 2.4	< 0.001

Data presented as mean ± standard deviation or median [interquartile range].

For the entire group, retropalatal airway absolute compliance was slightly higher than retroglossal airway compliance (3.2 ± 2.1 vs 2.1 ± 1.8 mm^2/cm H_2O, $p < 0.001$). More notably, the percent reduction in the retropalatal luminal area from end expiration (0 cm H_2O) to a pharyngeal pressure swing of −5 cm H_2O was greater than the percent reduction in the retroglossal luminal area (63% ± 16 vs 17 ± 13%, $p < 0.001$); thus, retropalatal *relative compliance* was therefore substantially higher than retroglossal relative compliance (11.9 ± 3.3 vs 3.2 ± 2.4%/cm H_2O, $p < 0.001$).

In 9 out of 14 patients, the absolute retropalatal compliance was greater than the retroglossal compliance. Fig. 5 shows individual graphs of three representative patients. In all patients, the retropalatal luminal area at end expiration was smaller than the retroglossal area, and in most cases it was approximately half as large. Of the patients studied, six were judged to have a "posteriorly located tongue" at end expiration, meaning the tongue base was touching or pushing against the epiglottis at end expiration. In the other, eight patients, the tongue was "anteriorly located" during end expiration, meaning it was not touching the epiglottis and the vallecula was clearly visible. Nevertheless, in both of these groups the retropalatal area was smaller than the retroglossal area at all phases of the respiratory cycle, including at peak negative inspiratory pressure. The retropalatal luminal area in the patients with posteriorly located tongue was 26.8 ± 11.8 mm^2, whereas in the patients with an anteriorly located tongue, it was 27.2 ± 16.2 mm^2 ($p = 0.9$).

3.2. NED and compliance correlation

NED was positively associated with the percent change of retropalatal luminal area from end-expiration to a pressure swing of –5 cm H_2O ($r = 0.47$; $p < 0.001$), as shown in Fig. 6. This suggests that NED may be a surrogate marker for retropalatal airway compliance. However, the same did not appear to be true for the retroglossal airway, since we found that NED was negatively correlated with the percent change in retroglossal luminal area ($r = -0.17$; $p = 0.03$). Finally, according to the classification described in a previous work (Genta et al., 2017) six patients in this study had tongue-related obstruction defined by a posterior displacement of the tongue narrowing both the velopharynx and oropharynx, four patients had isolated palatal collapse and, three patients had collapse at the pharyngeal lateral walls. Patients with posteriorly located tongue were found to have a small amount of

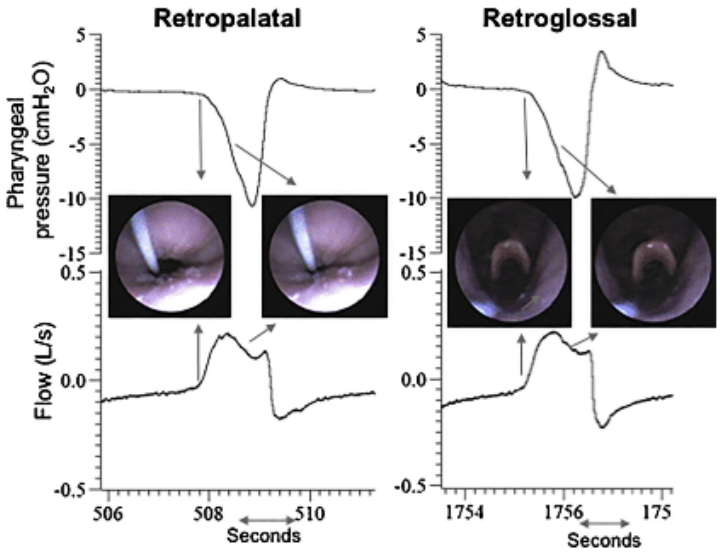

Fig. 3. Raw data of a representative subject showing the larger reduction of the retropalatal area proportionally to the retroglossal area for the same negative pharyngeal pressure swing. The arrows indicate the retropalatal and the retroglossal luminal areas at end-expiration (Pharyngeal pressure = 0 cm H_2O) and at a pharyngeal pressure swing of −5 cm H_2O. This subject's absolute retropalatal compliance was 1.8 mm^2/cm H_2O and the retroglossal was 1.0 mm^2/cm H_2O.

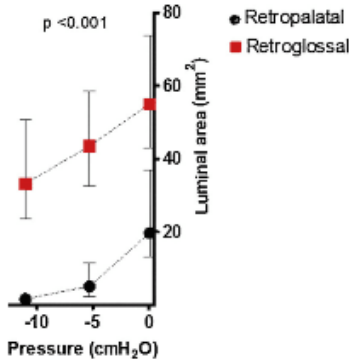

Fig. 4. Retropalatal luminal area was smaller than the retroglossal luminal area at all pharyngeal pressures, including end-expiration, −5 cm H_2O, and peak negative pharyngeal pressure ($p < 0.001$). The black dots represent the median luminal area from all breaths at retropalatal level analyzed at each time point (end-expiration, pharyngeal pressure swing of −5 cm H_2O and peak negative pressure). The red squares represent the median luminal area from all breaths at retroglossal level analyzed at each time point. The bars represent the interquartile ranges.

NED compared to the patients with an anteriorly located tongue (6 ± 5% vs 17.5 ± 10%, $p = 0.02$). This finding is consistent with our previous work (Genta et al., 2017).

4. Discussion

The major findings of the current study were:

1 The retropalatal airway was narrower than the retroglossal airway at all pharyngeal pressures, including end-expiration, −5 cm H_2O, and peak negative pharyngeal pressure.
2 Both absolute and relative retropalatal airway compliance were higher than retroglossal airway compliance.
3 NED was more closely associated with the dynamic reduction in retropalatal than retroglossal luminal area.

Our findings suggest that the higher vulnerability of the retropalatal airway to collapse is because it is both narrower and more compliant than the retroglossal airway. In addition, dynamic retropalatal airway narrowing is reflected in the inspiratory airflow shape (NED).

4.1. Retropalatal and retroglossal luminal areas

Our results agree with previous studies conducted during wakefulness showing that the retropalatal airway has the smallest cross sectional area in both awake normal subjects and patients with sleep disordered breathing (Cisonni et al., 2013; Schwab et al., 1995). Schwab et al. analyzed pharyngeal images obtained from MRI performed in a group of 68 awake subjects, including both normal controls and OSA patients (Schwab et al., 1995). They found that in all subjects the minimum cross-sectional area was in the retropalatal segment. Furthermore, computational fluid dynamics has also shown that the retropalatal region forms the most severe constriction within the pharynx in OSA patients (Cisonni et al., 2013). However, these studies were performed in awake subjects when pharyngeal muscle activation is known to be greater. Under general anesthesia, when pharyngeal muscle activity is diminished, Isono et. al. showed in 57 individuals that the maximum retropalatal area was smaller than the maximum retroglossal area (Isono et al., 1997). However, airway collapse in this study was achieved by a gradual reduction in CPAP, whereas our study examined the impact of the natural dynamic swings in inspiratory negative pressure on airway collapse.

Additionally, previous studies have shown that the retropalatal airway narrows more than the retroglossal airway from wakefulness to sleep (Borek et al., 2012; Trudo et al., 1998). Trudo et al. studied 15 normal subjects with MRI and showed a larger reduction in retropalatal versus retroglossal airway volume and area from wakefulness to sleep. However, only normal subjects were studied, and MRI provided only a static evaluation of the airway that was not synchronized to the respiratory cycle. In another study, Borek et al. compared retropalatal and retroglossal airway dimensions from wakefulness to sleep in OSA patients using drug-induced sleep endoscopy and found that the mean reduction in the retropalatal airway area was 84% compared to 39% in the retroglossal airway. However, again there are some methodological differences between this paper and our study. First, Borek and colleagues calculated percent change in the upper airway caliber from wake to sleep. This is a relative change in area, and thus values can be influenced by the starting size of the airway (small airways appear to have a greater compliance than large airways). Also, it was not a within-breath measurement and thus did not capture the dynamics

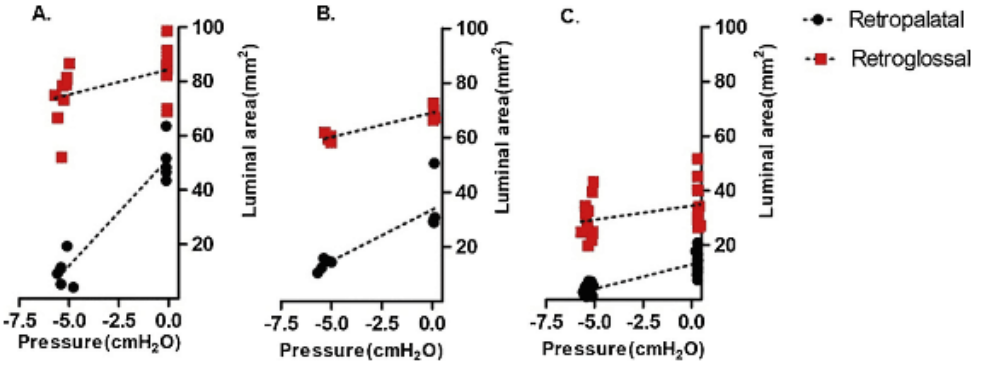

Fig. 5. Individual graphs of three representative subjects showing the absolute luminal area reduction from end-expiration to a pharyngeal pressure swing of −5 cm H_2O. Each black dot represents one breath at the retropalatal level both at end-expiration and at a pharyngeal pressure swing of −5 cm H_2O. Each red square represents one breath at the retroglossal level both at end-expiration and at a pharyngeal pressure swing of −5 cm H_2O. Subject A's absolute retropalatal compliance was 8.2 mm^2/cm H_2O and the retroglossal was 1.8 mm^2/cm H_2O ($p < 0.001$). Subject B's absolute retropalatal compliance was 3.7 mm^2/cm H_2O and the retroglossal was 1.8 mm^2/cm H_2O ($p = 0.01$). Subject C's absolute retropalatal compliance was 1.8 mm^2/cm H_2O and the retroglossal was 1.0 mm^2/ cmH_2O ($p = 0.02$).

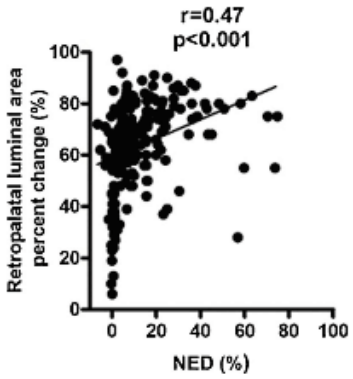

Fig. 6. NED was correlated with the retropalatal relative luminal area change (from end-expiration to a pharyngeal pressure swing of −5 cm H_2O).

during natural breathing. Moreover, propofol may influence upper airway collapsibility differently than sleep (Hong et al., 2013). In the current study we assessed absolute luminal areas using endoscopic images synchronized with the airflow signal during natural sleep. Nevertheless, our current findings, along with these previous studies, suggest that retropalatal area is smaller than retroglossal area across a broad range of conditions.

4.2. Retropalatal and retroglossal compliances

A handful of previous studies have examined pharyngeal compliance. Rowley et al compared changes in retropalatal and retroglossal cross-sectional area from wakefulness to sleep in two separate studies (Rowley et al., 1998, 2001). In the first study, they performed upper airway endoscopy in 8 normal subjects during wakefulness and natural sleep. Compliance was defined as the slope of the regression line of the retropalatal cross- sectional area versus pharyngeal pressure. They demonstrated that the retropalatal airway compliance during NREM sleep was significantly greater than the compliance during wakefulness. In another study, they analyzed the *retroglossal* airway compliance using a similar methodology in 10 normal subjects; they found no significant difference between the retroglossal compliance during NREM sleep and wakefulness. These studies showed that the retropalatal, but not the retroglossal, compliance increased from wakefulness to sleep. These previous studies are in line with our observations of an increased compliance from wakefulness to sleep. However, in both studies, only normal subjects were included. Additionally, the pharyngeal compliance measurements were made over a very small range of pharyngeal pressures (−1 to +1 cm H_2O) during eupneic breaths. In our study, we evaluated the luminal area changes at both pharyngeal levels in OSA patients during inspiratory flow limitation over a range of 5 cm H_2O of pharyngeal pressure.

