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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

ANÁLISE CINTILOGRÁFICA DA DEPOSIÇÃO PULMONAR DE RADIOAEROSSOL APÓS ASSOCIAÇÃO DA NEBULIZAÇÃO ATRAVÉS DOS DISPOSITIVOS *MESH* E JATO COM A VENTILAÇÃO NÃO INVASIVA EM INDIVÍDUOS NORMAIS E COM PNEUMOPATIAS OBSTRUTIVAS CRÔNICAS

VALDECIR CASTOR GALINDO FILHO

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal do Rio Grande do Norte Como requisito para a obtenção do título de doutor em Ciências da Saúde.

Orientadora: Profa. Dra. Armèle de Fátima Dornelas de Andrade

Co-orientadores: Prof. Dr. James B Fink e Profa. Dra. Simone Cristina Soares Brandão

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"A mente que se abre a uma nova ideia jamais voltará

ao seu tamanho original."

Albert Eisntein

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Dedico esta tese aos pacientes que nos concederam a possibilidade de aprendizagem e resolveram participar do estudo, muitas vezes vencendo algum tipo de indisposição momentânea ou dificuldades para chegar até o local da pesquisa.

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Artigo 3

Figure 1. Flow chart diagram of this study protocol.

Figure 2. Total pulmonary depositing reached by each nebulizer tested in this study. Wilcoxon Test. * p=0.005.

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VMN = vibrating mesh nebulizer and JN = jet nebulizer.

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Lista de Abreviaturas e Siglas

APN-C	Aerosol Professional Nebulizer Sinchonized
APN-S	Aerosol Professional Nebulizer
BiPAP	Bilevel positive airway pressure
CI	Capacidade inspiratória
CPAP	Continuous positive airway pressure
CRG	Chronic Respiratory Questionnaire
CVF	Capacidade vital forçada
DPI	Dry poder inhaler
DPOC	Doença Pulmonar Obstrutiva Crônica
EPAP	Expiratoy positive airway pressure
FC	Frequência cardíaca
$FEF_{25-75\%}$	Fluxo expiratório forçado em 25-75%
FI	Fluxo inspiratório
FTCU	Filtro trocador de calor e umidade
IC	Intervalo de confiança
IDR	Índice de deposição do radioaerossol
IMC	Índice de massa corporal
IPAP	Inspiratory positive airway pressure
IPPB	Intermittent positive pressure breathing
IRA	Insuficiência Respiratória Aguda
IRC	Insuficiência respiratória crônica
MDI	Metered dose inhaler

NJ	Nebulizador de jato
NM	Nebulizador de membrana
NU	Nebulizador ultrassônico
$PaCO_2$	Pressão parcial e gás carbônico
PAD	Pressão arterial diastólica
PaO_2/FiO_2	Índice de oxigenação
PAS	Pressão arterial sistólica
PAV	Proportional assisted ventilation
PCV	Pressure controll ventilation
PEEP	Positive end-expiratory pressure
PEEPi	Intrinsic positive end-expiratory pressure
PFE	Pico de fluxo expiratório
PSV	Pressure support ventilation
R i:e	Relação inspiração : expiração
ROI	Região de interesse
RR	Risco relativo
SpO_2	Saturação periférica de oxigênio
SUS	Sistema Único de Saúde
TC6min	Teste de caminhada de seis minutos
Ti	Tempo inspiratório
Ti/Ttot	Tempo inspiratório/tempo respiratório total
TOT	Tubo orotraqueal
UAA	Umidificação aquosa aquecida
VC	Volume corrente

VCV	Volume controll ventilation
VEF_1	Volume expiratório forçado no primeiro segundo
VNI	Ventilação não invasiva
VR	Volume residual
99mTC-DTPA	ácido dietilnotriaminopentaacético marcado com tecnésio

RESUMO

A via inalatória tem sido comumente utilizada para a deposição de drogas broncodilatoras diretamente no trato respiratório, principalmente pelos efeitos de respostas imediatas e por minimizar os efeitos colaterais sistêmicos observados pela via oral nos pacientes com doença respiratória crônica (asmáticos e doença pulmonar obstrutiva crônica – DPOC, dentre outras). Durante a fase de exacerbação, a ventilação não invasiva (VNI) tem sido utilizada na prática clínica nos pacientes com persistência do desconforto respiratório, tendo seus benefícios clínicos sido bem estabelecidos na literatura. O percentual de deposição pulmonar do radioaerossol utilizando o nebulizador de jato (NJ) durante o uso da pressão positiva atinge valores de 1 a 3%, porém uma nova geração de dispositivos para nebulização designado nebulizador de membrana (NM), têm mostrado resultados promissores em estudos com modelo animal e *in vitro*, pois a quantidade de radioaerossol depositada é duas vezes maior quando comparado ao NJ. Entretanto, nas bases de dados pesquisadas não foram evidenciados estudos *in vivo* envolvendo a associação da VNI com o NM em indivíduos normais, asmáticos e DPOC estáveis. Desta forma, os objetivos deste estudo foram: 1) quantificar a quantidade de radioaerossol depositado nos diferentes segmentos pulmonares (gradiente vertical – terços superior, médio e inferior; gradiente horizontal – regiões central, intermediária e periférica) e 2) analisar a deposição do radioaerossol nos diferentes compartimentos pulmonares (pulmonar e extrapulmonar) em indivíduo saudáveis, asmáticos e com DPOC, dispondo do NJ e NM associado à VNI. Desta forma, foram produzidos três artigos científicos, cujos desenhos de estudo foram ensaios clínicos do tipo *crossover*, envolvendo as diferentes amostras de sujeitos acima descritos. O método utilizado foi reproduzido semelhantemente em cada amostra através da randomização para eleição de qual dispositivo utilizar inicialmente e dividiu-se em duas fases: Fase 1 (VNI+NJ) e Fase 2 (VNI+NM). Para inalação utilizou-se o 99mTc-DTPA tecnésio) com radioatividade de 25 mCi, drogas broncodilatoras e solução salina (Soro fisiológico a 0.9%) até completar um volume de 3 mL dentro do nebulizador. Utilizou-se a VNI com dois níveis de

pressão (inspiratória = 12 cmH_2O e expiratória = 5 cmH_2O). Após a inalação, as imagens cintilográficas eram obtidas pela gama câmera e desenhadas as regiões de interesse (ROI), sendo de imediato realizada a análise nos diferentes compartimentos. Como resultados dos três artigos produzidos, observamos maior deposição do radioaerossol com o NM quando comparado ao NJ, sendo observado 972013±214459 contagens *versus* 386025±130363 (p=0.005) contagens nos indivíduos normais; 1198479±434174 contagens *versus* 426803±151758 contagens (p = 0.005) nos asmáticos e 1867044±456120 contagens *versus* 579729±312261 contagens (p=0.005) nos pacientes com DPOSC. Também foi observado nas três amostras analisadas, maior deposição da massa do aerossol inalada no NM em comparação ao NJ (23.07% *versus* 6.13%, p=0.005; 22.75% *versus* 7.27%, p=0.005; 19.90% *versus* 7.03%, p=0.008) nos indivíduos normais, asmáticos e com DPOC, respectivamente. Ainda, em termos percentuais, verificou-se maior deposição a nível pulmonar e menor volume residual no dispositivo NM comparado ao NJ. Concluindo, os três artigos tratam-se dos primeiros ensaios clínicos *crossover* envolvendo a VNI em associação ao NM, tendo evidenciado maior deposição do radiaerossol em comparação ao NJ em indivíduos saudáveis (depositou > 2,5 vezes mais), asmáticos (depositou > 2,8 vezes mais) e com DPOC (deposição > 3 mais). Estes resultados podem direcionar os profissionais da Área de Saúde que utilizam a prática inalatória, no momento de escolher qual dispositivo de inalação capaz de otimizar a deposição pulmonar dos aerossóis durante o tratamento das doenças respiratórias crônicas.

Palavras-chave: Cintilografia pulmonar, nebulizador, radioaerossol, volume residual, asma, doença pulmonar obstrutiva crônica.

1. INTRODUÇÃO

As nebulizações e o uso da ventilação não invasiva têm sido comumente empregados na abordagem terapêutica de pacientes com doenças respiratórias crônicas, na tentativa de aliviar o desconforto respiratório e durante o período de estabilização destas doenças, desde o hospital até o domicílio dos pacientes[1-4].

Estes grupos de patologias do trato respiratório caracterizam-se pela limitação crônica ao fluxo expiratório, expressando-se através da dispnéia e da limitação durante a realização das diferentes atividades da vida diária, culminado com piora na qualidade de vida destes pacientes[5-7]. Dentre as patologias apontadas como responsáveis pela obstrução das vias aéreas, destacam-se a Asma e a Doença Pulmonar Obstrutiva Crônica (DPOC), sendo esta última representada pelo enfisema e a bronquite crônica[8,9].

Durante as exacerbações das doenças pulmonares crônicas, ocorre aumento da resistência ao fluxo aéreo, ocasionando o aumento do trabalho respiratório e a piora das trocas gasosas[8-10]. Atualmente, o primeiro recurso terapêutico apontado para abordagem no tratamento destes pacientes atendidos nas emergências tem sido a inalação dos agonistas β_2-adrenérgicos, cujo efeito é rápido e bastante eficaz[11-16].

Além disso, nos pacientes que evoluem com piora do desconforto respiratório, a VNI poderá ser disponibilizada na tentativa de reverter à insuficiência respiratória aguda (IRA), tendo alguns estudos demonstrado significativa redução da sobrecarga imposta à musculatura respiratória, melhora dos dados espirométricos, melhora dos parâmetros respiratórios e

hemogasimétricos, redução da necessidade de intubação e decréscimo da mortalidade hospitalar[17-29]. Apesar dos efeitos da VNI serem bem estabelecidos, são poucos os estudos que avaliaram a associação da VNI com as nebulizações em indivíduos asmáticos e com DPOC[30-33].