4.3. Negative effort dependence

NED or "scooping" is a key feature of inspiratory flow limitation in OSA patients (Owens et al., 2014; Wellman et al., 2014). Previous work by our group showed that a low NED (absence of scooping) is a predictor of a posteriorly located tongue (Genta et al., 2017). The present study extends our previous observations by demonstrating that NED is associated primarily with the reduction in retropalatal, as opposed to retroglossal, luminal area. That is, greater NED is a recognizable manifestation of a greater retropalatal contribution to airflow obstruction in OSA. This finding provides the physiological framework for developing tools to discriminate between retropalatal and retroglossal contributions to OSA. Distinguishing between retropalatal and retroglossal airway collapse has implications for responses to therapies such as oral appliance therapy and pharyngeal surgery (Isono et al., 1999; Okuno et al., 2016).

4.4. Limitations

This study has several limitations. First, the use of the pressure catheter as a reference to convert dimensions into absolute area may contribute a degree of measurement uncertainty as it relies on subjective assessment of the catheter diameter in the endoscopic images. However, this methodology has been used previously (Launois et al., 1996; Rowley et al., 1998) and was considered adequate for making comparisons between the two pharyngeal levels. We note that our measures of percent luminal area change did not rely on precise catheter diameter assessment. Regardless, the differences in diameter between the retropalatal and retroglossal regions were quite large. Second, luminal area calculations may be affected by movement of the scope and difficulty defining the plane of measurements. To avoid this, only images without change in the relationship of the scope to anatomic landmarks in different planes were analyzed. Third, luminal area measurements from endoscopic images may also be subject to image distortion and amplification of the wide view lenses, as well as the ability to accurately detect the edge of the airway lumen. To minimize this, we corrected for lens distortion (Matlab function "lensdistort", available online at the Matlab Central File Exchange), and only images

in which the airway lumen was clearly visible were analyzed. Forth, we acknowledge that the pharyngeal pressure swing at the retropalatal level may be smaller than at the epiglottic region (where the pharyngeal pressure catheter was located). However, retropalatal compliance could be even greater if the pharyngeal pressure swing at the retropalatal level had been measured. Fifth, a pressure swing of −5 cm H_2O for luminal area and NED calculations was used in order to standardize the measurements for comparison, which may have underestimated NED. Finally, due to the invasiveness of the study, the sample size was small. Nevertheless, the 14 subjects represented a variety of collapse sites/mechanisms and the outcomes were clear and reached strong statistical significance.

5. Conclusion

In conclusion, the retropalatal airway is narrower and more collapsible than the retroglossal airway. Additionally, patients with a more pronounced retropalatal compliance exhibit a greater NED ("scooping" of inspiratory airflow); this finding paves the way for personalized interventions based on non-invasive recognition of the site of collapse in OSA.

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Disclosure statement

Drs. Marques, Genta, and Messineo declare no conflicts of interest. Dr. Taranto received personal fees as a consultant for Novion Pharmaceuticals and Cambridge Sound Management outside the submitted work. Dr. Sands received personal fees as a consultant for Cambridge Sound Management and Nox Medical outside the submitted work. Dr. Azarbarzin received personal fees as a consultant for Somnifix outside the submitted work. Dr. Wellman received personal fees as a consultant for Bayer, Somnifix, Cambridge Sound Management and Nox Medical outside the submitted work. Dr. White is the Chief Scientific Officer for Philips Respironics and is a consultant to Night Balance.

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2.3 Artigo 3: Citação Completa

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Structure and Severity of Pharyngeal Obstruction Determine Sleep Apnea Response to Oral Appliances

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At a Glance Commentary

Scientific Knowledge on the Subject: Some patients with obstructive sleep apnea (OSA) respond well to oral appliance therapy but others do not for reasons that are unclear. Available evidence suggests that tongue-related obstruction and less-severe collapsibility may promote successful oral appliance intervention. No study has previously combined structure and severity of pharyngeal obstruction to predict responses to oral appliance therapy.

What This Study Adds to the Field: Here we used gold-standard measurements to demonstrate that patients with a posteriorly-located tongue (natural sleep endoscopy) exhibit a preferential improvement in collapsibility (lowered "Pcrit") with oral appliances. We also show that patients with both posteriorly-located tongue and less severe collapsibility (predicted responder phenotype) exhibit greater improvements in OSA severity (reduction in event frequency by 83%, in contrast to 48% in predicted non-responders, $p<0.001$). Our study suggests that the structure and severity of pharyngeal obstruction determine the phenotype of sleep apnea patients who benefit maximally from oral appliance efficacy.

ABSTRACT

Objectives: A major limitation in the administration of oral appliance therapy for obstructive sleep apnea (OSA) is that therapeutic responses remain unpredictable. Here we tested the hypotheses that oral appliance therapy 1) reduces pharyngeal collapsibility preferentially in patients with posteriorly-located tongue, and 2) reduces OSA severity best in patients with a posteriorly-located tongue and less-severe baseline pharyngeal collapsibility.

Methods: Twenty-five OSA patients underwent upper airway endoscopy during natural sleep to assess tongue position (type I: vallecula entirely visible; type II: vallecula obscured; type III: vallecula and glottis obscured), as well as obstruction due to other pharyngeal structures (e.g. epiglottis). Additional sleep studies with and without an oral appliance were performed to measure collapsibility (critical closing pressure, Pcrit) and OSA severity (apnea-hypopnea index, AHI).

Results: Overall, oral appliance therapy reduced Pcrit by 3.9±2.4 cmH_2O (mean±SD) and the AHI by 69%. Therapy lowered Pcrit by 2.7±0.9 cmH_2O more in those with posteriorly-located tongue (types II-III) compared to those without (type I), $p<0.008$. Posteriorly-located tongue ($p=0.03$) and lower baseline collapsibility ($p=0.04$) were significant determinants of a greater-than-average AHI response to therapy. Predicted responders (type II-III *and* Pcrit<1 cmH_2O) exhibited a greater reduction in the AHI (83±9 vs. 48±8%$_{baseline}$, $p<0.001$) and a lower treatment AHI (9±6 vs. 32±15 events/hr, $p<0.001$) than predicted non-responders.

Conclusion: The site and severity of pharyngeal collapse combine to determine oral appliance efficacy. Specifically, patients with a posteriorly-located tongue plus less-severe collapsibility are the strongest candidates for oral appliance therapy.

Abstract Word Count: 240

Key words: pharyngeal collapsibility, endoscopy, Pcrit, phenotyping, personalized medicine

INTRODUCTION

Oral appliances are increasingly being prescribed for obstructive sleep apnea (OSA) treatment in patients who do not tolerate first-line therapy with continuous positive airway pressure (CPAP) or are unwilling to try CPAP[1]. In unselected patients, oral appliances are less efficacious than CPAP (i.e. less reduction in apnea-hypopnea index [AHI]), but can potentially achieve similar effectiveness at improving health outcomes, likely due to superior adherence to oral appliance therapy[2,3]. A major limitation to administration of oral appliances as a first-line therapy is that responses to therapy remain largely unpredictable based on patient characteristics[4]. The key baseline determinants of responses to oral appliance therapy remain unclear.

Available evidence suggests that at least two key pharyngeal factors determine oral appliance efficacy. First, patients with less-severe pharyngeal *collapsibility* have greater responses to therapy. Patients with a lower CPAP requirement, supine-dependent OSA, or a lower BMI—features of less-severe collapsibility—exhibit slightly better average responses[5,6]. Direct measurement of collapsibility (using CPAP drops, see Methods) has confirmed this relationship[7], but results have been inconsistent, indicating that collapsibility alone is not a sufficiently-strong predictor[8,9]. Second, available data suggest that the pharyngeal site or *structure* causing obstruction should be relevant. For example, in a small study (N=12) oropharyngeal collapse (based on a multi-tip pharyngeal pressure catheter) was a predictor of oral appliance responses[10]. Very recently, in a study run in parallel to our current investigation, tongue base obstruction (rather than palate, pharyngeal lateral walls, or epiglottis) seen on drug-induced sleep endoscopy was found to increase the likelihood of a strong oral appliance response[11]. Intuitively, patients with tongue-related obstruction are expected to exhibit a preferential improvement in

collapsibility with mandibular advancement. To date, no study has combined measures of *structure* and *severity* of collapsibility to explain the heterogeneity of oral appliance responses. Accordingly, in the current study we tested two specific hypotheses: 1) patients with posteriorly-located tongue exhibit a greater improvement in collapsibility with therapy, and 2) patients with posteriorly-located tongue and less-severe collapsibility exhibit greater reductions in OSA severity (AHI) with therapy. To test these hypotheses, patients underwent overnight sleep studies to assess the pharyngeal structure causing obstruction via natural sleep endoscopy, and to assess the acute effect of oral appliances on both collapsibility and OSA severity (AHI) versus baseline. Aspects of this study have been presented previously in abstract form[12].

METHODS

Participants

Patients with a previous diagnosis of OSA of any severity were invited to participate in the study. The age range was 21 to 70 years. Exclusion criteria included heart failure, central sleep apnea, periodontal disease, insufficient teeth (less than 8 teeth in each maxillary and mandibular arch), and temporomandibular joint dysfunction. The study was approved by the Institutional Review Board at Brigham and Women's Hospital. Written informed consent was obtained from all patients before participation in the study.

The study was registered on clinicaltrials.gov (NCT02489591). We emphasize that our study was not a trial aimed at assessing the efficacy of oral appliances in general; rather we aimed to explain heterogeneity of oral appliance efficacy using gold standard measures of structure and severity of pharyngeal collapsibility.

In total, we enrolled 43 participants. Four patients had dental conditions inappropriate for oral appliance use. Four patients could not sleep during the endoscopy night, and 2 patients could not

sleep during the baseline night. Six patients did not exhibit OSA on the baseline night without the oral appliance (AHI<10 events/hour) and were therefore ineligible. Two additional patients did not return for the sleep study with oral appliance (lost to follow-up). Overall, 25 patients with OSA (AHI>10 events/hour) completed the protocol (see Figure E1 in the online data supplement). 22/25 patients had an AHI>20 events/hr.

Protocol

The participants underwent three overnight sleep studies at least one week apart: night 1: sleep endoscopy; night 2: baseline Pcrit determination and AHI; and night 3: oral appliance Pcrit determination and AHI.

Oral appliance

All participants used a duobloc titratable oral appliance device holding the mandible fixed at their maximum comfortable protrusion. 8/25 patients used their own custom-fit devices (6 SomnoDent Herbst and 1 SomnoDent Classic, SomnoMed; 1 Narval CC, Resmed). A customizable titratable thermoplastic device (BluePro, BlueSom) was provided for the remaining 17/25 patients during the overnight studies. Devices were administered only for the single night of the oral appliance study.

Instrumentation

On all study nights, participants were instrumented with electrodes for sleep staging: electroencephalography (C4-A1, O2-A1), left and right electrooculography, and submental electromyography (125 Hz). Subjects breathed via a sealed nasal mask connected to a pneumotachometer (Hans-Rudolph, Kansas City, MO; Validyne, Northridge, CA) to measure airflow (500 Hz).

Night 1: Sleep Endoscopy

We performed natural sleep endoscopy at atmospheric pressure (off CPAP) to define the primary structure(s) contributing to pharyngeal obstruction for each participant. A 2.8 mm-diameter pediatric bronchoscope (model BFXP-160F, Olympus, Tokyo, Japan) was inserted through the right nostril following topical application of a decongestant (oxymetazoline 0.05%) and anesthetic (lidocaine 4%). Endoscopic images (30 frames/second) were synchronized with the sleep and respiratory signals and saved using Spike 2 software (Cambridge Electronic Design, Cambridge, England).

The participants were asked to sleep in the supine position with the neck in a neutral position. Initially, the bronchoscope´s tip was placed in the nasopharynx above the palate in order to observe the pattern of velopharyngeal narrowing/obstruction. The tip was then advanced to the oropharynx to observe the oropharyngeal and hypopharyngeal structures. The position of the scope was adjusted if necessary to include a close and clear view of each pharyngeal level.