Vale ressaltar que os dados reportados na literatura sugerem que a liberação dos aerossóis através dos nebulizadores de jato (NJ) em associação a VNI resultam em baixa deposição pulmonar das drogas, tornado o uso destes dispositivos questionáveis quanto à eficácia no manuseio das doenças pulmonares crônicas[34,40]. Entretanto, uma nova geração de nebulizadores denominados de *vibrating mesh nebulizers*[41-44], traduzido para o português como nebulizadores de membrana (NM), tem apresentado resultados promissores durante a realização de estudos *in vitro* e com modelos animais, resultando na deposição dos radioaerossóis duas vezes maior em comparação ao NJ[45,46].

Apesar dos achados acima descritos, não foram encontrados nas bases de dados pesquisadas estudos utilizando o NM durante a aplicação da VNI em indivíduos saudáveis ou com alguma patologia do sistema respiratório.

2. JUSTIFICATIVA

Quando atendidos nas unidades de emergência ou no próprio domicílio, pacientes com asma e DPOC têm como primeira linha terapêutica a utilização das nebulizações na tentativa de favorecer a broncodilatação dos condutos aéreos estreitados e consequentemente, aliviar os sintomas relacionados ás alterações fisiopatológicas da doença. Somando a isto, a

utilização de pressão positiva não invasiva bifásica, também designada de VNI, tem sido utilizada na abordagem destes pacientes, cujos benefícios clínicos encontram-se bem reportados na literatura.

Um estudo recentemente publicado pelo nosso grupo, envolvendo pacientes asmáticos durante a crise, demonstrou-se que a realização da VNI concomitantemente a nebulização não aumentou a deposição do radioaerossol pulmonar quando comparada apenas com a nebulização. Entretanto, observou-se melhora significativa da função pulmonar com aumento do volume corrente (VC), redução do volume minuto (VM) e da frequência respiratória (FR), bem como melhora dos parâmetros da espirometira (volume expiratório forçado no primeiro segundo - VEF1, capacidade vital forçada - CVF, pico de fluxo expiratório - PFE e capacidade inspiratória - CI), os quais apresentaram ganhos significativos em comparação ao grupo controle. Acredita-se que à associação da VNI com a nebulização propiciou o alívio dos sintomas clínicos devido à broncodilatação mecânica proveniente do uso da pressão positiva neste grupo de asmáticos agudizados.

Com o avanço tecnológico, novos protótipos de nebulizadores têm surgido no mercado e estudos têm sido realizados na tentativa de obterem-se informações a cerca do funcionamento e do rendimento destes dispositivos. Assim, o NM apresenta características importantes no que concerne ao tamanho das partículas produzidas, no menor volume residual ao final da nebulização e aumento da deposição dos aerossóis duas vezes maior em comparação ao NJ, porém estes estudos foram realizados em modelos animais e *in vitro*, existindo uma lacuna de informações quanto a estes resultados *in vivo*.

Além disso, vale a pena ressaltar a importância da verificação dos resultados obtidos destes estudos em indivíduos saudáveis e com diferentes patologias pulmonares crônicas (asma, DPOC, fibrose cística e bronquiectasia), principalmente nas implicações clínicas advindas do uso dos broncodilatadores na função pulmonar destes pacientes, considerando-se os resultados apontados no tocante a maior adeposição dos aerossóis com o uso do NM.

Desta forma, a realização desta pesquisa é de relevante interesse, pois nas bases de dados pesquisadas não foram evidenciados estudos envolvendo o uso dos NM em comparação aos NJ durante o uso da VNI em portadores de patologias pulmonares crônicas e em indivíduos normais, avaliados através de cintilografia pulmonar. Os possíveis resultados poderiam direcionar os profissionais de saúde que lidam com estas duas estratégias terapêuticas, no que tange a eficácia do uso destes inaladores em conjunto com a VNI durante as exacerbações, ou ainda, durante os períodos de estabilização da doença.

É imprescindível evidenciar que, de acordo com dados obtidos da literatura, existe um subgrupo de indivíduos com DPOC que não possuem habilidade no manuseio dos nebulímetros dosímetrados e liofilizados, sendo a inalação realizada através de NJ, apesar da baixa quantidade de deposição pulmonar observada. Ainda, no tocante ao uso de cintilografia pulmonar seria possível analisar o padrão de deposição dos radioaerossóis liberados pelos diferentes dispositivos de nebulização entre indivíduos saudáveis em comparação aos asmáticos e pacientes com DPOC.

3. HIPÓTESE

- A associação da nebulização com a VNI aumenta a deposição pulmonar do radioaerossol quando utilizado o NM em comparação ao NJ em indíviduos saudáveis e nos asmáticos e DPOC estáveis.

4. OBJETIVOS

4.1 Objetivo Geral:

- Analisar a deposição de radioaerossol através da inalação com os NM e NJ em associação a VNI utilizando-se a cintilografia pulmonar em indivíduos saudáveis, em pacientes asmáticos e DPOC estáveis.

4.2 Objetivos Específicos:

- Quantificar o índice de deposição do radioaerossol (IDR) em ambos os pulmões através da inalação com os NM e NJ em associação a VNI utilizando-se a cintilografia pulmonar em indivíduos saudáveis e naqueles com asma e com DPOC estáveis.
- Comparar o IDR nos gradientes vertical (terços superior, médio e inferior) e horizontal (regiões central, intermediária e periférica) entre os grupos, através da inalação com os NM e NJ em associação a VNI utilizando-se a cintilografia pulmonar em indivíduos saudáveis e naqueles com asma e DPOC estáveis.

- Comparar intragrupo a deposição do radioaerossol nos gradientes vertical e horizontal dos NM e NJ após inalação associada com a VNI em indivíduos utilizando-se a cintilografia pulmonar em indivíduos saudáveis e naqueles com asma e com DPOC estáveis.
- Analisar a deposição pulmonar e extrapulmonar (estômago, vias aéreas superiores, máscara de VNI, nebulizador, circuito do ventilador, filtro inspiratório e filtro expiratório) do radioaerossol através da inalação com os NM e NJ utilizando-se a cintilografia pulmonar em indivíduos saudáveis, asmáticos e com DPOC estáveis.
- Comparar a massa do radioaerossol inalado (pulmões, vias aéreas superiores e estômago) através da inalação com os NM e NJ utilizando-se a cintilografia pulmonar em indivíduos saudáveis, asmáticos e com DPOC estáveis.
- Analisar o padrão de distribuição dos radioaerossóis nos indivíduos saudáveis, asmáticos e com DPOC estáveis.

5. MÉTODO

5.1 Desenho do estudo e sujeitos envolvidos

Os três artigos originais que são resultado deste estudo, tratam-se de ensaios clínicos do tipo *crossover* (Fase 1) envolvendo indivíduos saudáveis e pacientes asmáticos e com DPOC estáveis (classificados como moderados a

severos), de ambos os sexos e com idade entre 18 e 70. O estudo foi realizado no Departamento de Medicina Nuclear e no Laboratório de Fisioterapia Cardio-respiratória do Departamento de Fisioterapia da Universidade Federal de Pernambuco em associação com a *Georgia State University*. A coleta dos dados foi iniciada após a aprovação do protocolo de estudo pelo Comitê de Ética e Pesquisa da Universidade Federal de Pernambuco e todos os pacientes assinaram o consentimento por escrito para participar do estudo (CEP/CCS/UFPE N^{o} 094/11).

5.2 Critérios de inclusão e exclusão

Como critérios de inclusão para o grupo dos indivíduos saudáveis foram considerados: idade entre 18 e 60 anos; serem de ambos os sexos; sem história de doença pulmonar; CVF ou VEF_1 igual ou maior a 80% do valor previsto[47]; sem história de tabagismo; sem doença respiratória ou cardiovascular; possuir habilidade para entender os comandos verbais solicitados durante os experimentos e o desejo expresso através da assinatura do termo de consentimento livre e esclarecido em participar do estudo. Por outro lado, considerou-se como critérios de exclusão pacientes gestantes e que fossem incapazes de tolerar o uso da VNI[48].

No grupo de asmáticos, considerou-se como critérios de inclusão: idade entre 18 e 60 anos; serem de ambos os sexos; asma moderada a severa estável (VEF_1 > 60% e > 80% e pico de fluxo expiratório – PFE com uma variação de 30% do valor predito)[47]; passado mais de um ano desde o

diagnóstico de asma brônquica; nenhuma exacerbação do quadro de asma nos últimos seis meses; não tabagista; capazes de atender aos comandos verbais e que tenha dado o consentimento para participar no estudo. Como critérios de exclusão, foram considerados: presença de dispnéia, relato de doença cardiopulmonar (DPOC, pneumonia, insuficiência cardíaca, infarto agudo do miocárdio, pneumotórax); hipertermia; instabilidade hemodinâmica (frequência cardíaca - FC > 150 bpm e pressão arterial sistólica < 90 mmHg); presença de arritmias; gestação e contra-indicações do uso da VNI[49].

Com relação aos pacientes com DPOC, foram considerados os seguintes critérios de inclusão: diagnóstico de DPOC moderada a severa estabilizada (50% ≤ VEF_1 < 80% ou 30% ≤ VEF_1 < 50% dos valores preditos)[8]; sem exacerbações da doença nos últimos seis meses; idade entre 18 e 70 anos; de ambos os gêneros; sem história recente de tabagismo; capacidade em entender os comandos verbais e que consentissem participar no estudo. Nesta amostra, os critérios de exclusão assinalados foram: agudização do quadro clínico; outras doenças cardiopulmonares que não fossem DPOC (insuficiência cardíaca, pneumonia, infarto agudo do miocárdio, pneumotórax); hipertemia; alterações hemodinâmicas (FC > 150 bpm e pressão arterial sistólica - PAS < 90 mmHg); gestantes e qualquer contraindicação ao uso da VNI[48].

5.3 Mensuração dos parâmetros

A avaliação inicial constou da coleta dos dados antropométricos (idade, peso, altura e índice de massa corporal - IMC) e dos seguintes

parâmetros cardiopulmonares: FR, saturação periférica de oxigênio (SpO_2); FC, PAS e pressão arterial diastólica (PAD) usando o oxímetro de pulso (ACTIVE - Ecafix, São Paulo, Brasil) e um manômetro manual de pressão (Welch Allyn^{TM} DS 44-11 Beaverton, Oregon, EUA). Após, foi realizada a espirometria (Micro Loop 8 / Cardinal Health, Inglaterra, Reino Unido), baseada no protocolo da *American Thoracic Society*, a qual permite uma variação de 0.2L entre as mensurações obtidas e a média de três medidas realizadas[50].

5.4 Protocolo de Inalação

O protocolo de inalação foi dividido em duas fases: Fase 1 – VNI+NJ (grupo controle) e Fase 2 - VNI+NM (grupo experimental). A ordem para determinar qual fase iniciar primeiro foi realizada através de randomização (*Random Allocation Software* – versão 2.0), sendo a segunda mensuração obtida uma semana após, com o intuito de evitar resíduo do material radioativo nos pulmões a possibilidade de viés. Houve sigilo de alocação quanto à randomização, pois a mesma não foi realizada pelo pesquisador principal, mas por outro pesquisador envolvido no mesmo projeto de pesquisa. Entretanto, não foi possível realizar o cegamento, pois não havia a possibilidade de não ser visualizado o tipo de nebulizador acoplado ao circuito de VNI.

Para inalação utilizou-se o ácido dietilnotriaminopentaacético marcado com tecnésio (99mTc-DTPA), cuja radioatividade foi fixada em 25 millicuries[51]. Ambos os nebulizadores foi preenchidos com 2.5 mg de salbutamol e 0.25 mg de brometo de ipatropium, acrescido de solução salina (Soro fisiológico 0.9%)

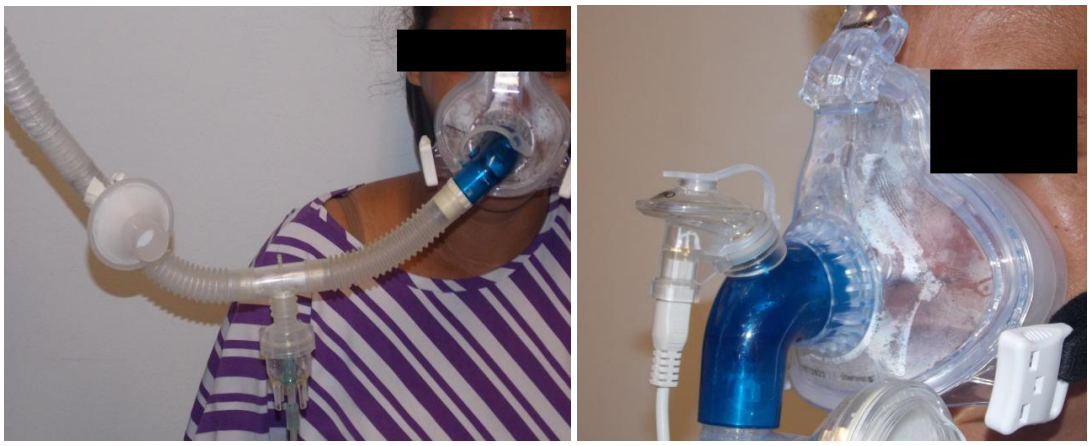
até completar 3 mL dentro do recipiente do nebulizador. O NJ (Misty Max, Air Life, Yorba Linda, EUA) foi posicionado no circuito de VNI dispondo-se de uma peça "T", as partículas produzidas com um faixa de tamanho de 5 µm (dados fornecidos pelo fabricante) e o fluxo de oxigênio poi titulado em 8 L/min. Além disso, o NM (Aeroneb Solo, Galway, Irlanda) foi posicionado na própria máscara de VNI através de uma peça em "joelho" (Elbow Kit, Respironics®, Murrysville, Pennsylvania, EUA), conectado a uma fonte de energia elétrica e as partículas produzidas na faixa de 1 µm. A figura 1 ilustra os dois tipos de nebulizadores utilizados nas duas fases do estudo.

A **B**

Figura 1. Nebulizadores utilizados durante os experimentos. A representa o NM juntamente com o conector apropriado para o funcionamento elétrico do aparelho e B representa o NJ.

Para a realização da VNI utilizou-se o *"bilevel positive airway pressure"* (BiPAP - Synchrony, Respironics®, Murrysville, Pennsylvania, EUA)

dispunha de dois níveis de pressão, sendo a pressão inspiratória ajustada em 12 cmH_2O e a pressão expiratória em 5 cmH_2O, aplicada através de máscara facial (Comfort Full 2, Respironics®, Murrysville, Pennsylvania, EUA), a qual foi fixada na face do indivíduo através de presilhas. Os valores pressóricos requeridos durante a VNI foram ajustados depois de um período de adaptação, antes de iniciar a inalação acoplada a VNI, com o intuito de evitar assincronia entre o ventilador e os indivíduos[32,52]. A figura 2 ilustra o posicionamento de ambos os nebulizadores utilizados durante os experimentos.



A **B**

Figura 2. Posicionamento dos dispositivos de nebulização utilizadores em durante a VNI. A representa o local de fixação do NJ no circuito de VNI e B demonstra a posição utilizada para o NM.

Após acoplar o dispositivo de inalação a VNI, o tempo de finalização da inalação no NJ foi determinado até o surgimento de um som "triturante", com interrupções espaçadas no surgimento da névoa. Esperou-se 60 segundos após o surgimento deste som para que fosse considerada a finalização da

nebulização. No caso do NM, o término da inalação foi determinado quando cessou a produção da névoa por completo pelo dispositivo.

5.5 Análise Cintilográfica

Imediatamente após a inalação, os participantes eram encaminhados da sala de inalação para o setor de aquisição das imagens. Todos foram orientados a sentar em uma cadeira com o tórax posterior posicionado em frente para a gama câmara (STARCAM 3200 GE, Califórnia, EUA) para obtenção da aquisição das contagens radioativas durante um período de 300 segundos, dispondo-se de uma matrix de 256 x 256. Depois, foram obtidas as contagens com o participante posicionado sentado na cadeira, com o tórax anterior de frente para a gama câmera, a fim de obterem-se as contagens relativas a vias aéreas superiores (face). Posteriormente, foram analisadas as contagens no nebulizador, circuito de VNI, filtro inspiratório, filtro expiratório e máscara facial. As contagens relativas à deposição do radioisótopo no estômago foram obtidas no mesmo momento da aquisição das imagens nos pulmões. Foram utilizadas correções quanto ao decaimento do tecnécio durante a obtenção das contagens a nível extrapulmonar, pois o tempo de obtenção das imagens diferiu entre os diferentes segmentos.

A análise da deposição nos compartimentos pulmonar e extrapulmonar foram expressas como valor percentual da contagem total obtida a partir da massa de radiaoerossol gerada por cada nebulizador. O radioaerossol

inalado foi considerado a soma das contagens depositadas nas vias aéreas superiores, pulmões e estomâgo[53].

As regiões de interesse (ROI) foram delimitadas de acordo com estudo prévio[51] realizado pelo grupo do Laboratório de Fisioterapia Cárdio-respiratória, considerando-se como gradiente vertical a divisão dos pulmões em terços superior, médio e inferior. No tocante ao gradiente horizontal, considerou-se a divisão em regiões central, intermediária e periférica[51]. O índice de deposição do radioaerossol (IDR) foi expresso como valor absoluto e foi calculado de acordo com as contagens depositadas em cada ROI.

No tocante a análise qualitativa das imagens obtidas através da cintilografia pulmonar, consideram-se as áreas mais claras como sendo aquelas com maior deposição do radioaerosol (regiões quentes – cores branca e amarela) e as mais escuras representam menor deposição do radioaerosol inalado (regiões mais frias – cores violeta e azul), conforme ilustrado na figura 3.

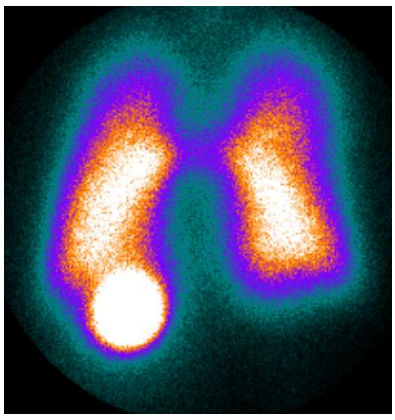


Figura 3. Representação da deposição do radioaerosol no interior do trato respiratório. As áreas claras (branco e amarelo) demosntram maior concentração do radiaerosol e as áreas escuras equivalem a menor distribuição do radioaerosol (violeta e azul).