The presence of the following structures causing collapse was identified: posteriorly-located tongue, isolated palatal collapse, pharyngeal lateral walls collapse, and epiglottic collapse[13-15]. Tongue position was categorized into three types based on the relationship between the tongue base and the epiglottis [16]: In type I the tongue base was clearly separated from the epiglottis, and the entire vallecula and glottis were visible. In type II the tongue base was touching the epiglottis (obliterating the vallecula) but not pushing the epiglottis posteriorly, thus allowing the glottis to be clearly seen. Finally, in type III the tongue base was pressing the epiglottis posteriorly such that the glottis could not be seen. The classification was performed by two investigators, and discrepancies were resolved by a third investigator.

Nights 2 and 3: Collapsibility and OSA severity

On each night (baseline, oral appliance) a split-night design was implemented, with the first ~2 hours of sleep used to assess passive pharyngeal collapsibility and the remainder of the night used to assess OSA severity (AHI) and other sleep characteristics.

Patients fell asleep in the supine position on 4 cmH_2O of CPAP delivered via a modified device (Pcrit 3000, Philips Respironics) capable of delivering pressures between +20 and -20 cmH_2O. Once asleep, CPAP was increased to the minimum level that eliminated snoring, hypopneas, and inspiratory flow limitation ("holding pressure"). Once stable stage N2 or N3 sleep was observed at the holding pressure, CPAP was abruptly dropped to various subtherapeutic levels for five breaths, with at least 1 min at the holding pressure in between drops. CPAP was dropped to progressively lower levels until complete obstructive apnea occurred. If there was an arousal during any pressure drop, the CPAP was returned to the holding pressure until stable sleep resumed. To quantify collapsibility, we assessed the passive pharyngeal critical closing pressure (Pcrit) as follows: data were manually-selected using custom-designed software (Matlab, The MathWorks, Natick, MA) to determine the peak inspiratory flow for breaths 3 and 4 during each pressure drop. Pcrit was determined as the zero-flow intercept from the linear regression of peak flow vs. nasal pressure, as previously described[17].

After ~2 hours of sleep, the CPAP device was turned off and disconnected. For the remainder of the night (~4 hours), participants were left to breathe freely without CPAP (but still with the oral appliance if night 3) for the assessment of sleep apnea severity (AHI). Respiratory events and arousals were scored by a registered polysomnographic technologist using recommended American Academy of Sleep Medicine guidelines[18]. Hypopneas were based on a ≥30% reduction

in airflow with either a ≥3% desaturation or arousal. The technologist was not aware of whether the sleep study was baseline or with oral appliance.

Statistical analysis

Descriptive characteristics are presented as mean ± SD for continuous variables unless specified otherwise. Data analysis was performed using SPSS statistical software (version 20, SPSS Inc., Chicago, IL), and MATLAB (Statistics and Machine Learning Toolbox, Mathworks, Natick MA, USA). Statistical significance was considered at $p<0.05$.

Primary analyses: 1.) To test the specific hypothesis that patients with posteriorly-located tongue exhibit a greater improvement in collapsibility with oral appliances (hypothesis 1), data from all 25 participants with AHI>10 at baseline were assessed. Multivariable linear regression was used to test for an association between the change in collapsibility with intervention (Pcrit on oral appliance minus Pcrit at baseline) and tongue-related obstruction (tongue types I, II, III as a continuous variable, denoted by 0, 0.5, 1 respectively), adjusting for additional contributors as needed (epiglottic, palate, lateral walls). 2.) To test the specific hypothesis that patients with posteriorly-located tongue and less-severe collapsibility respond preferentially to oral appliance treatment (hypothesis 2), our primary analysis was limited to patients with AHI >20 events/hour, to minimize the influence of random night-to-night variability (i.e. SD of AHI is ~9 events/hour)[19,20]. Logistic regression analysis was used to explain greater-than-average responses ("responders") versus poorer-than-average responses ("non-responders") to oral appliance therapy; a 70% historical average reduction in AHI was used as the cutoff to define responders/non-responders and thereby maximize statistical power[21]. Baseline Pcrit and tongue-position category (continuous variable, as above) were used to explain responder/non-responder status, while adjusting for baseline AHI (potential confounder).

Post-hoc analyses: To the above models, we sequentially included-then-removed the 3 additional endoscopic variables (presence versus absence of isolated palate, lateral walls and epiglottic obstruction) to test if these factors also contributed to change in collapsibility and AHI with intervention.

We also sought to define a subgroup of *predicted responders* based on structure and severity of obstruction who preferentially benefitted from oral appliance therapy. For this analysis we selected parameters (baseline Pcrit, posteriorly-located tongue isolated palate, lateral walls and epiglottic obstruction) using a forward stepwise procedure and sought to predict responder/non-responder status. Receiver operating characteristic analysis was used to select the optimal cutoff (maximizing sensitivity plus specificity). The predictive value of this model was then tested using leave-one-out cross validation (including variable selection procedure), i.e. each patient was defined as a "predicted responder" or "predicted non-responder" based on a modified version of the model that was developed with their data held out. Tongue position was modelled in three ways that were all made available for inclusion (continuous variable as above; types II and III pooled vs. I; types I and II pooled vs. III). Of note, backward-elimination could not be used as it would yield an over-specified model (i.e. there is always one site of collapse).

The primary outcome variable for hypothesis 2 was the AHI. Secondary outcome variables were arousal index, proportion of sleep in stage 1, and self-reported sleep quality (slept "better", "same", or "worse" on therapy versus baseline). These outcomes were compared between "predicted responders" and "predicted non-responders".

RESULTS

Twenty-five OSA patients (age 49 ± 11 years; 17 men and 8 women) were studied. The subjects' characteristics are presented in Table 1. Patients' maximal protrusion range was 7.3 ± 2.0 mm and the maximum comfortable advancement with the oral appliance was 75 ± 13% of the total range. Patients were categorized into 3 mutually-exclusive categories as follows: tongue type I (n=5); tongue type II (n=8); and tongue type III (n=12) (Figure 1).

Role of pharyngeal structure on the change in upper airway collapsibility

Overall, oral appliance therapy reduced Pcrit by 3.9 ± 2.4 cmH_2O, from a value of -0.6 ± 1.9 cmH_2O at baseline to -4.5 ± 2.7 cmH_2O on treatment (n=25, p<0.001). A reduction in Pcrit was evident within all three tongue type categories (Figure 2): in those with tongue types I, II, and III, oral appliance therapy lowered Pcrit by 2.6 ± 1.3 cmH_2O (n=5, p=0.019), 4.5 ± 2.7 cmH_2O (n=8, p<0.001) and 4.1 ± 2.5 cmH_2O (n=12, p<0.001) respectively.

Primary analysis: With tongue-related obstruction as a continuous variable (types I, II, III denoted 0, 0.5, 1), the ~2 cmH_2O greater reduction in Pcrit with tongue-related obstruction was not significant in univariate analysis (Table 2, Model 1), but became significant with the inclusion of epiglottic obstruction in the model analysis (Table 2, Model 2).

Epiglottic obstruction was associated with a non-significant additional reduction in Pcrit (~2 cmH_2O, Table 2, Models 2-3). Lateral wall obstruction and isolated palate obstruction were not significant determinants of the change in Pcrit (+1.0 cmH_2O for lateral wall obstruction; negligible effect of isolated palate). Pooling data from tongue types II and III led to stronger models (Table 2, compare Models 6-7 to models 1-2).

Role of pharyngeal structure and collapsibility on the responses to therapy

Overall, oral appliance therapy reduced the AHI by 69%, from a value of 56.7 ± 21.5 events/hr at baseline to 18.6 ± 15.8 events/hr on treatment (n=22, p<0.001). The effects of oral appliances on polysomnographic parameters (off CPAP) are shown in Table 3.

A reduction in AHI with oral appliance therapy was evident within all three tongue type categories: in those with tongue types I, II, and III, oral appliance therapy lowered AHI by 49 ± 10% (n=5, p=0.002), 85 ± 9% (n=7, p<0.001) and 68 ± 19% (n=10, p<0.001) respectively.

Primary analysis: Posteriorly-located tongue (continuous variable, see above) and lower baseline collapsibility were both significantly associated with greater odds of being a responder versus non-responder to oral appliance therapy (Table 4, Model 1; multivariable logistic regression), after adjusting for baseline AHI.

Neither epiglottic obstruction, lateral wall obstruction, nor isolated palatal collapse were independently associated with responses.

Defining the structure and collapsibility phenotype of responders to therapy

As distinct from the above hypothesis testing, we developed a phenotypic predictive model to define a subgroup of "predicted responders" and "predicted non-responders" based on pharyngeal structure and severity of obstruction. Forward stepwise logistic regression selected just two variables for inclusion: posteriorly-located tongue (defined as type II or III rather than type I) and Pcrit. The final prediction model was equivalent to the following: *Predicted responders* were defined by posteriorly-located tongue (tongue-related type II or III) *and* less-severe collapsibility (baseline Pcrit<1 cmH_2O). Before cross-validation, this approach detected responders accurately in 19/22 patients (86%), with positive predictive value of 11/13 (85%) and negative predictive value of 8/9 (89%). When this approach was repeated using left-out data

(cross-validation) results were similar: Accuracy was 18/22 (82%), positive predictive value was 10/12 (83%) and negative predictive value was 8/10 (80%). Notably, "predicted responders" exhibited a median reduction in AHI that was substantially greater than in "predicted non-responders" (83% versus 48%, $p<0.001$; see Table E1 in the online data supplement). This finding was upheld when including participants with $10<AHI<20$ events/hour (76% versus 48%, $p=0.003$).

DISCUSSION

The major findings of the current study were:

1. Patients with posteriorly-located tongue (type II or III) exhibited a greater improvement in pharyngeal collapsibility with oral appliance therapy.
2. The combination of posteriorly-located tongue and less-severe collapsibility (baseline Pcrit<1 cmH_2O) yielded a greater reduction in OSA severity with oral appliance.

The efficacy of oral appliances in OSA treatment is highly variable. Reported mean reductions in AHI range between 24% and 72%[4]. Therefore, investigators have sought predictors of oral appliance therapy success. In a large retrospective study that included 425 OSA patients, Sutherland et al. studied predictors using a classification and regression tree (CART) model that included anthropometric and polysomnographic variables (e.g. AHI and body-mass index)[22]. The final model resulted in a correct classification between responders and non-responders of only 64% (AUC = 66%). Upper airway endoscopy has also been used to predict oral appliance therapeutic success based on the improvement of pharyngeal narrowing with mandibular advancement. A recent study using upper airway endoscopy during wakefulness failed to predict response to oral appliance[23]. Another study performed during drug-induced sleep had a

reasonable sensitivity to predict therapeutic success (0.71%) but low specificity (0.33%)[24]. In the present study, a phenotypic predictive model that included the pharyngeal structure causing collapse identified during natural sleep endoscopy in combination with baseline pharyngeal collapsibility demonstrated good accuracy (82%) to detect responders to oral appliance therapy.

Posteriorly-located tongue and oral appliance therapy

Imaging studies with MRI have shown that oral appliances induce anterior movement of the tongue base[25,26]. A greater rate of success with oral appliances have been reported among patients with primary oropharyngeal collapse rather than velopharyngeal collapse[10,27]. Ng et al. studied 12 patients using multisensor catheters with and without mandibular advancement to determine upper airway closing pressures and the sites of collapse[10]. They found that all patients with primary oropharyngeal collapse achieved an AHI<5/hr with the oral appliance therapy. Using bilateral anterior magnetic stimulation of the phrenic nerve during wakefulness to identify the site of upper airway collapse, Bosshard et al. also found that patients with oropharyngeal collapse had better responses compared to those with velopharyngeal collapse[27]. However, both studies did not evaluate the specific pharyngeal structures causing obstruction (e.g. tongue versus epiglottis versus lateral walls). The current study adds to these previous observations by showing that patients with posteriorly-located tongue had greater improvements in collapsibility and OSA severity with oral appliance therapy.

Pharyngeal collapsibility and oral appliance therapy

Oral appliances are known to improve pharyngeal collapsibility in general[7,28-30]. Kato et al. evaluated six patients under general anesthesia with and without an oral appliance. They produced progressively increasing amounts of mandibular protrusion and found a dose-dependent improvement in pharyngeal closing pressure[28]. Similarly, Ng et. al found a significant

decrease in upper airway closing pressure (-1.6 ± 0.4 to -3.9 ± 0.6 cmH_2O) in ten patients with oral appliance therapy[29]. More recently, Edwards et. al reported improvements in upper airway collapsibility with oral appliance therapy under both passive (ventilation through a passive airway at eupneic ventilatory drive) and active (ventilation on zero CPAP when the muscles are maximally active) conditions[7]. In the present study, we found that overall oral appliance reduced Pcrit by 3.9 ± 2.4 cmH_2O. This finding is congruent with a recent study measuring Pcrit in seven patients during sleep at neutral bite and 100% mandibular advancement (0.7 ± 2.7 to -5.7 ± 4.1 cmH_2O)[30]. However, we extended previous observations by showing that oral appliances induce a larger Pcrit reduction among patients with posteriorly-located tongue as compared to those without posteriorly-located tongue (e.g. isolated palatal or isolated lateral walls collapse). We also were able to select an optimal baseline Pcrit cutoff (+1 cmH_2O) as a determinant feature for our phenotypic predictive model.

Oral appliances in severe OSA patients

Previous studies have shown that patients with severe OSA may be successfully treated with oral appliances, but they generally failed to predict the ideal candidate[9,31]. In the current study a reduction of 80% in AHI from 53 to 9 events/hr with oral appliance therapy was observed in the subgroup of predicted responders. Notably, 92% of these patients had severe OSA. These findings suggest that a prediction model that includes the presence of posteriorly-located tongue and a low pharyngeal collapsibility could be used to enable oral appliances to be recommended for treatment of OSA patients of any severity.

Limitations

This study has several limitations. First, due to the invasiveness of the studies, the sample size was necessarily small. However, the different structures causing pharyngeal collapse were well

represented, and clear changes in the outcome variables were observed. Second, the type of oral appliance was not standardized. Despite this limitation, we achieved sizable reductions in AHI with comparable mandibular advancement in all groups, suggesting that the treatment was generally effective. Third, we studied patients on oral appliances for a single night of therapy. It is often considered that mandibular advancement should be titrated gradually over weeks to yield maximum benefit; however we emphasize that our average single-night treatment effect (69% reduction in AHI) is nearly identical to the ~70% reduction observed in longer trials[32,33]. A gradual titration approach is likely helpful for subjective benefit. Indeed, our small study and single night of therapy was not enough to demonstrate differences in subjective benefit between subgroups, which we would expect to observe over time; further investigation is needed. Fourth, upper airway endoscopy during natural sleep and Pcrit measurement using CPAP drops are physiological methods not suitable for clinical practice. However, methods to assess the pharyngeal structure causing collapse using non-invasive airflow shape analysis have been developed[13-15]. Likewise, pharyngeal collapsibility can now be estimated from routine diagnostic polysomnography[34,35]. By identifying the phenotypic characteristics of responders, our study provides the foundation for the focused development of new methods to identify patients who have less-severe posteriorly-located tongue and are likely candidates for oral appliance therapy.

Conclusion

In conclusion, the pharyngeal structure causing obstruction and upper airway collapsibility are strong determinants of oral appliance efficacy. A prediction model that included posteriorly-located tongue and a less collapsible upper airway was able to accurately predict oral appliance therapeutic success.

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DISCLOSURES

Drs. Marques, Genta, and Messineo declare no conflicts of interest. Dr. Taranto received personal fees as a consultant for Novion Pharmaceuticals and Cambridge Sound Management outside the submitted work. Dr. Sands received personal fees as a consultant for Cambridge Sound Management, Nox Medical and Merck outside the submitted work. Dr. Azarbarzin received personal fees as a consultant for Somnifix outside the submitted work. Dr. Wellman received personal fees as a consultant for Bayer, Somnifix, Cambridge Sound Management and Nox Medical outside the submitted work. Drs. Wellman and Taranto have a financial interest in Apnimed Corp., a company developing pharmacologic therapies for sleep apnea. Their interests were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies. Dr. White is the Chief Scientific Officer for Philips Respironics and is a consultant to Night Balance.

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TABLES

Table 1. Participant characteristics

Parameters	Patients with AHI>10 (N=25)	Patients with AHI>20 (N=22)
Age (years)	49 ± 11	50 ± 12
Sex, M:F (N)	17:8	16:6
Body-mass-index, BMI (kg/m^2)	32.0 ± 7	32.5 ± 6
Neck circumference (cm)	40.8 ± 4.8	41.6 ± 4.3
Comorbidities, n (%)		
Hypertension	7 (28)	6 (27)
Diabetes	3 (12)	2 (9)
Hypercholesterolemia	3 (12)	3 (13)

Data presented as mean ± standard deviation.

Table 2. Effect of Oral Appliances on Collapsibility by Pharyngeal Structure

Parameters	Patients with AHI>10* (N=25)				Patients with AHI>20 (N=22)			
	N	β±SEM	p	F-test, p	N	β±SEM	p	F-test, p
Model 1:								
Intercept		-3.0±0.7	0.0003	0.14		-3.1±0.7	0.0004	0.10
Tongue-Related Obstruction	5:8:12	-1.7±1.1	0.14		5:7:10	-2.0±1.1	0.10	
Model 2:								
Intercept		-2.2±0.8	0.018	**0.022**		-2.4±1.0	0.014	**0.033**
Tongue-Related Obstruction	5:8:12	-2.7±1.1	**0.025**		5:7:10	-2.9±1.2	**0.026**	
Epiglottic Obstruction	21:4	-1.8±1.1	0.09		18:4	-1.4±1.0	0.18	
Model 3:								
Intercept		-3.7±0.8	<0.0001	0.072		-4.0±0.8	0.0001	0.14
Epiglottic Obstruction	21:4	-2.1±1.1	0.072		18:4	-1.8±1.2	0.14	
Model 4:								
Intercept		-4.4±0.6	<0.0001	0.17		-5.1±1.0	<0.0001	0.5
Lateral Wall Obstruction	18:7	1.2±0.9	0.17		17:5	1.3±1.8	0.5	
Model 5:								
Intercept		-4.0±0.7	<0.0001	0.9		-2.4±1.0	0.014	0.8
Isolated Palate Obstruction	18:7	-0.1±1.0	0.9		15:7	0.3±1.0	0.8	
Model 6:								
Intercept		-2.6±0.6	0.0002	**0.035**		-2.6±0.6	0.0002	**0.016**
Tongue Type II-III vs Type I	5:20	-1.8±0.8	**0.035**		5:17	-2.2±0.8	**0.016**	
Model 7:								
Intercept		-1.9±0.8	0.023	**0.009**		-2.0±0.8	0.022	**0.01**
Tongue Type II-III vs Type I	5:20	-2.7±0.9	**0.008**		5:17	-2.9±0.9	**0.006**	
Epiglottic Obstruction	21:4	-1.5±0.9	0.11		18:4	-1.3±1.0	0.20	

*Primary analysis. Multivariate linear regression model results are shown. The dependent variable is the change in collapsibility (critical collapsing pressure, Pcrit) on oral appliance therapy minus baseline (ΔPcrit). Model 1 describes the effect of tongue-related obstruction on ΔPcrit, with tongue-related obstruction modelled as a continuous variable (tongue types I, II and II were denoted by 0, 0.5, 1 respectively). Model 2 is Model 1 plus the additional effect of epiglottic obstruction (selected using forward-stepwise inclusion); further inclusion of isolated palate and lateral wall status did not improve the model. Models 3-5 describe remaining univariate relationships. Model 6 describes the effect of tongue-related obstruction with tongue types II and III pooled (i.e. type I is denoted by 0 and types II and III are denoted by 1). Model 7 is Model 6 with the additional effect of epiglottic obstruction. F-test p-values indicate significance of the overall model (versus a constant). Model weights were used to balance influence of unevenly-distributed subgroups.

Table 3. Sleep architecture and sleep disordered breathing parameters

	Patients with AHI>10 (N=25)			Patients with AHI>20 (N=22)*		
	Baseline	Oral appliance	p value	Baseline	Oral appliance	p value
Total sleep time (min)	180 ± 73	218 ± 62	**0.001**	166 ± 64	212 ± 63	**<0.001**
Sleep efficiency (%)	66 ± 18	77 ± 16	**<0.001**	63 ± 17	76 ± 16	**<0.001**
NREM 1 (%)[#]	38.8 ± 26.4	17.6 ± 13.3	**<0.001**	40.5 ± 27.1	18.5 ± 13.7	**<0.001**
NREM 2 (%)	44.1 ± 20.6	53.4 ± 12.9	0.05	43.4 ± 21.7	52.5 ± 12.4	**0.02**
NREM 3 (%)	4.6 ± 7.8	10.1 ± 12.0	**0.01**	4.0 ± 6.4	10.8 ± 12.6	**0.004**
REM (%)	13.1 ± 10.7	18.0 ± 9.3	**0.02**	12.8 ± 10.6	17.1 ± 9.2	0.07
Arousal index (events/hr)[#]	57.0 ± 30.2	29.5 ± 20.2	**<0.001**	60.9 ± 29.8	31.6 ± 20.7	**<0.001**
Total AHI (events/hr)[†]	51.6 ± 24.4	17.4 ± 15.3	**<0.001**	56.7 ± 21.5	18.6 ± 15.8	**<0.001**
AHI_{NREM} (events/hr)	52.0 ± 25.1	14.6 ± 15.8	**<0.001**	57.3 ± 21.7	16.1 ± 16.2	**<0.001**
AHI_{REM} (events/hr)	36.7 ± 25.4	24.8 ± 19.5	0.05	38.2 ± 26.2	26.0 ± 19.6	0.08
Mean SaO_2 (%)	97.5 ± 1.5	97.4 ± 1.9	0.88	97.3 ± 1.5	97.2 ± 4.0	0.70
Minimum SaO_2 (%)	85.7 ± 8.7	87.8 ± 7.6	0.19	86.2 ± 7.5	87.1 ± 7.8	0.38
Pcrit (cmH_2O)	-0.6 ± 1.9	-4.5 ± 2.7	**<0.001**	-0.3 ± 1.9	-4.6 ± 2.8	**<0.001**

*Primary analysis. [†]Primary outcome variable. [#]Secondary outcome variable. Data are presented as mean ± SD. AHI: apnea-hypopnea index; NREM: non-rapid eyes movement sleep; REM: rapid eyes sleep; SaO_2: arterial blood oxygen saturation.

Table 4. Structure and severity of obstruction explain oral appliance responses

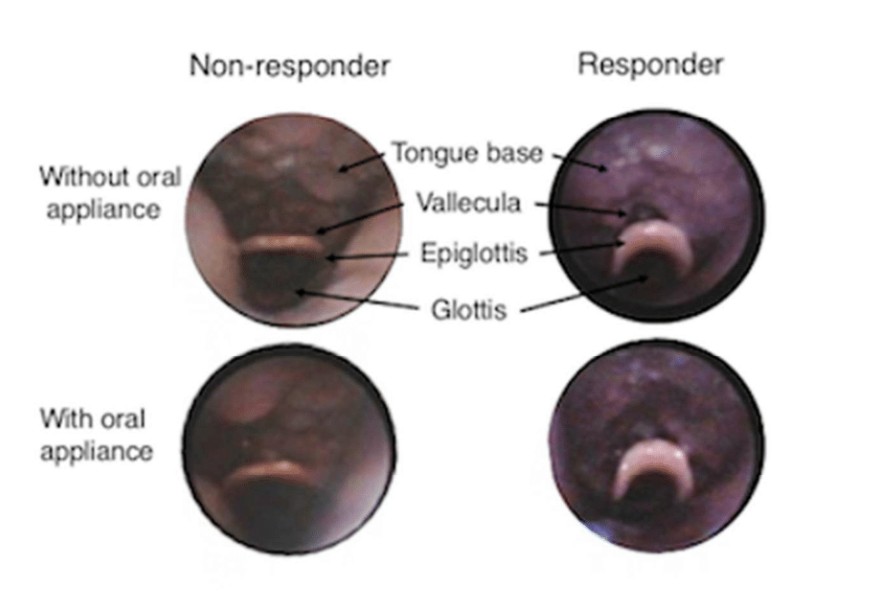
Parameters	Patients with AHI>10 (N=25)				Patients with AHI>20* (N=22)			
	β	Odds Ratio (95%CI)	p	F-test, p	β	Odds Ratio (95%CI)	p	F-test, p
Model 1:								
Intercept	-3.2		0.10		-6.9		0.10	
Posteriorly-located tongue	3.6	37 (1.3-1064)	**0.036**		13.5	$\times 7.5\times10^{5}$ ($2.7\text{-}2.0\times10^{11}$)	**0.034**	
Collapsibility, Pcrit (cmH_2O)	-0.7	÷2.1 (0.92-4.8)	0.075	**0.039**	-3.6	÷37 ($1.14\text{-}1.1\times10^{3}$)	**0.042**	**0.0005**
Baseline AHI (events/hr)	0.0		0.6		0.0		0.4	

*Primary analysis. AHI: apnea-hypopnea index; β represents the non-standardized regression coefficients. Odds ratios for Pcrit are shown as the increased odds for being a responder (greater reduction in AHI than a 70% historical average reduction) per unit *reduction* in Pcrit (denoted by division ÷ symbol). Neither the additional inclusion of epiglottic obstruction (p=0.36), isolated palate obstruction (p=0.21), nor lateral wall obstruction (p=0.9) to Model 1 were significant.