5.6 Cálculo Amostral

O cálculo amostral foi baseado em estudo piloto previamente realizados, envolvendo os diferentes grupos de indivíduos saudáveis, asmáticos e com DPOC. Para tal, utilizou-se um programa de internet específico para ensaio clínico do tipo crossover (desenvolvido por David Schoenfeld, apoiado pela MGH Mallinckrodt General Research Center, versão do Javascript e desenvolvida por REMorse), o qual levou em consideração o desvio padrão de observações repetidas no mesmo indivíduo e o desvio padrão obtido entre duas medidas em momentos distintos no mesmo indivíduo de uma das variáveis analisada no estudo, sendo considerado um poder acima de 80% e nível de significância de 0.05. Assim, verificou-se um quantitativo de 10 indivíduos saudáveis, 10 asmáticos e 5 pacientes com DPOC, porém neste último grupo foi composto por 9 pacientes, considerando-se as possíveis perdas em decorrência do padrão de deposição durante a análise.

5.7 Achados primários e secundários

Como achado primário considerou-se o IDR nos pulmões e como achados secundários o balanço da massa de radioaerossol que alcançou os compartimentos pulmonar e extrapulmonar.

5.8 Análise estatística

Para análise estatística, utilizou-se o Teste de Shapiro-Wilk para verificação da normalidade das variáveis e em seguida, o Teste de Wilcoxon, Teste de Friedman e o Teste de Comparação Multivariada de Dunn, considerando-se um intervalo de confiança de 95% ($p<0.005$) através do softawe SPSS versão 20.0 (SPSS Inc., Chicago, Illinois, EUA) e Graphpad Prisma versão 4.0 (Graph Pad Software In., San Diego, Califórnia, EUA).

6. REVISÃO DE LITERATURA

As doenças pulmonares obstrutivas têm como principal característica a presença de dispnéia, a qual ocasiona limitação crônica ao fluxo expiratório, verificado elevação da resistência das vias aéreas e progressiva perda da capacidade dos pacientes em realizar as suas atividades da vida diária[5,8]. Tanto a asma quanto a DPOC são apontadas como responsáveis pela obstrução ao fluxo expiratório nestes pacientes, sendo esta última representada pelo enfisema pulmonar e bronquite crônica[6-9].

Com relação ao aspecto epidemiológico, a asma é considerada uma das doenças pulmonares mais comuns nos países desenvolvidos e subdesenvolvidos, tendo nos últimos anos aumentado sua prevalência em todo o mundo[54]. A prevalência da asma na cidade do Recife é considerada a segunda mais alta do Brasil e esta prevalência tem aumentado nas crianças e adultos, favorecendo um maior número de hospitalizações e gastos por parte do Sistema Único de Saúde (SUS)[7;55].

A DPOC também apresenta alta prevalência nos diferentes países e o número elevado de pacientes diagnosticados tornou-se um grande desafio para os serviços de saúde, com conseqüente aumento nos gastos com medicamentos e internações, bem como as co-morbidades relacionadas ao aparelho cardiovascular presentes nesta população[8,56-59].

Apesar de serem consideradas doenças crônicas, de caráter inflamatório e limitante do fluxo aéreo, estas entidades diferem do ponto de vista fisiopatológico. Na asma ocorre expressiva hiper-responsividade brônquica,

edema na parede da mucosa e hipersecretividade, reversível espontaneamente ou na vigência de tratamento, manifestando-se clinicamente por episódios recorrentes de sibilância, dispnéia, particularmente á noite ou de manhã ao despertar[10,54].

Por outro lado, a DPOC caracteriza-se pelo aumento dos espaços aéreos distais ao bronquíolo terminal com destruição das paredes alveolares, com conseqüente perda da tração radial e colapso das vias aéreas a expiração (enfisema pulmonar), ou ainda, espessamento da parede das vias aéreas com hiperplasia das células glandulares e maior produção de muco, o que ocasiona tosse crônica com expectoração mucosa ou purulenta, cuja duração é de pelo menos 3 meses e durante 2 anos consecutivos (bronquite crônica)[5]. Em ambas as condições, a inflamação crônica determina estreitamento nas vias aéreas devido à destruição do parênquima pulmonar e perda da retração elástica dos pulmonar[6,8,60].

Somando-se a isto, ocorrerá hiperinsuflação dinâmica, o que dificulta a desinsuflação pulmonar e promove aprisionamento aéreo com aumento da capacidade residual funcional (CRF) e do volume residual (VR), favorecendo o aumento da pressão positiva expiratória final nas unidades alveolares - PEEP (*positive end-expiratory pressure*), designada de PEEP-intrínseca (PEEPi)[61].

6.1 O uso da inaloterapia nas doenças respiratórias obstrutivas

O uso de medicamentos em forma de aerossol no tratamento das infecções do sistema respiratório tem uma longa história na medicina, sendo

considerada uma das mais antigas formas terapêuticas de liberação de drogas diretamente no trato respiratório[12]. A utilização das nebulizações datam do ano de 2000 d.C., a partir da tradicional Medicina Ayurvédica Indiana através do uso de ervas anticolinégicas para inalação[12].

No Egito, utilizavam-se a inalação de vapores provenientes de ervas com propriedades anticolinérgicas, mas um dos pioneiros no emprego terapêutico da inalação dispondo de dispositivos rústicos foi Hipocrátes[13]. A inalação da fumaça emanada de ervas era uma prática constante, incluindo o uso de outras substâncias como *datura*, *lobelia* e *belladona* adicionada ao bálsamo, resinas e arsênicos. Ainda no século XIX, essa prática retornou com o uso de cigarros, contendo folhas de *Datura stramonium* com efeitos atropínicos[12,13].

O marco da terapia inalatória deu-se através do uso da norepinefrina inalada produzida pelo nebulizador DeVilbiss no.4027. Na década de 1950, surgiu o nebulizador de Wright e, na década seguinte, os nebulizadores ultrassônicos (NU), cuja eficácia é ainda amplamente questionada[12].

Com o desenvolvimento tecnológico, surgiram os nebulímetros dosimetrados - MDI (*metered-dose inhaler*)[65]. Apesar de sua praticidade, esses aparelhos apresentam algumas limitações, como a dificuldade em coordenar o momento do disparo do spray com o início da inspiração. Na tentativa de minimizar esta incoordenação e a deposição do fármaco na orofaringe foram desenvolvidos os espaçadores e as câmaras para uso em associação aos MDIs[12].

Posteriormente, surgiram os nebulímetros liofilizados ou de pó seco – DPI (dry-powder inhaler), porém era necessária a geração de um fluxo inspiratório (FI) na ordem de 50 l/min. Além disso, foram fabricadas as válvulas inspiratórias unidirecionais de maneira que o aerossol fosse liberado apenas quando o paciente inalasse, permitindo assim diminuída deposição das partículas na orofaringe[12,36].

Desta forma, a via inalatória é preferencialmente utilizada para administração de fármacos broncodilatadores na reversão da obstrução das vias aéreas na asma e na DPOC em pacientes atendidos nos serviços de emergência hospitalares[14-16]. Somando-se a isto, o uso da via inalatória para administração de fármacos propicia efeitos quase imediatos, devido à atuação da droga diretamente no sítio de ação, sendo por isto preconizada no tratamento das doenças pulmonares crônicas[12]. Deve-se considerar também como vantagem a redução dos efeitos colaterais quando comparada a administração oral das drogas, minimizando prováveis repercussões sistêmicas, e podendo também alterar a reologia do muco através da hidratação das secreções ressecadas[13].

6.2 Tipos de nebulizadores

Dentre os dispositivos utilizados para inalação de drogas broncodilatoras no tratamento das doenças respiratórias crônicas, os nebulizadores têm sido preconizados e dados reportados da literatura demonstram melhora da função pulmonar com o uso destes dispositivos[11,14-16].

Entretanto, alguns fatores poderão interferir na deposição das partículas produzidas por estes dispositivos, tais como: o tamanho das partículas do aerossol; os mecanismos físicos responsáveis pela deposição (impactação, sedimentação e difusão browniana); a anatomia do sistema respiratório; o padrão ventilatório empregado durante a inalação e o tipo de *interface* paciente-nebulizador (máscara ou boquilha)[66].

Somando-se a isto, o nível de titulação do gás utilizado durante a nebulização, o volume da solução, a temperatura da solução a ser nebulizada, o volume residual, o tempo dispendido na nebulização, o design dos nebulizadores, o manuseio e o processo de higieneização após o uso podem ser apontados como fatores que irão afetar diretamente o rendimentos destes dispositivos[15,16,66-69].

Do ponto de vista clínico, destacam-se no mercado para comercialização dois tipos de nebulizadores: o NJ e o NU. A diferença entre estes dois tipos de aparelhos consiste apenas no princípio biofísico responsável por gerar a névoa do aerossol[13,70].

O NJ preconiza como princípio biofísico para a produção névoa o efeito Bernoulli, no qual ocorre a passagem do gás através de um orifício estreito, favorecendo uma queda da pressão e um aumento na velocidade do gás que suga o líquido pelo orifício do capilar, quebrando em partículas que serão inaladas pelo paciente[12,13].

Em decorrência do aprimoramento tecnológico, os NJs evoluíram no *design* e mecanismo de operação, evitando-se a perda da névoa produzida durante a expiração e propiciando um melhor aproveitamento das drogas

inaladas. Desta forma, surgiram outras categorias de NJs, destacando-se: os nebulizadores com débito constante, nebulizadores com ventilação assistida (*open vent*) e nebulizadores dosimetrados[13].

Os nebulizadores de débito constante são os comumente utilizados nos hospitais e enfermarias, operam com a liberação continua da névoa durante todo o ciclo respiratório, o que ocasiona perda em torno de 20% do aerossol durante a expiração do paciente e aproximadamente 60 a 70% de perda pelo nebulizador para o meio externo, resultando em perda da medicação durante a inalação[13,66].