FIGURES LEGENDS

Figure 1. Examples of endoscopic views of 2 representative patients without and with oral appliance. The patient who did not respond to therapy was classified (off oral appliance) with tongue type I; Pcrit decreased from -1.7 to -5.2 cmH_2O, and the AHI reduced from 54 to 30 events/hr with oral appliance. The patient who responded to therapy was classified with tongue type II, Pcrit decreased from -1.0 to -9.0 cmH_2O, and the AHI reduced from 64 to 6 events/hr with oral appliance.

Figure 2. Individual data illustrating the effect of oral appliances on collapsibility (Pcrit) by tongue type. Presence of additional sites of collapse (P=palate; L=lateral walls; E=epiglottis) is marked along the corresponding patient circle. Open circles correspond to the patients with baseline AHI < 20 events/hr. Responders to oral appliance therapy are represented in green and non-responders are represented in red. The dashed box indicates the "predicted responders" to oral appliance therapy (tongue type II or III *and* Baseline Pcrit<1 cmH_2O).



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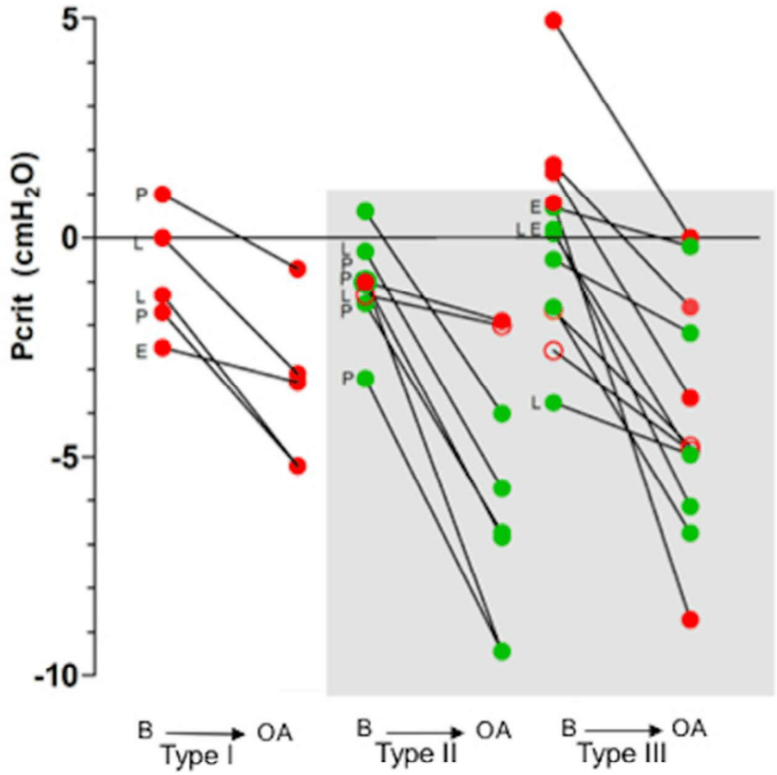
150x100mm (75 x 75 DPI)



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Online Data Supplement

Structure and Severity of Pharyngeal Obstruction Determine Oral Appliance Response in Obstructive Sleep Apnea

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Table S1. Effects of oral appliances in "predicted responders" versus "predicted non-responders"

	Predicted Responders Tongue Type II or II *and* Baseline Pcrit<1 cmH_2O (N=13)			Predicted Non-responders Tongue Type I *or* Pcrit>1 cmH_2O (N=9)			Group Difference p
	Baseline	Oral appliance	p	Baseline	Oral appliance	p	
Total sleep time (min)	151 ± 57	222 ± 60	**0.008**	177 ± 69	199 ± 69	0.013	0.843
Change, absolute	44 ± 50			48 ± 45			
Sleep efficiency (%)	66 ± 16	80 ± 14	**0.001**	59 ± 18	70 ± 19	0.021	0.672
Change, absolute	13 ± 11			11 ± 12			
NREM 1 (%)	38 ± 27	13 ± 13	**0.001**	44 ± 27	26 ± 11	0.051	0.404
Change, absolute #	-25 ± 21			-17 ± 21			
NREM 2 (%)	44 ± 24	51 ± 11	0.249	41 ± 18	53 ± 14	0.028	0.670
Change, absolute	7 ± 29			12 ± 13			
NREM 3 (%)	5 ± 7	17 ± 13	**0.002**	2 ± 5	3 ± 3	0.735	**0.011**
Change, absolute	11 ± 11			0 ± 5			
REM (%)	13 ± 10	18 ± 8	**0.048**	13 ± 11	15 ± 11	0.580	0.664
Change, absolute	6 ± 9			2 ± 12			
Total AHI (events/hr)	53 ± 20	9 ± 6	**0.001**	61 ± 23	32 ± 15	0.008	**<0.001**
Change, %*	83 ± 9			48 ± 8			
AHI_{NREM} (events/hr)	60 ± 25	7 ± 5	**<0.001**	55 ± 19	29 ± 17	<0.001	**0.012**
Change, absolute	49 ± 17			-30 ± 11			
AHI_{REM} (events/hr)	52 ± 26	27 ± 34	0.051	27 ± 21	39 ± 18	0.310	0.791
Change, absolute	16 ± 21			7 ± 31			
Arousal index (events/hr)	56 ± 30	25 ± 17	**0.001**	67 ± 30	41 ± 22	0.011	**0.023**
Change, %#	58 ± 19			34 ± 25			
Mean SaO_2 (%)	97 ± 2	97 ± 2	0.576	97 ± 1	97 ± 2	0.953	0.806
Change, absolute	0.2 ± 0.8			0.0 ± 1.7			
Minimal SaO_2 (%)	87 ± 7	88 ± 9	0.624	83 ± 8	85 ± 5	0.362	0.769
Change, absolute	0.6 ± 5.3			1.3 ± 5.9			
Subjective sleep quality with OA Vs baseline (% better)#	62			44			0.352
Mandibular advancement (%)	74 ± 7			73 ± 19			0.951

*Primary outcome. #Secondary outcome. Data presented as mean ± SD; AHI: apnea-hypopnea index. Data from patients with baseline AHI>20 events/hr are shown. Predicted responders and non-responders data were based on leave-one-out cross validation predictions.

Supplemental Figures

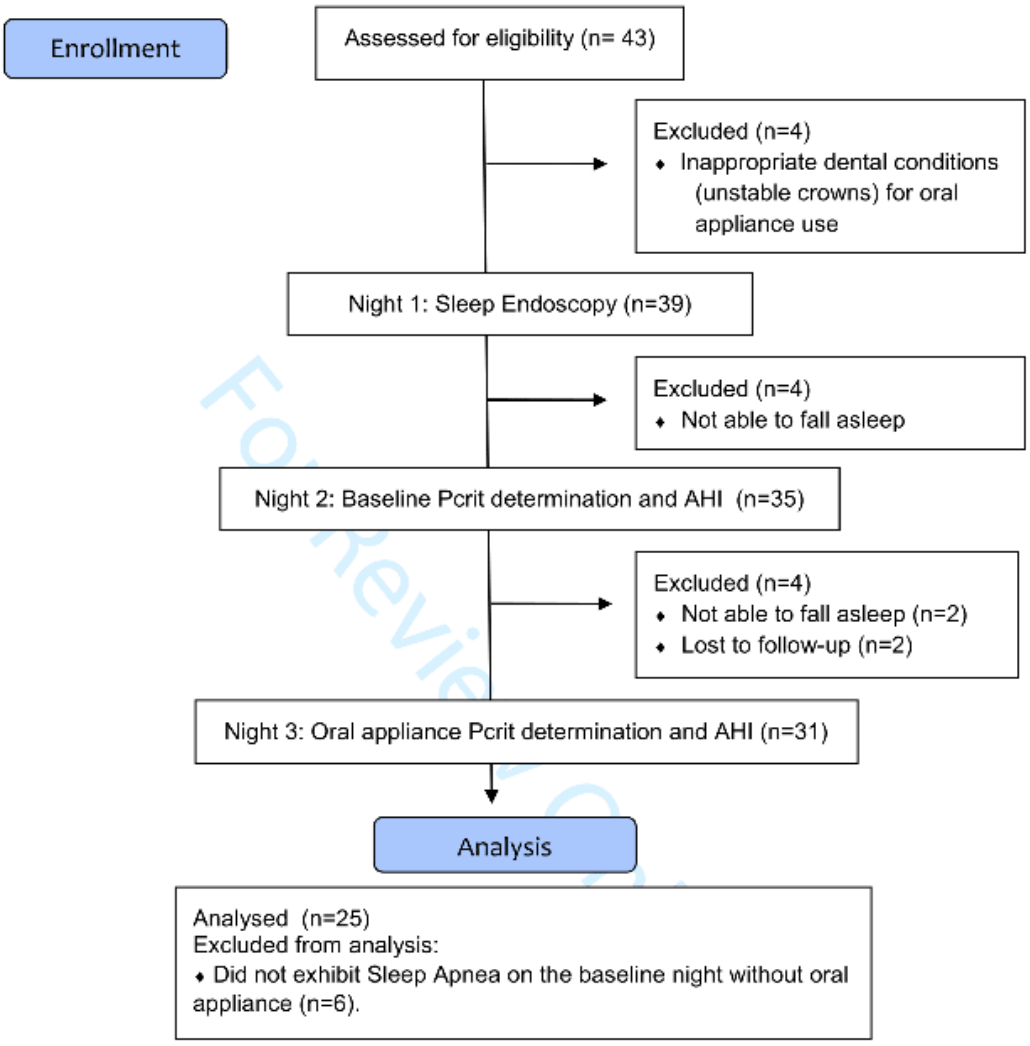

Figure S1. Study flow diagram. 43 participants were enrolled for the study. Four patients had dental conditions inappropriate for oral appliance use. Four patients could not sleep during the endoscopy night, and 2 patients could not sleep during the baseline night. Six patients did not exhibit OSA on the baseline night without the oral appliance (AHI<10 events/hour). Two additional patients did not return for the sleep study with oral appliance (lost to follow-up). Overall, 25 patients with OSA (AHI>10 events/hour) completed the protocol.

3 Análise crítica dos artigos

3.1 Análise crítica do artigo 1

No artigo 1, avaliamos o efeito da mudança de decúbito de supino para lateral na patência da faringe. Analisamos o impacto da mudança de decúbito no padrão de obstrução da faringe através de sonoendoscopia durante o sono natural. O padrão de obstrução da faringe foi agrupado em 3 tipos: associado à língua, caracterizado pela posição posteriorizada da língua; não associado à língua (obstrução provocada pelo palato mole ou paredes laterais da faringe) ou associado à epiglote. Nossa hipótese era de que pacientes com obstrução associada à língua apresentariam melhora significativa da patência faríngea na posição lateral devido ao alívio do efeito da gravidade que empurraria posteriormente a língua quando em posição supina.

Vinte e quatro pacientes participaram do estudo. Simultaneamente à sonoendoscopia, foram registrados o fluxo aéreo e a pressão faríngea durante o sono natural em ambos os decúbitos supino e lateral. Para a visualização do padrão de obstrução da faringe o endoscópio era inicialmente posicionado na velofaringe acima do palato mole e a seguir na orofaringe. Para a avaliação da patência da faringe, foram medidos os picos de fluxo inspiratório e volume minuto das respirações com limitação ao fluxo aéreo (ausência de aumento do fluxo apesar da negativação da pressão faríngea). Esse critério foi utilizado devido a correlação existente entre o pico de fluxo inspiratório e a área seccional transversa da faringe observado durante a limitação ao fluxo[37].