Os dispositivos de nebulização com ventilação assistida possuem uma válvula inspiratória que favorece o aumento na quantidade de partículas contidas no volume corrente inspirado pelo paciente de acordo com o fluxo gerado. O aerossol é gerado durante a exalação, mas permanece relativamente contido dentro da câmara de inalação, como no caso do nebulizador Pari LC Plus[13,67].

Teoricamente, o nebulizador dosimetrado é mais eficaz com ativação e liberação do aerossol durante a inspiração do paciente, pois contém uma válvula com sistema de mola (*spring-loaded*) que interrompe a névoa durante a fase expiratória, no caso das marcas Monaghan Aero-Eclipse, Medicator e Circulaire[13,66,67].

Diferentemente do NJ, o NU têm como princípio biofísico o efeito piezoelétrico responsável pela formação dos aerossóis, a partir da vibração de um cristal na freqüência de 1 a 3 MHz, o qual transmite essa vibração até a superfície do líquido com pulverização da solução e consequentemente, formando as pequenas partículas respiráveis[12,13].

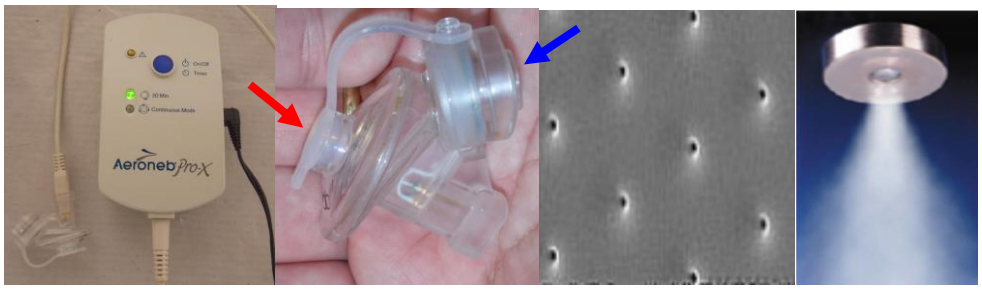
Atualmente, duas teorias são aceitas para explicar o mecanismo de desintegração e produção do aerossol no NU. A primeira teoria foi denominada de onda capilar, a qual preconiza a formação da névoa como resultante da produção de ondas capilares sobre a superfície do líquido contido no interior do nebulizador, quebrando-se e originando as partículas respiráveis. A segunda teoria é a da cavitação alternativa, a qual aponta a produção do aerossol a partir de choques produzidos pela explosão de bolhas de ar próximo à superfície do líquido. Essas duas teorias foram incorporadas, sendo proposta a formação da névoa proveniente das ondas capilares e impelidas pelas bolhas de ar[13].

Recentemente, um terceiro tipo de nebulizador tem sido comercializado, o qual é designado "*vibrating mesh nebulizer*" (*Mesh*), traduzido para a língua portuguesa como nebulizador de membrana (NM). Diferentemente das outras categorias de nebulizadores, o NM encerra uma membrana contendo milhares de pequenas perfurações, as quais irão determinar o tamanho das partículas produzidas de acordo com o diâmetro das perfurações. As vibrações responsáveis pela produção dos aerossóis são provenientes de um elemento piezo que converte a eletricidade em vibrações mecânicas na ordem de 128 kHz (1/10 da frequência gerada no NU), expulsando o líquido através das pequenas perfurações da membrana em pequenas partículas aerolizadas[41-46].

Estes dispositivos apresentam várias vantagens com relação aos outros tipos de nebulizadores, dentre elas podem ser destacadas: são portáteis; são silenciosos; não requerem um longo tempo de uso; funcionam sem compressores; não adicionam gás nos circuitos de ventilação mecânica; funcionam com baterias; apresentam menor volume residual; não resfriam; não

aquecem e podem ser nebulizadas diferentes tipos de drogas concomitantemente[15,16,43,71].

As partículas produzidas durante a inalação dependem do tamanho das perfurações contidas na placa do aparelho e das propriedades físico-químicas das drogas formuladas. Por esta razão, podem ser nebulizadas suspensões, ou outras moléculas como proteínas e genes[43]. A figura 4 ilustra de forma esquemática o funcionamento do NM.



(A) (B) (C) (D)

Figura 4. Representação esquemática do funcionamento do NM. Obseve que o dispositivo possui uma base (A) para poder conectá-lo a fonte de eletricidade e propiciar a formação da névoa do aerosol pelo efeito piezoelétrico. Em (B) pode-se observar a entrada para colocação da solução a ser aerolizada (seta vermelha) e a região do dispositivo contendo a placa com as microperfurações que irão produzir partículas de menor tamanho (seta azul). (C) representa as microperfurações de tamanho microscópico e (D) mostra a névoa do aerosol saindo do dispositivo.

Alguns estudos publicados na literatura compararam a eficácia do NM em comparação ao NJ. Assim, O´Callaghan et al[72] comparou os dispositivos de

nebulização Pari LC plus (NJ) e o Aerogen (NM) utilizando-se como gás o heliox em pacientes com obstrução pulmonar. Evidenciaram significativo rendimento do NM através de um maior percentual de partículas menor que 5 µm e maior aproveitamento da droga nebulizada[72].

Tezuka et al[73] evidenciaram maior concentração plasmática de corticóide inalado e melhora dos sintomas da asma através do uso de NM quando comparado a outros tipos de nebulizadores em crianças asmáticas durante um período de 12 semanas. Somando-se a isto, estes autores verificaram redução significativa do nível de cortisol num prazo de 4 semanas quando comparado aos valores basais.

Ainda, Johnson et al[74] também demonstraram maior eficácia do NM (Omron Micro Air) em comparação ao NJ (Pari LC + Pari Pro Neb Ultra compressor) no tocante a massa de aerossol gerada e no menor tempo de nebulização durante a inalação de DNase recombinante humana I no tratamento de pacientes com fibrose cística.

Com relação à utilização dos NM em pacientes com DPOC, Goodman et al[75] analisaram o nível de satisfação na utilização do dispositivo I-neb AAD System (NM) em comparação outros NJs durante três meses e aplicaram um questionário de qualidade de vida (*Chronic Respiratory Questionnare* – CRQ). Estes autores verificaram maior satisfação com o dispositivo I-neb AAD System, com melhora do nível de dispnéia e da fadiga.

Apesar dos vários trabalhos acima descritos, são escassos os estudos envolvendo o uso dos dispositivos NM em associação a VNI na Asma e na DPOC, principalmente enfocando os aspectos de melhora clínica através da

análise da função pulmonar e a deposição de radioaerossol nos diferentes segmentos pulmonares, principalmente a distribuição pulmonar regional da ventilação.

6.3 Aspectos técnicos inerentes ao uso da VNI nas doenças respiratórias obstrutivas

A VNI tem sido empregada como terapia coadjuvante no tratamento clínico de vários tipos de IRA, demonstrando efetividade em condições patológicas como a asma e a DPOC[17,20,21,25-27,30-32].

Este tipo de suporte ventilatório pode ser definido como à aplicação de pressão positiva nas vias aéreas de indivíduos sem a necessidade de um tudo endotraqueal[76]. Dentre as modalidades ventilatórias utilizadas durante a VNI, destacam-se: pressão contínua nas vias aéreas – CPAP (*continuous positive airway pressure*), ventilação controlada a volume – VCV (*volume controll ventilation*), ventilação controlada a pressão – PCV (*pressure controll ventilation*), ventilação com pressão de suporte – PSV (*pressure suport ventilation*), ventilação assistida proporcional – PAV (*proportional assisted ventilation*) e do *bilevel*, também designado de BiPAP ou dois níveis pressóricos [48,49]. No tocante ao BiPAP, aplica-se um nível pressórico mais elevado durante a inspiração (IPAP - *inspiratory positive airway pressure*) e outro nível menor durante a fase expiratória (EPAP – *expiratory positive airway pressure*)[48,49].

A maioria dos estudos envolvendo DPOC e asma utilizam as modalidades CPAP ou BiPAP[24,48,78,81-83]. Na CPAP utiliza-se apenas um nível de

pressão, a qual é mantida durante todo o ciclo respiratório, objetivando o aumento da CRF, o recrutamento das unidades alveolares colapsadas e pouco ventiladas, a redução do *shunt* intrapulmonar, melhora na oxigenação e redução do trabalho respiratório[49,76-79]. Recomenda-se um valor mínimo de 10 cmH_2O para garantir os efeitos acima descritos, porém a utilização de 5,3 ± 2.8 cmH_2O foi apontado como melhor nível de conforto pelos pacientes asmáticos[84].

No caso do *bilevel*, é instituído um nível mais elevado de pressão inspiratória, objetivando reduzir o trabalho da musculatura inspiratória, diminuindo a carga imposta a estes músculos e a outro nível menor durante a fase expiratória, na tentativa de recrutar os alvéolos, revertendo as alterações da relação ventilação/perfusão e também vencendo os níveis de PEEPi ocasionados pelo aprisionamento aéreo nas afecções obstrutivas[10,25,48,52]. Recomenda-se uma IPAP ajustada de forma a garantir 6-8 ml/kg e FR < 30 ipm, sendo o valor da EPAP inferior ao da PEEPi, sugerindo-se iniciar com 5-6 cmH_2O[76-79].

O sucesso da VNI depende de alguns aspectos técnicos, dentre eles a escolha do tipo de máscara para aplicação do suporte nas doenças respiratórias crônicas[48,49]. Atualmente estão disponibilizadas para comercialização, diferentes tipos de máscara nasais, orofaciais, facial total e capacetes. Em se tratando de IRA, observou-se melhor adaptação dos pacientes através do uso da máscara oronasal devido ao vazamento do fluxo de ar pela cavidade oral, sendo as máscaras nasais indicadas para o uso nos pacientes com doença pulmonar crônica[48].