Contrário à nossa hipótese, os pacientes com obstrução relacionada à língua não apresentaram melhora quando mudaram de posição supina para lateral. Aqueles pacientes

que tinham colapso não associado à língua apresentaram melhora da patência da faringe caracterizada pelo aumento do pico de fluxo aéreo inspiratório e do volume minuto em decúbito lateral comparado ao supino. Particularmente interessante foi nosso achado de que os pacientes que apresentavam colapso da epiglote foram os que tiveram maior incremento da patência da faringe.

O comportamento da patência da faringe dos pacientes com obstrução relacionada à língua tem algumas implicações fisiopatológicas. Em pacientes com estreitamento da região orofaríngea, a obstrução da via aérea em posição supina não se explica apenas pela gravidade que empurra a língua posteriormente já que a mudança na direção gravitacional no decúbito lateral não resultou em melhora da patência faríngea nesses pacientes. Esse achado pode ser melhor compreendido ao se considerar a língua uma estrutura cilíndrica com volume constante (independente das forças agindo sobre ela como gravidade e ativação muscular)[38].

Nossos dados nos levaram a especular que o aumento do volume da língua (por depósito de gordura por exemplo), e por isso posteriormente posicionada, teria pouco espaço para se mover na orofaringe independente do decúbito supino ou lateral. No caso de pacientes com língua de menor volume e mais anteriormente posicionada, o movimento da língua decorrente da ativação muscular contra as forças de colapso consegue evitar a obstrução com a mudança do decúbito de lateral para supino[39].

Em relação a epiglote, a literatura mais recente tem indicado que a ocorrência de obstrução da epiglote é um fenômeno mais frequente do que previamente descrito. Estudos empregando a sonoendoscopia para a avaliação dinâmica da via aérea superior durante sono natural ou induzido têm relatado que até 30% dos pacientes com AOS podem apresentar obstrução de epiglote[40]. Além disso, alguns estudos indicaram que o tratamento com CPAP

pode não ser totalmente efetivo em pacientes com colapso de epiglote, assim como a terapia com AIO de avanço mandibular[41,42]. Dentre as técnicas cirúrgicas (epiglotectomia) não há estudos controlados sobre a eficácia de cada uma delas, porém são descritos potenciais efeitos colaterais. Os achados do nosso estudo sugerem que os pacientes portadores de AOS com obstrução da epiglote podem se beneficiar da terapia posicional. Dessa forma, a identificação do padrão de obstrução da via aérea superior, em especial a presença de obstrução da epiglote, contribui para a individualização na recomendação da terapia posicional.

Dentre as limitações deste estudo, a primeira está relacionada a sua natureza fisiológica com instrumentação para visualização da via aérea superior durante o sono e medidas de fluxo aéreo que restringiram o número de voluntários. Entretanto, os diferentes padrões de obstrução avaliados foram bem representados e foram possíveis análises objetivas para o desfecho de patência da faringe. A presença do endoscópio e do cateter de pressão na via aérea dos pacientes poderia influenciar nas medidas de fluxo aéreo realizadas. Para minimizar esse efeito, as medidas de pico de fluxo inspiratório e volume minuto das respirações em que o endoscópio estava posicionado na orofaringe não foram incluídas na análise. Além disso, um estudo prévio demonstrou que a colapsabilidade da via aérea não se altera com a presença de um cateter faríngeo[43].

Na medida em que análises não-invasivas do fluxo aéreo respiratório para identificação dos padrões de obstrução faríngea têm sido desenvolvidas, os pacientes com obstrução da epiglote poderão ser mais facilmente reconhecidos e encaminhados para terapia posicional.

3.2 Análise crítica do artigo 2

Na AOS a obstrução da região da velofaringe é mais frequente do que da orofaringe[32,33]. Um dos motivos para o predomínio de colapso palatal é que a velofaringe é mais estreita do que a orofaringe[44]. Outro possível mecanismo, que ainda não havia sido estudado, para o predomínio de colapso da velofaringe seria que a complacência do palato (estrutura mais delgada e leve) fosse maior do que a complacência das estruturas da orofaringe incluindo a língua.

No artigo 2, avaliamos o estreitamento da velofaringe e da orofaringe durante a inspiração e calculamos a complacência dessas estruturas por meio de medidas de área e pressão faríngea. Nossos achados indicaram que a velofaringe apresenta menor área que a orofaringe, independente da pressão faríngea. Nós observamos também que a velofaringe tem maior complacência do que a orofaringe. Além disso, notamos que a variação da área da velofaringe se associava ao fenômeno da dependência ao esforço negativo (DEN). DEN se refere à redução do fluxo aéreo inspiratório após o pico inicial por interferência da pressão inspiratória negativa[45]. Esse fenômeno tem sido observado em muitos pacientes com AOS, levando a variabilidade de formatos de curvas inspiratórias. Os dados deste artigo confirmam que as estruturas da faringe envolvidas na obstrução da via aérea têm complacências diferentes, gerando diferentes graus de DEN e, consequentemente, diferentes padrões de curva de fluxo aéreo inspiratório.

A maior limitação deste artigo é que as medidas de área dos lúmens nas regiões da velofaringe e orofaringe por meio da sonoendoscopia podem ser afetadas por movimentos do endoscópio e distorções de imagem devido às propriedades da lente do endoscópio (grande

angular). Porém, foram utilizados marcos anatômicos bem estabelecidos para as medidas e correção da distorção da imagem por software de processamento de imagens.

Para o futuro, por meio de análises não-invasivas das curvas de fluxo inspiratório poderá se inferir sobre a presença de obstrução predominante de velofaringe ou orofaringe. Esse reconhecimento tem um potencial papel na indicação de tratamentos cirúrgicos faríngeos para a AOS.

3.3 Análise crítica do artigo 3

O AIO tem sido amplamente indicado para o tratamento da AOS. Porém, a redução média do IAH com o uso do AIO varia entre 24 a 72%[46]. A variabilidade individual na resposta ao tratamento com AIO representa um grande desafio na indicação dessa modalidade terapêutica. Alguns fatores relacionados aos pacientes como idade mais jovem, sexo feminino e pacientes com menor índice de massa corpórea (IMC), além de IAH mais baixos tem acurácia variável como preditores de sucesso terapêutico[19]. Por outro lado, parâmetros polissonográficos como predominância de eventos respiratórios no estágio do sono REM e AOS posicional (predominância de eventos obstrutivos no decúbito dorsal) não se mostraram bons preditores para a eficácia do tratamento com AIO de avanço mandibular[47] Assim, não é possível predizer com acurácia a resposta ao AIO no controle da AOS.

A hipótese do artigo 3 era que os dois maiores determinantes para o sucesso terapêutico do AIO seriam a estrutura faríngea envolvida na obstrução e a colapsabilidade da via aérea superior definida pela Pcrit.

Vinte e cinco pacientes participaram do estudo, que contava com três noites de avaliação. A primeira para realização de sonoendoscopia. Nas outras duas noites, foram realizadas polissonografias com e sem o AIO para determinação da gravidade da apneia e da Pcrit. Mostramos que as maiores reduções da colapsabilidade faríngea com o AIO ocorreram nos pacientes com obstrução associada à língua, caracterizada pela posição posteriorizada da língua. A presença da língua posteriorizada, combinada com menor colapsabilidade da faringe no momento inicial foram determinantes de melhor resposta terapêutica demonstrada pela maior redução do IAH com o AIO.

A completa caracterização do colapso da via aérea superior nos pacientes com AOS, considerando tanto as estruturas quanto a colapsabilidade faríngea durante o sono natural, contribuiu para compreender melhor porque alguns pacientes apresentam boa resposta ao tratamento com AIO enquanto outros pacientes não apresentam resposta. Nossos dados indicaram um modelo fenotípico preditor de reposta terapêutica com AIO que combina a baixa colapsabilidade faríngea (Pcrit < 1 cmH_2O) com a presença da língua posteriorizada.

Vale ressaltar que rotineiramente na prática clínica muitos profissionais não consideram a possibilidade do tratamento com AIO para pacientes com AOS grave. Entretanto, muitos desses pacientes não se adaptam ao CPAP ou não desejam usar o CPAP e permanecem sem nenhum tratamento, expostos a todas as consequências deletérias da doença[9]. Neste estudo o subgrupo de pacientes para os quais o modelo preditor apontou resposta positiva ao AIO apresentou redução de 80% no IAH (de 53 para 9 eventos/hora) e a grande maioria desses pacientes tinha AOS grave (IAH >30 eventos/hora). Nossos achados sugerem que a recomendação do AIO para tratamento da AOS baseada nos fenótipos

fisiopatológicos de colapso faríngeo pode aumentar a acurácia na predição de eficácia do tratamento.

Assim como nos outros dois artigos já comentados anteriormente, empregamos neste estudo medidas fisiológicas da obstrução da faringe na AOS com três noites de avaliação o que limitou o número de voluntários. Além disso, as avaliações foram pontuais e não a longo prazo. Entretanto, nosso objetivo era avaliar o efeito imediato do AIO sobre a Pcrit e o IAH.

Apesar da sonoendoscopia em sono natural e da medida da Pcrit com manobras de redução de CPAP não serem métodos de avaliação de fácil execução e usualmente reservados a pesquisa, trabalhos bem recentes têm indicado a possibilidade de predição dessas informações por meio de sinais da polissonografia diagnóstica padrão[48]. Ao distinguir as características fenotípicas dos pacientes que respondem positivamente ao uso do AIO, o nosso estudo fornece fundamentos para identificar os pacientes candidatos a essa modalidade terapêutica.

4 Conclusões

Os achados dos estudos realizados nos permitem concluir que o padrão de obstrução faríngeo e a colapsabilidade da via aérea superior são fatores determinantes na resposta individual às modalidades terapêuticas alternativas para tratamento da AOS.

Os pacientes com colapso de epiglote apresentaram melhora da patência da faringe com o decúbito lateral e assim podem se beneficiar da terapia posicional para AOS. A região retropalatal é mais estreita e apresenta maior complacência que a região retroglossal em pacientes com AOS, e a identificação da presença de obstrução predominante retropalatal por de análises não-invasivas da curva respiratória tem um potencial papel na indicação de tratamentos cirúrgicos faríngeos para a AOS. Finalmente, os pacientes com língua posteriorizada e menor colapsabilidade da faringe, mesmo com AOS grave, são bons candidatos para o uso do AIO para tratamento da doença.

A estratégia de se investigar e conhecer melhor os fenótipos fisiopatológicos da AOS pode contribuir para que mais modalidades terapêuticas de forma mais personalizada sejam oferecidas aos pacientes.

5 Anexos

5.1 ANEXO A – Projeto de pesquisa aprovado pela CAPPesq

CARACTERIZAÇÃO DO COLAPSO DA VIA AÉREA SUPERIOR NA SELEÇÃO DE PACIENTES CANDIDATOS AO USO DE APARELHO INTRA-ORAL PARA TRATAMENTO DA APNEIA OBSTRUTIVA DO SONO

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Resumo:

A Apneia Obstrutiva do Sono (AOS) é caracterizada por obstrução recorrente da faringe durante o sono. A adesão ao tratamento padrão-ouro com CPAP (Continuous Positive Airway Pressure) não é a ideal, variando de 30 a 60%. Faz-se necessário o aperfeiçoamento de terapias alternativas ao CPAP. Dentre elas, os aparelhos intra-orais (AIO) de avanço mandibular tem sido cada vez mais recomendados por sua boa aceitação. Porém, a variabilidade individual na resposta ao tratamento com AIO representa um grande desafio na indicação dessa modalidade terapêutica. A sonoendocopia envolve a avaliação dinâmica da faringe durante o sono e também têm sido empregada para visualizar a magnitude e padrões de obstrução faríngea com e sem avanço mandibular. A pressão crítica de fechamento da faringe (Pcrit) é um método de avaliação da colapsabilidade da via aérea superior realizada durante o sono. Os objetivos do trabalho são correlacionar a estrutura de colapso faríngeo com alterações na colapsabilidade faríngea (Pcrit) associada ao uso do AIO e determinar o limiar da Pcrit preditor de resposta positiva ao tratamento com AIO para cada uma das estruturas de colapso faríngeo. A hipótese do estudo é que a estrutura faríngea envolvida na obstrução e a colapsabilidade da via aérea superior definida pela Pcrit predizem o sucesso terapêutico dos AIOs. Participarão deste estudo 40 pacientes de ambos os sexos, na faixa etária de 18 a 70 anos, com diagnóstico de AOS (índice de apneia-hipopneia> 5 eventos/hora). Os pacientes serão submetidos a visualização endoscópica da via aérea superior durante sono natural para identificação das estruturas faríngeas a determinação da Pcrit e IAH na presença e na ausência do aparelho intra-oral de avanço mandibular.