Ainda, no tocante aos aspectos técnicos, existem outros acessórios disponibilizados para a aplicação da VNI que são as presilhas e válvulas exalatórias. Com relação a essas últimas, apesar do maior volume de ar contido no interior da máscara, a reinalação com o uso deste tipo de máscara é semelhante às máscaras oronasais, porém os capacetes podem aumentar a reinalação devido ao elevado espaço-morto e maior complacência de suas paredes[78,80].

Com relação às indicações do uso deste suporte ventilatório, destacam-se o uso nas exacerbações da DPOC, asma, imunossupressão, pós-transplantes, pneumonia, pós-redução pulmonar, pós-operatório de cirurgias abdominais e torácicas, pós-extubação, como estratégia de desmame da ventilação mecânica e em pacientes terminais[48,49]. Entretanto, o nível de evidência alcançado em cada uma das indicações é variável, tendo em algumas destas situações clínicas a necessidade de mais informações, na tentativa de alcançar maior evidência científica[48,49].

Outro aspecto importante para o sucesso da VNI, diz respeito a adequada seleção dos pacientes que irão ser submetidos ao uso da pressão positiva. A utilização da VNI está contra indicada nos pacientes que evoluem com rebaixamento do nível de consciência ou agitação psicomotora, dificuldade em manter a permeabilidade da via aérea superior (inclusive com integridade dos mecanismos de deglutição e tosse eficaz), instabilidade hemodinâmica severa com uso de aminas vasoativas, arritmias complexas, distensão abdominal, naúseas ou vômitos (facilidade de broncoaspiração), trauma facial, lesão aguda e/ou sangramento de via aérea, hemorragia digestiva alta e infarto

agudo do miocárdio. Com relação aos pacientes pós-operatório de cirurgia gástrica e durante o período gestacional[48,49,77],a utilização de suporte ventilatório ainda é controversa.

6.4 Fatores que interferem na liberação dos aerossóis com o uso da VNI

Os efeitos clínicos obtidos a partir da inalação das drogas broncodilatadoras dependem da quantidade adequada de droga que necessita ser depositada nos pulmões. Desta forma, a quantidade de droga que alcança o trato respiratório inferior poderá ser predita baseando-se em modelos que representam as vias aéreas e a utilização de ventilação mecânica simulando condições clínicas[87].

A utilização de determinados tipos de inaladores consegue predizer fielmente o percentual possível da droga depositada com o uso da pressão positiva, como é o caso dos nebulímetros dosimetrados testados *in vitro*[88,89]. Entretanto, em se tratando dos nebulizadores, a quantidade de droga a ser depositada nos pulmões só poderá ser predita mediante situações específicas de funcionamento dos dispositivos, principalmente no tocante ao tempo requerido para a liberação de uma quantidade conhecida da droga[90]. Desta forma, para serem obtidos efeitos benéficos no tratamento das afecções respiratórias crônicas, necessário se faz conhecer os possíveis fatores que possam interferir na deposição dos aerossóis com o uso da pressão positiva[87].

Existem vários fatores que afetam a liberação dos broncodilatadores durante o uso da ventilação mecânica, os quais podem ser classificados de

acordo com três categorias: fatores relacionados ao ventilador; fatores relacionados ao circuito do ventilador e fatores relacionados aos dispositivos de inalação[91].

Além disso, a falta de atenção e o não reconhecimento destes fatores não propiciam apenas significante deposição da droga no circuito do ventilador e na via aérea artificial, mas também na eficiência do aerossol liberado[91].

6.4.1 Fatores relacionados ao ventilador

Vários estudos investigaram os efeitos dos fatores pertinentes ao ventilador disponibilizado para a aplicação de pressão positiva. Assim, o modo ventilatório, o volume corrente (VC), a relação entre o Ti/Ttot (tempo inspiratório / tempo respiratório total), o tempo inspiratório (Ti), o fluxo inspiratório (FI), o mecanismo de disparo e a forma de onda inspiratória são apontados como responsáveis por influenciar os aerossóis em pacientes usando a ventilação mecânica[11,88,89,92-95].

O modo ventilatório influencia a liberação do aerossol para as vias aéreas inferiores, conforme demonstrado por Fink et al[88] ao demonstrar os efeitos do modo ventilatório na dose do broncodilator liberado através de MDI, acoplado ao espaçador em um modelo *in vitro* simulando a ventilação mecânica em adultos. Foram comparados os modos VCV, PCV e CPAP com adequação dos parâmetros ventilatórios e observaram que com um VC de 800 ml e mantendo-se o circuito de ventilação seco, as deposições forma similares nas modalidades

VCV e PCV, porém a deposição foi maior quando se dispôs da CPAP. Destacaram ainda que a deposição dos aerossóis nesta modalidade aumentou acima de 30% quando comparada a modalidade na qual os ciclos respiratórios foram controlados.

Ainda no tocante as modalidades de ventilação, Hess et al[93] analisou a liberação de albuterol obtida através de 4 jatos no MDI com espaçador e de 4 mL de solução colocada no NJ utilizando os modos ventilatórios VCV e PVC, cujo VC foi 600 mL, FR programada em 15 ipm e PEEP de 5 cmH_2O e consideraram o tempo inspiratório de 1 ou 2 segundos. Ainda, levaram em consideração duas situações pulmonares distintas que foram alta complacência / alta resistência e baixa complacência / baixa resistência. Os autores observaram que a deposição com o MDI não diferiu, independente do modo ventilatório, tempo inspiratório ou situação pulmonar, mas a deposição com o NJ diferiu de acordo com as condições utilizadas. Constatou-se que o NJ dobrou o quantitativo de deposição quando analisado modo VCV em 1 ou 2 segundos e com a alta complacência / alta resistência pulmonar, porém reduziu a deposição do aerossol quando utilizou-se a situação de baixa complacência / baixa resistência pulmonar.

Dentre as modalidades de ventilação utilizada, atualmente os dois níveis de pressão utilizadas (*BiPAP*) tem sido utilizado na abordagem dos pacientes com asma e DPOC, minimizando o desconforto respiratório e reduzindo sobremaneira o trabalho imposto pela musculatura respiratória[17,20,21,25,27,30-33]. A diferença entre as pressões inspiratória e

expiratória (IPAP – EPAP) representa o nível de pressão suporte inspiratória, podendo ambas as pressões serem empregadas independentemente[42].

De acordo com dados na literatura, o VC utilizado durante a aplicação da pressão positiva deverá ser maior do que o quantitativo de volume capaz de preencher a traquéia colocada no circuito de ventilação e o tubo orotraqueal (TOT) entre o nebulizador e o paciente. Postula-se que com o nebulizador posicionado no ramo inspiratório do circuito de ventilação mecânica, exatamente a 6 cm da peça em Y, o VC proveniente da traquéia do circuito, da peça Y e do TOT deverá ser maior que 150 mL. A utilização de um VC maior que 500 mL em adultos aumentou a liberação do aerossol para o trato respiratório inferior proveniente de um MDI posicionado distalmente do TOT[88]. Entretanto, apesar do aumento do VC incrementar a deposição pulmonar dos aerossóis, vale ressaltar o cuidado ao serem utilizados altos valores de VC devido ao risco de volutrauma (maior que 8-10 mL/Kg)[95].

A relação Ti/Ttot aumentada ocasiona aumento na liberação do aerossol através do TOT independente do tipo de dispositivo gerador da névoa. No caso dos nebulizadores que geram a névoa continuamente, este conceito se aplica de forma efetiva, mas no caso do MDI isto não se aplica na mesma magnitude, pois o aerossol é gerado num curto espaço de tempo. Fink et al[88] demonstrou que a liberação de albuterol em um modelo in vitro usando o MDI pode variar quanto se utilizou a relação Ti/Ttot de 0.25 e 0.50, cuja variação do FI foi de 40 e 80 L/min. Observaram que ocorreu aumento da droga depositada nos pulmões com o aumento da relação Ti/Ttot, porém com incremento na deposição durante a variação do fluxo de 40 L/min *versus* 80 L/min.

No tocante ao FI, sabe-se que altos fluxos irão promover turbulência e ocasionara a impactação inercial das partículas do aerossol, sendo os baixos valores de FI responsáveis por promover maior deposição da névoa nos pacientes sob o uso de pressão positiva[88,96]. Recomenda-se reduzir o FI o máximo possível, mas de forma a alcançar um valor que seja tolerável pelo paciente. De acordo com Fink et al[88], mensurações *in vivo* e após constatação *in vitro* com o MDI em 10 pacientes sob ventilação mecânica, evidenciaram o dobro da deposição das partículas utilizando FI de 40 L/min em comparação ao de 80 L/min. Ainda, recomenda-se utilizar o FI de 30-50 L/min na tentativa de otimizar a deposição das drogas broncodilatadoras durante a ventilação com pressão positiva na tentativa de minimizar a PEEPi[95].

Os dispositivos que ofertam pressão positiva atualmente utilizam o disparo à pressão ou a fluxo contínuo ("*flow bias"*), objetivando reduzir o trabalho respiratório por parte do paciente. O disparo a fluxo poderá afetar o rendimento das nebulizações devido ao fato de diluir o aerossol e aumentar a quantidade da solução que escapa para o ramo expiratório do circuito de ventilação durante os ciclos respiratórios. Por outro lado, este tipo de disparo não afeta o MDI devido à sincronização durante a liberação do aerossol não é afeta por este mecanismo de disparo[88].

Estudo realizado por Ari et al[95], analisou a influência do disparo do disparo a fluxo de 2 e 5 L/min, utilizando o NJ e o NM para promover a liberação de albuterol em um modelo de ventilação mecânica em adultos, ajustando os parâmetros ventilatórios da seguinte forma: VC = 500 mL; FR = 20 ipm; FI = 60 L/min; PEEP = 5 cmH_2O e onda de fluxo descendente. Como achado,

observaram que o aumento do fluxo inspiratório ocasionou aumento da deposição pulmonar da droga e a utilização do fluxo mais baixo promoveu maior deposição da medicação.

Finalmente, outro fator que afeta diretamente a liberação do aerossol pulmonar diz respeito ao tipo de onda de fluxo utilizada durante o suporte ventilatório. A onda quadrada propicia menor deposição do aerossol quando comparada as ondas descendente e sinusoidal. Isto poderia ser justificado pelo início súbito e duração do pico de fluxo, ocasionado acentuada turbulência. De acordo com dados da literatura, a influência do tipo de onda alta mais os nebulizadores em comparação ao MDI[91].

Hess et al[93] analisou as ondas de fluxo quadrada e descendente através de um modelo experimental de pulmão in vitro, observaram que FI menor que 36 L/min afetaram a deposição do aerossol de acordo com o tipo de onda de fluxo utilizada apenas nos NJ, não afetando o MDI.

6.4.2 Fatores relacionados ao circuito do ventilador

Dentre os fatores que afetam a liberação da névoa durante a ventilação por pressão positiva, destacam-se: tipo de circuito; uso de TOT aquecimento e umidificação; densidade do gás inalado e o uso de adaptadores para acoplar o inalador no circuito de ventilação[89,97-103].

A maior parte dos dispositivos projetados para a VNI utiliza circuito único de ventilação sem a presença do ramo exalatório[42]. Para tal, dispõe-se de um orifício de exalação no próprio circuito ou na máscara, porém existe a

possibilidade de reinalação do gás expirado. Isto poderá ser evitado aumentado o fluxo de exalação, utilizando nível mais elevado da CPAP, utilizando-se uma válvula que evite reinalação ou incorporando o orifício de exalação na máscara ao invés do circuito[97,98].

A utilização de um TOT afeta diretamente a quantidade do aerossol depositado no trato respiratório inferior, tendo sido demonstrado *in vitro* que a redução do diâmetro do TOT incorre em menor deposição da névoa[91]. Corgan e Bishop[99] observaram redução de 3% da droga utilizando-se um TOT de 6.0mm e 6.5% quando o diâmetro aumentou par 9.0mm. Semelhantemente, o estudo direcionado por Takaya et al[100], observou a deposição do aerossol com variação do diâmetro de TOT de 5 a 7.5mm e evidenciou que menor eficácia na deposição no diâmetro menor. Esta deposição torna-se ainda menor, em se tratando de vias aéreas artificias utilizadas em pediatria, tendo sido observada significativa redução com diâmetros entre 4 e 8.5mm. Ainda, constatou-se que experimento in vivo encontrou redução de 2.6 e 7% no rendimento do nebulizador depositado no TOT.

No que diz respeito ao uso de um traqueóstomo, O´Riordan et al[39] testaram o nebulizador preenchido com 2 mL de solução salina marcada com radioisótopo em 7 pacientes sob assistência ventilatória mecânica via traqueostomia e evidenciaram que 3% da dose nominal do radiaoerossol depositou-se no tubo de traqueostomia quando comparado ao quantitativo que alcançou os pulmões.

O aquecimento e umidificação do circuito de ventilação durante o uso da pressão positiva em adultos e crianças tornou-se necessário pelo fato de

prevenir ressecamento da mucosa respiratória e reduzir a possibilidade de broncoespasmo ao ser respirado ar seco e frio[91]. Porém, durante o uso de ventilação mecânica, a liberação de droga nos pulmões pelo MDI e nebulizadores é reduzida em 40% ou mais quando se utiliza um sistema de umidificação acoplado ao sistema de ventilação em comparação a não utilização de umidificação[88,89,96,95]. Isto poderia ser justificado devido ao aumento da higroscopicidade das partículas inaladas, as quais aumentam de tamanho devido à adição de moléculas de água, tornando as partículas menos absorvíveis e ocasionando redução da deposição pulmonar[91].

Apesar disto, não se recomenda a retirada da umidificação aquosa aquecida (UAA) para a realização durante a terapia inalatória, pois requere desconexão do circuito de ventilação, interrompendo a ventilação do paciente e seria necessário esperar vários minutos para que o circuito estivesse totalmente seco[101].

Assim, enquanto a umidificação aquosa afeta a deposição do aerossol tanto nos dispositivos de ventilação mecânica invasiva e VNI, a utilização de um filtro trocador de calor e umidade (FTCU) entre o nebulizador e o dispositivo de VNI não altera o tamanho das partículas produzidas[102]. Entretanto, este tipo de umidificador poderá funcionar como barreira mecânica e deverá ser removido do circuito durante a inalação e recolocado logo a pós o procedimento[91].

A densidade do gás inalado também afeta diretamente a deposição das partículas no trato respiratório, principalmente na vigência de alto FI, o que ocasiona turbulência na passagem do fluxo de gás nas vias aéreas estreitadas. Desta forma, a inalação de uma mistura de heliox com oxigênio reduz esta

turbulência, pois a baixa densidade do gás cria fluxos laminares dentro das vias aéreas com evidente aumento da deposição pulmonar da droga[103].

Segundo Goode et al[104], uma mistura de heliox/oxigênio na ordem de 80/20 liberada a partir do MDI e do NJ aumentou significativamente a deposição do aerossol acima de 50% quando comparado com a inalação apenas com o oxigênio dispondo-se dos mesmos dispositivos. Ainda, Hess et al[105] administrou diferentes doses de broncodilator com diferentes taxas de fluxo usando oxigênio ou heliox na tentativa de determinar o efeito com a inalação deste gás em dois tipos diferentes de nebulizadores. Estes autores observaram que a massa do aerossol inalado e o tamanho das partículas produzidas apresentaram redução significante em ambos os dispositivos.

Somando-se a isto, muitos circuitos de ventilação sofreram adaptação quanto ao uso de nebulização, tendo sido criado um adaptador para acoplar o MDI no momento de realizar a inalação, sendo posicionado entre o TOT e a peça Y, porém estes dispositivos foram especificamente adaptados para uso com o MDI[89,91].

6.4.3 Fatores relacionados aos dispositivos de inalação

Alguns fatores relacionados aos dispositivos de inalação também irão afetar a liberação do aerossol para os pulmões, destacando-se: tipo de inalador; posição do inalador no circuito e os fatores diretamente ligados aos nebulizadores (tipo de nebulizador, volume residual e titulação do fluxo de gás)[91,107-111].

Vários estudos *in vitro* e *in vivo* têm sido conduzidos na tentativa de quantificar a deposição pulmonar do MDI e dos nebulizadores. Especificamente, os estudos in vitro indicam que o aerossol liberado para o trato respiratório inferior pode variar de 0 até 42% com o uso dos nebulizadores e de 0.3% até 97.5% com o MDI[34,38,88,89,94].

A posição do nebulizador no circuito de ventilação também afeta a liberação do aerossol. Quanto da utilização de um TOT, o dispositivo de inalação deverá ser colado distante do TOT, pois isto propicia ao aumento de deposição pulmonar do broncodilatador, pois o circuito irá funcionar como um espaçador acumulando aerossol entre os ciclos respiratórios[91].

O tipo de nebulizador, levando-se em consideração a mesma marca do dispositivo, tem sido observado variabilidade na produção do aerossol[94,107-108]. De acordo com dados reportados na literatura, NJ parecem ser menos eficientes quando comparados ao NU e ao NM, inclusive este último apresenta uma alta taxa de aerossol em um curto espaço de tempo[94,109,110].

Alvine et al[107] analisaram a frequência do mal funcionamento, variabilidade no rendimento do nebulizador e o tamanho das partículas em 8 modelos de JN e verificaram uma diferença no rendimento dos dispositivos que variou de 575 a 129% dentro de um modelo específico. Ainda, Loffert et al[108] testaram 17 NJ comercialmente disponíveis, os quais foram preenchidos com 2 mL de solução salina e 0.5 mL de albuterol. Após o uso, demonstraram que o rendimento dos dispositivos apresentou significante variação no tocante ao tempo de nebulização e na quantidade de droga liberada para os pulmões.

O VR corresponde à quantidade de líquido que resta ao final da nebulização dentro do recipiente do nebulizador. Este VR poderá variar de 0,1 a 2.4 mL, a depender do protótipo de nebulizador[41]. Os NJs apresentam maior VR, nebulizam uma menor proporção da droga e não funcionam satisfatoriamente com um volume abaixo de 2 mL de solução. Desta forma, recomenda-se a utilização de 4 a 5 mL de solução para nebulizar[112]. Contrariamente, os NMs apresentam menor VR em comparação aos NJs e NUs, observando-se uma variação no VR de 0.1 a 0.5 mL, porém são mais dispendiosos e os modelos existentes são limitados para uso em pacientes com ventilação mecânica invasiva ou VNI[41,87].

Com relação ao fluxo de gás, o NJ foi projetado para operar com diferentes níveis de fluxo, sendo que cada modelo inventado apresenta o nível de fluxo específico para operação. Estes valores podem variar de 2 a 8 L/min e em situações na qual o fluxo é titulado em um valor mais baixo, irá ocorrer alteração no tamanho das partículas com consequente alteração na deposição das drogas. Ainda, o fluxo é inversamente proporcional ao tempo requerido para nebulização, ou seja, a utilização de altos fluxos irá reduzir o tempo necessário para liberar certo quantitativo de droga[91].