Palavras-chave: apneia obstrutiva do sono, aparelho intra-oral, sonoendoscopia, colapsabilidade faríngea.

1. Introdução:

A apneia obstrutiva do sono (AOS) é caracterizada por obstrução recorrente da faringe durante o sono, resultando em hipóxia intermitente e fragmentação do sono(1). Os sintomas diurnos como sonolência excessiva, bem como sua associação com consequências cardiovasculares, metabólica, neurocognitivas e qualidade de vida reduzida demandam tratamento adequado(2)(3). O tratamento da AOS com CPAP (Continuous Positive Airway Pressure) é o mais eficaz, porém a adesão relatada em diversos estudos não é a ideal (30 a 60% de adesão)(4). Dessa forma, torna-se essencial o desenvolvimento e aperfeiçoamento de terapias alternativas ao CPAP.

A sonoendocopia envolve a avaliação dinâmica da faringe durante o sono (5) e também têm sido empregada para visualizar a magnitude e padrões de obstrução faríngea com e sem avanço mandibular(6)(7). Muitos centros realizam a sonoendoscopia durante sedação com midazolam ou propofol, o que pode aumentar a colapsabilidade da faringe(8). A sonoendoscopia permite a avaliação do nível e estrutura associada à obstrução da faringe. Nos pacientes com AOS, a obstrução da via aérea é causada por colapso de uma ou mais estruturas faríngeas: palato mole, paredes laterais da orofaringe, base da língua e epiglote. A estrutura faríngea causadora da obstrução e sua associação com o resultado do tratamento com aparelhos intra-orais também têm sido considerada um potencial preditor de resposta(9).

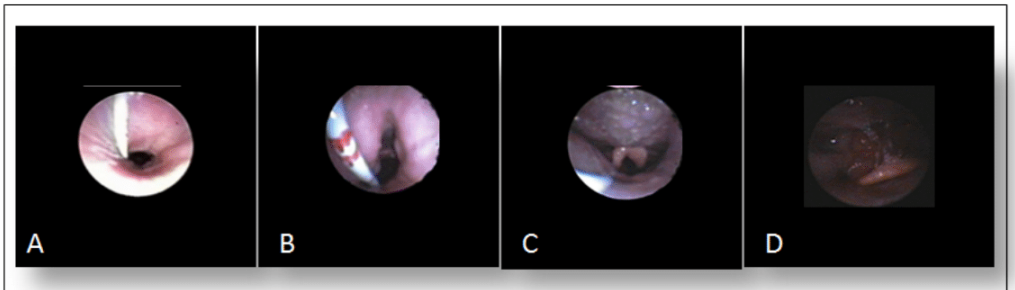

Figura 1: Visualização endoscópica da obstrução faríngea. A) Palato mole ; B)Paredes laterais; C)Base de lingua; D) Epiglote.

Os aparelhos intra-orais (AIO) têm sido amplamente indicados para o tratamento da AOS. Os dispositivos de avanço mandibular são os mais comumente empregados, porém as taxas de sucesso terapêutico (resolução da AOS ou Indice de Apneia/Hipopneia-IAH <5 eventos/hora) variam entre 29% a 71% conforme o estudo(10)(11). Pacientes portadores de AOS submetidos à sonoendoscopia que apresentaram melhora da patência da faringe após a colocação do aparelho de avanço mandibular, apresentaram melhora mais significativa da AOS do que pacientes sem melhora do calibre da faringe.(12). Os mecanismos de ação do aparelho intra-oral não são totalmente compreendidos. Estudos de imagem realizados em pacientes acordados mostram que o avanço mandibular com os AIO aumenta o calibre da faringe, predominantemente nas dimensões laterais da região da velofaringe, possivelmente devido às conexões de tecidos moles entre a língua e as paredes faríngeas laterais(13). Entretanto, são necessários mais estudos sobre o efeito dinâmico do avanço mandibular nas estruturas e colapsabilidade faríngeas, em especial durante o sono natural.

A variabilidade individual na resposta ao tratamento com AIO representa um grande desafio na indicação dessa modalidade terapêutica. Vários fatores relacionados aos pacientes como idade mais jovem, gênero feminino e pacientes não obesos além de índices de apneia/hipopneia mais baixos já foram sugeridos como indicadores de sucesso terapêutico(14)(15). Entretanto, completa resolução da AOS com uso de AIO pode ocorrer em pacientes mais graves ou mais obesos(16)(17)(18).

Cefalometria tem sido usada para identificar características anatômicas relacionadas a resposta terapêutica com AIO favorável, porém com resultados inconsistentes(19). Recente revisão da literatura sobre o tema sugere que nenhum parâmetro cefalométrico, como comprimento de palato mole e planos mandibular e maxilar, apresentou evidência suficiente para ser usado confiavelmente na predição de resposta favorável aos tratamentos não-CPAP (20).

As informações reportadas através de polissonografia também não mostraram valor preditivo para resposta terapêutica com AIOs. Os fenótipos polissonograficos com AIH predominante no estágios do sono REM ou não REM e AOS posicional (IAH em posição supina e não supina) não se mostraram bons preditores para a eficácia do tratamento com AIO de avanço mandibular (21).

A pressão crítica de fechamento da faringe (Pcrit) é um método de avaliação da colapsabilidade da via aérea superior realizada durante o sono, sendo definida como a pressão na via aérea na qual ocorre o colapso da faringe (22). O efeito do avanço mandibular na colapsabilidade da via aérea superior já foi demonstrado em indivíduos normais e portadores de apneia leve (5 <IAH< 15) durante sono induzido com midazolam (23)(24). A Pcrit apresentou significante redução (5,4cmH2O em média) com avanço mandibular médio de 7mm. Em outro estudo realizado em pacientes sob anestesia geral, a mandibula foi avançada em 2, 4 e 6mm e resultou em redução da Pcrit dose dependente (25).

Nós propomos que os dois maiores determinantes basais para o sucesso terapêutico dos AIOs são a estrutura faríngea envolvida na obstrução e colapsabilidade da via aérea superior definida pela pressão crítica de fechamento da faringe (Pcrit). Nossa hipótese é que os AIO de avanço mandibular são:

1- estrutura-específicos e vão funcionar de maneira ideal a depender da estrutura primariamente causadora da obstrução ;

2- apresentam capacidade limitada de melhorar a patência da via aérea superior e serão mais efetivas em pacientes com faringe menos colapsável.

A completa caracterização do colapso da via aérea superior nos pacientes com AOS considerando tanto as estruturas quanto a colapsabilidade faríngeas durante o sono natural permitirá compreender porque alguns pacientes apresentam boa resposta ao tratamento com AIO enquanto outros pacientes não apresentam resposta. Além disso, essas informações em conjunto

poderão ser utilizadas como instrumento de seleção dos pacientes candidatos ao uso de AIO de avanço mandibular para tratamento da AOS. A fim de caracterizar o colapso da via aérea superior e a resposta ao tratamento com AIO, pacientes com AOS serão submetidos a visualização endoscópica do colapso faríngeo durante sono natural e a determinação da Pcrit e IAH na presença e na ausência do aparelho intra-oral de avanço mandibular.

2. Objetivos:

2.1)Correlacionar a estrutura de colapso faríngeo com alterações na colapsabilidade faríngea (Pcrit) associada ao uso do Aparelho Intra-Oral.

2.2)Determinar o limiar de Pcrit preditor de reposta positiva ao tratamento com Aparelho Intra-Oral para cada uma das estruturas de colapso faríngeo.

3. Métodos:

3.1) Polissonografia:

Os pacientes serão monitorizados durante a noite através de dois canais de eletroencefalograma (C3-A2, O2-A1), dois canais de eletro-oculograma e eletromiografia submentoniana.

3.2) Pressão critica de fechamento da faringe (Pcrit)

Os indivíduos usarão uma máscara nasal conectada a um pneumotacógrafo aquecido (modelo 3700A, Hans Rudolf, Kansas City, MO) e um transdutor de pressão diferencial (Validyne, Northbridge, CA) para medição do fluxo aéreo. Os sinais amostrados serão registrados em um

sistema de aquisição de dados Spike2 (Cambridge, UK). Um dispositivo de CPAP modificado (Philips Respironics, Murrysville, PA) capaz de gerar pressões positivas e negativas será conectado à máscara. As medidas da pressão de colapso da faringe serão realizadas em decúbito dorsal.

Após o início do sono, a pressão de CPAP será aumentada a fim de se suprimir a limitação ao fluxo aéreo. Esse nível de pressão será usado como a pressão de manutenção de CPAP para cada indivíduo. Assim que pelo menos 2 minutos de sono nos estágios 2 ou 3 tiverem sido alcançados, a pressão de CPAP será reduzida abruptamente por 5 respirações. As manobras de redução da pressão de CPAP serão repetidas com pressões progressivamente menores para induzir a limitação ao fluxo aéreo e negativação da pressão intraluminal.

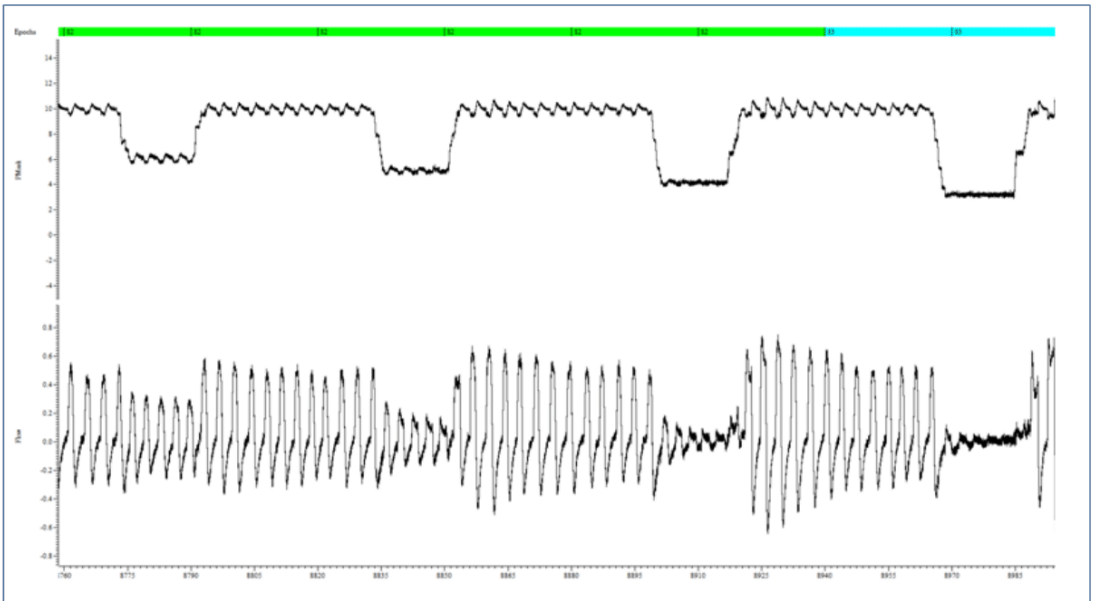

Figura 2: Sequência de reduções da pressão de CPAP com indução de limitação ao fluxo aéreo. Epochs= Epocas de estagiamento do sono, S2= NREM2 2 e S3= NREM 3; Pmask=pressão de máscara; Flow= fluxo aéreo

3.3) Pressão faríngea

A medida da pressão faríngea será realizada através de um cateter especialmente desenhado que tem 6 sensores de pressão distando 1,5 cm um do outro, a partir de sua extremidade distal (Millar, Houston, TX, USA). O cateter será posicionado 1 cm abaixo da base da língua sob visualização direta, após a utilização de descongestionante nasal (oximetazolina 0,05%) e anestesia tópica (lidocaína 4%).

3.4) Sonoendoscopia

A faringe será visualizada com um broncoscópio pediátrico de 2,8mm de diâmetro com canal de trabalho (Olympus, Japão) e sem sedação. O endoscópio será passado por um orifício selado na máscara após aplicação de descongestionante nasal (oximetazolina 0,05%) e anestésico tópico (lidocaína 4%). Durante o exame, o endoscópio será posicionado em 3 níveis da faringe: velofaringe, parede lateral da faringe e epiglote. As imagens serão adquiridas a 30 quadros por segundo e sincronizadas com os demais sinais biológicos através do sistema de aquisição de dados (Spike 2).

3.5) Aparelho intra-oral de avanço mandibular

Um dispositivo padrão pré-fabricado de avanço mandibular (Blue Pro, BlueSom, Paris, France) será fornecido para cada paciente para uso durante as noites do protocolo. Trata-se de um aparelho intra-oral em material termoplástico, ajustável e titulável. A mandíbula será posicionada em 70% da máxima protrusão mandibular do indivíduo. O dispositivo apresenta mecanismo que mantém a máxima protrusão da mandibula consistente com o conforto do paciente durante o sono. O ajuste do aparelho será realizado após entrevista e exame clínico na primeira noite do protocolo.

3.6) Pacientes

Serão convidados a participar do estudo pacientes do ambulatório de distúrbios do sono da Disciplina de Pneumologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, portadores de AOS (índice de apnéia-hipopnéia > 5 eventos/ hora), de ambos os sexos, na faixa etária dos 18 aos 70 anos.

Os indivíduos que apresentarem outros distúrbios do sono (insônia, parasonias, narcolepsia, apnéia central do sono), doenças da tireóide não controladas, diabetes, insuficiência cardíaca congestiva, insuficiência renal ou distúrbios neurológicos graves serão excluídos do estudo. Pacientes com número insuficiente de dentes (minimo de 8 dentes em cada arcada dentária), doença periodontal e distúrbio têmporo-mandibular serão excluídos. Também serão excluídos pacientes com história prévia de reação alérgica a lidocaína ou oximetazolina.

Os pacientes serão esclarecidos sobre todos os procedimentos a serem realizados e serão incluídos apenas após a assinatura do Termo de Consentimento Livre e Esclarecido (TCLE).

4. Protocolo de estudo:

Os pacientes serão submetidos a três noites de estudos: primeira noite para sonoendoscopia e duas noites para polissonografia com e sem o AIO em ordem aleatória.

Em cada visita os pacientes deverão se apresentar ao laboratório do Sono, 2 horas antes do seu horário habitual de dormir e em jejum de pelo menos 2 horas. Na primeira visita será conduzida uma entrevista clínica e exame físico detalhados. Durante o exame físico, a orofaringe será classificada conforme o Índice de Mallampati modificado (anexo 1). Serão medidas as circunferências cervical e abdominal. A seguir será colocado e ajustado o AIO temporário para as noites de estudos. Na sequencia, serão colocados os sensores para a polissonografia. Após a anestesia e vasoconstrição tópica de uma das narinas, será locado o cateter de pressão faríngea ao

nível da base da língua. O correto posicionamento do cateter será confirmado por inspeção da cavidade oral. Será então colocada uma máscara nasal conectada ao pneumotacógrafo. Neste momento, será aplicado vasoconstritor e anestésico tópico na outra narina e o endoscópio será passado através de um orifício na máscara. Inicialmente o endoscópio será posicionado na região retropalatal.

O paciente será instruído a se deitar em posição supina e convidado a dormir. Logo que alcançar sono estável, a pressão de CPAP será aumentada até que não ocorra limitação ao fluxo aéreo (pressão de manutenção). Após pelo menos 2 minutos de sono em estágios 2 ou 3 com respiração estável na pressão de manutenção, a pressão do CPAP será progressivamente reduzida por períodos de 3 minutos até que seja observada restrição ao fluxo inspiratório (caracterizado pelo não aumento do fluxo inspiratório concomitante à redução da pressão intraluminal) e negativação significativa da pressão intraluminal (>= -10cmH_2O). A seguir, o endoscópio será reposicionado na região retroglossal e posteriormente na região da epiglote. As manobras de redução da pressão de CPAP descritas acima para a indução da restrição ao fluxo inspiratório serão repetidas em cada nível da faringe (velofaringe, parede lateral da faringe e epiglote). Categorização da obstrução da via aérea será realizada de acordo com a estrutura causadora da obstrução nas seguintes categorias: obstrução relacionada a lingua, obstrução palatal isolada, obstrução das paredes faríngeas laterais e obstrução epiglótica. A seguir o paciente será solicitado a usar o AIO e as manobras serão repetidas.

Para a segunda e terceira noites, serão colocados os sensores para a polissonografia e a máscara nasal conectada ao pneumotacógrafo. O paciente será instruído a se deitar em posição supina e convidado a dormir. Na primeira parte da noite (aproximadamente 2 horas) será realizado o procedimento para medida da Pcrit. Após o início do sono, a pressão do CPAP será aumentada a fim de suprimir a limitação ao fluxo aéreo. Esse nível de pressão do CPAP será usado como a pressão de

manuntenção de CPAP para cada paciente. Uma vez que pelo menos 2 minutos de estágio do sono 2 ou 3 sejam atingidos, a pressão de CPAP será abruptamente reduzida em 1-2 cmH2O durante a expiração por 5 respirações. A pressão de CPAP será então retornada à pressão de manutenção por 1 minuto antes de nova redução. Este processo de queda progressiva da CPAP prosseguirá até a ocorrência de uma apneia obstrutiva. Se houver um despertar durante a queda de pressão, o CPAP será retornado a pressão de manuntenção até que o paciente volte a atingir os estágios 2 ou 3 do sono. Os dados serão analisados por meio de um software escrito em Matlab (MathWorks, Inc., Natick, MA) O pico de fluxo inspiratório será plotado contra a pressão nasal para determinar a Pcrit. Na segunda parte da noite, os pacientes serão monitorados para polissonografia clínica padrão para determinar o IAH. As polissonografias serão laudadas conforme critérios da Academia Americana de Medicina do Sono(26).

5. Cálculo amostral e análise dos dados

As variáveis contínuas serão reportadas como média e desvio padrão ou mediana e intervalo interquartil conforme a distribuição dos dados. Distribuição normal será testada através do método de Kolmogorov-Smirnof. As variáveis categóricas serão reportadas em porcentagem.

Alterações na Pcrit serão avaliadas em cada um dos 4 subgrupos pre-definidos de colapso faringeo através de análise de variância e comparadas entre os grupos através do teste post-hoc de Student-Newman. Assim, serão determinadas as estruturas mais favoráveis ao tratamento com AIO. A distância de protrusão mandibular será incorporada com um fator de confusão. Essa analise estatistca revelará valores limiares de Pcrit (para dada distância de protrusão) que resultará em resposta positiva ao tratamento com AIO para cada estrutura faríngea de colapso.

Cálculo amostral

O cálculo amostral foi feito tendo como base um modelo de regressão linear múltipla. A variação percentual do IAH é a varíavel dependente e Pcrit, IAH basal e a estrutura de colapso são as variáveis independentes. Para um tamanho do efeito esperado de 0.35, poder de 80% e alfa de 0.05, serão necessários 36 indivíduos. Considerando possíveis ocorrências de perdas amostrais serão recrutados 40 individuos.

6. Cronograma

TRIMESTRE	1º	2º	3º	4º	5º	6º	7º	8º
Revisão da literatura	X	X	X	X	X	X	X	X
Submissão do protocolo e TCLE ao Comitê de ética e pesquisa	X							
Recrutamento dos pacientes		X	X	X	X	X		
Protocolo de avaliação		X	X	X	X	X		
Análise dos dados					X	X	X	
Redação do manuscrito							X	X

Será validado após aprovação do comitê de ética.

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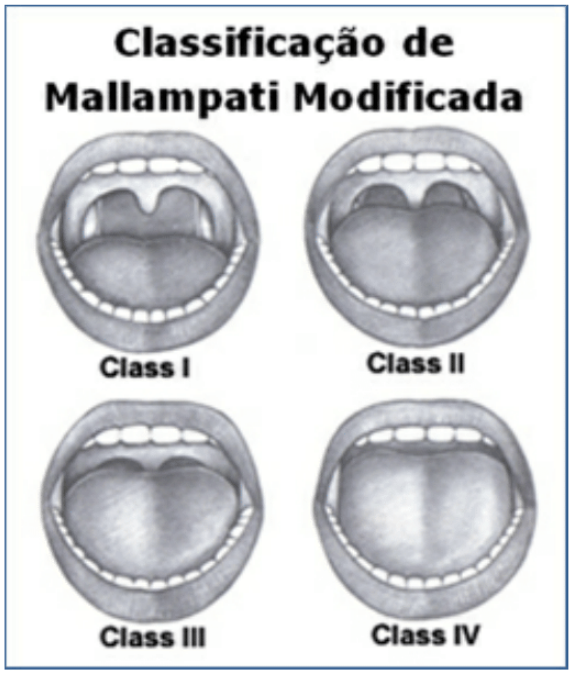
Anexo 1:


Classificação de
Mallampati Modificada
Class I
Class II
Class III
Class IV

5.2 ANEXO B – Aprovação da Comissão de Ética

4126/14/106

Hospital das Clínicas da FMUSP
Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq

PROJETO DE PESQUISA

Título: AVALIAÇÃO DA COLAPSABILIDADE SEGMENTAR DA FARINGE NA APNEIA OBSTRUTIVA DO SONO
Pesquisador Responsável: Dr Pedro Rodrigues Genta
Pesquisador Executante: Dra Melânia Dirce Oliveira Marques
Versão: 2
CAAE: 37908714.9.0000.0068
Finalidade Acadêmica: Doutorado
Instituição: HCFMUSP
Departamento: COMISSÃO CIENTÍFICA DO INCOR

PARECER CONSUBSTANCIADO DO CEP

Registro on-line: 12780

Número do Parecer: 1.415.153

Data da Relatoria: 17/02/16

Apresentação do Projeto: Trata-se se solicitação de inclusão de subprojeto ao estudo principal. O subprojeto tem como título: CARACTERIZAÇÃO DO COLAPSO DA VIA AÉREA SUPERIOR NA SELEÇÃO DE PACIENTES CANDIDATOS AO USO DE APARELHO INTRA-ORAL PARA TRATAMENTO DA APNEIA OBSTRUTIVA DO SONO. A hipótese do estudo é que a estrutura faríngea envolvida na obstrução e a colapsabilidade da via aérea superior definida pela Pcrit predizem o sucesso terapêutico dos Aparelhos Intra-Orais (AIOs). O estudo estima a participação de 40 pacientes de ambos os sexos, na faixa etária de 18 a 70 anos, com diagnóstico de AOS (índice de apneia-hipopneia> 5 eventos/hora). Os pacientes serão submetidos à visualização endoscópica da via aérea superior durante sono natural para identificação das estruturas faríngeas a determinação da Pcrit e IAH na presença e na ausência do aparelho intra-oral de avanço mandibular.

Objetivo da Pesquisa: 1.Correlacionar a estrutura de colapso faríngeo com alterações na colapsabilidade faríngea (Pcrit) associada ao uso do Aparelho Intra-Oral; 2.Determinar o limiar de Pcrit preditor de reposta positiva ao tratamento com Aparelho Intra-Oral para cada uma das estruturas de colapso faríngeo.

Avaliação dos Riscos e Benefícios: Risco mínimo, devidamente assinalado no TCLE.

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Comentários e Considerações sobre a Pesquisa: O subprojeto (com a inclusão da pesquisadora Dra. Melânia Dirce Oliveira Marques) poderá contribuir para o conhecimento dos mecanismos envolvidos na Apnéia Obstrutiva do Sono.

Considerações sobre os Termos de apresentação obrigatória: Termos apresentados de forma adequada.

Recomendações: Sem recomendações adicionais.

Conclusões ou Pendências e Lista de Inadequações: Sem pendências.

Situação do Parecer: Aprovado.

Necessita Apreciação da CONEP: Não.

COMISSÃO CIENTIFICA
RECEBIDO
26/02/16
fabiane

São Paulo, 22 de Fevereiro de 2016

Prof. Dr. Alfredo José Mansur
Coordenador
Comissão de Ética para Análise
de Projetos de Pesquisa - CAPPesq

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