6.5 Associação das nebulizações com a VNI nas doenças respiratórias crônicas

A VNI tem demonstrado cada vez mais sua aplicabilidade clínica no tratamento da IRA, através de evidências satisfatórias quanto à melhora das

trocas gasosas, a redução da fadiga muscular respiratória e à necessidade de intubação traqueal no tratamento da IRA em asmáticos e pacientes com DPOC[17-21,30-32,26-28]. Inclusive, alguns estudos demonstraram redução da mortalidade e diminuição do tempo de hospitalização em pacientes selecionados com IRA secundária a DPOC[22-24].

Pacientes com IRA ou insuficiência respiratória crônica (IRC) em uso da VNI, requerem a inalação de broncodilatadores para alívio da obstrução das vias aéreas[83]. Inicialmente, estas drogas foram administradas através do uso da respiração por pressão positiva intermitente – IPPB (*intermittent positive pressure breathing*) nos pacientes asmáticos, mas não foi evidenciado benefícios clínicos, inclusive foi observada piora das trocas gasosas e surgimento de barotrauma. Esses resultados podem ser questionáveis devido a severidade da doença e os estudos não serem controlados[112,113].

Na tentativa de determinar qual a melhor técnica para liberação do aerossol nos pacientes com o auxílio da VNI, têm sido utilizados modelos *in vitro*, como no estudo de Parkes e Bersten[114], que utilizaram a CPAP (10 cmH_2O) durante a inalação de broncodilatador num modelo que simula as vias aéreas. Além disso, neste mesmo trabalho, testaram em pacientes asmáticos a inalação do radioaerossol através do NBJ e associada à VNI, tendo sido observada uma redução da deposição no modelo *in vitro* e no estudo clínico, não houve diferença significativa quanto a reversão da obstrução.

A utilização da CPAP em estudos *in vivo* tem demonstrado efeito broncodilatador na reversão da obstrução brônquica na asma, reduzindo o trabalho da musculatura respiratória e melhorando as trocas gasosas[115,116].

Desta forma, observou-se que o uso desse suporte após broncoprovocação com metacolina, melhorou o broncoespasmo e aumentou o VEF_1[117].

No entanto, nem sempre é utilizada simultaneamente a nebulização associada à VNI, mas observou-se correção das alterações hemogasimétricas, diminuição da FR, diminuição da necessidade de sedação nos pacientes e aumento do índice de oxigenação (PaO_2/FiO_2) apenas com a VNI (CPAP + PSV) durante as exacerbações da asma[114]. Além dos benefícios clínicos acima descritos, também se observou redução do uso da musculatura acessória e da sensação de dispnéia, sem verificar associação com outras comorbidades quando comparou a VNI com o tratamento conservador em uma amostra de crianças com obstrução brônquica[118]. Resultados similares também foram encontrados com o uso do BIPAP em crianças asmáticas atendidas na Unidade de Terapia Intensiva Pediátrica, inclusive com menor ou nenhuma necessidade de sedação dessas crianças[18].

Pollack et al[30] foi um dos pioneiros na associação das nebulizações durante a aplicação da VNI ao analisar pacientes com asma moderada a severa e verificou aumento no PEF após a liberação das drogas β2-agonistas através do BiPAP (IPAP = 10 cmH_2O e EPAP = 5 cmH_2O) em comparação ao grupo que realizou apenas a nebulização. De acordo com os achados do estudo, estes autores afirmaram que melhora no marcador de obstrução broncopulmonar seria devido a maior liberação do aerossol no interior das vias aéreas como resultado da aplicação da pressão positiva.

O primeiro ensaio clínico controlado e randomizado envolvendo o uso do BiPAP em pacientes asmáticos no setor de emergência hospitalar foi descrito

por Holley et al[119], ao analisar os efeitos deste suporte em 35 pacientes asmáticos, sendo 19 alocados no grupo experimental (BiPAP) e 16 no grupo controle. Este estudo objetivou determinar se o uso da VNI com máscara nasal poderia reduzir a taxa de intubação e a permanência no hospital. Porém, este ensaio clínico foi interrompido devido a presença de viés durante o recrutamento dos pacientes, ocasionado incerteza quanto a sua validade. Assim, não encontraram significância quanto à taxa de intubação e a permanência hospitalar.

Posteriormente, Soroksky et al[17] analisaram os efeitos da VNI em um grupo com asma severa internados no departamento de emergência e divididos em dois grupos (grupo controle – utilizou um placebo, sendo a VNI aplicada com apenas 1 a 2 cmH2O e grupo experimental – VNI com dois níveis de pressões, sendo a IPAP e EPAP ajustadas de forma a garantir conforto durante a ventilação dos pacientes). Vale ressaltar que os pacientes não realizaram a VNI concomitantemente ao uso da inalação, mas caso os pacientes necessitassem de nebulização, a VNI seria interrompida e logo após, os pacientes retornariam ao suporte. Como achados, os autores verificaram melhora espirométrica (VEF_1, CVF e PFE), alívio do desconforto respiratório e redução da taxa de intubação. Estes resultados foram atribuídos a broncodilatação mecânica experimentada pelos pacientes com o uso da VNI.

Soma et al[20] verificaram os benefícios da VNI em 44 pacientes com asma leve a moderada, os quais foram divididos em dois grupos (grupo controle, n=14, receberam apenas hidrocortisona endovenosa e grupo experimental, n=30, receberam hidrocortisona endovenosa e VNI). Ainda, o grupo

experimental foi submetido á randomização e subdividido em dois grupos designados de alta pressão (n=16, IPAP = 8 cmH_2O e EPAP = 6 cmH_2O) e baixa pressão (n=14, IPAP = 6 cmH_2O e EPAP = 4 cmH_2O). Verificou-se, após 40 minutos de uso da pressão positiva, melhora significativa do VEF_1 nos subgrupos da VNI em relação ao grupo controle, bem como redução na percepção de esforço pela Escala de Borg no subgrupo alta pressão em relação ao controle. Além disso, não houve necessidade de hospitalização ao retorno ao departamento de emergência.

Brandão et al[31] verificou a liberação de drogas broncodilatoras durante a VNI com o dois níveis de pressão no departamento de emergência em asmáticos, os quais foram alocados em três grupos: controle (apenas nebulizou) experimental 1 (nebulização com VNI, IPAP = 15 cmH_2O e EPAP = 5 cmH_2O), e experimental 2 (nebulização com VNI, IPAP = 15 cmH2O e EPAP = 10 cmH2O). Observou-se aumento significativo no VEF1, CVF e PFE nos grupos que utilizaram a VNI, porém a melhora do PFE foi ainda maior no grupo cujo delta de pressão (IPAP – EPAP) foi de 10 cmH_2O, tendo os autores sugerido este achado devido ao maior recrutamento alveolar ocorrido através da ventilação colateral com estes níveis pressóricos.

Além disso, Gupta et al[21] aplicaram VNI em um grupo de asmáticos exacerbados randomizados em dois grupos, tendo o grupo controle (n=25) recebido tratamento medicamentoso e o grupo experimental (n=28) foi tratado com VNI (IPAP = 12 cmH_2O e EPAP = 5 cmH_2O). Como resultado, observou-se aumento significativo do VEF1, redução do tempo de hospitalização e da dose de broncodilator necessária para o alívio dos sintomas respiratórios.

Os estudos envolvendo a utilização da VNI associada à nebulização *in* vivo são escassos. Antecedendo o uso da VNI com o *bilevel*, Dolovich et al[119] aplicaram a IPPB durante a administração de broncodilatadores em 9 pacientes com bronquite crônica com o intuito de comparar a inalação com o NJ associado a VNI apenas a nebulização em respiração espontânea. Ainda, neste protocolo utilizaram uma pressão inspiratória de 15 cmH_2O e observaram redução de 30% na deposição pulmonar e maior deposição do radiaoerossol na orofaringe, traquéria de vias aéreas superiores no grupo que realizou a VNI em comparação ao grupo que apenas nebulizou. Estes autores justificaram este fato devido ao aumento do FI durante o uso da IPPB, podendo esta redução na deposição afetar diretamente o alívio da broncoconstrição nestes pacientes.

Por outro lado, no estudo de Faroux et al[120] não foi observado diferença na deposição regional ou na homogeneidade do aerossol depositado nos pulmões de 18 crianças com Fibrose Cística estável ao utilizar a modalidade PSV durante a nebulização. Como resultado, verificaram aumento em 30% após a inalação com a VNI sem aumento da impactação do radioaerossol nas vias áereas proximais.

De acordo com França et al[52], a utilização nebulização com uso da pressão positiva (IPAP = 12 cmH2O e EPAP = 5 cmH2O) em 13 indivíduos normais resultou em maior deposição do radioaerossol no grupo que apenas realizou a inalação em comparação ao grupo que foi submetido a inalação com o BiPAP. Ainda, observou-se no grupo nebulização uma correlação positiva entre o VC e a quantidade do radioaerosol depositado nos pulmões.

Recentemente, nosso grupo realizou um ensaio clínico controlado e randomizado[32] envolvendo asmáticos no departamento de emergência para analisar os efeitos cardiopulmonares e a deposição pulmonar do radioaerossol marcado com técnesio-99 através de cintilografia pulmonar. Para tal, os pacientes foram randomizados em dois grupos: controle (n=11, nebulização de inalação de β2-agonista) e experimental (n=10, inalação de β2-agonista associado a VNI pelo BiPAP, IPAP = 12 cmH_2O e EPAP = 5 cmH_2O). Apesar de não ter sido evidenciada diferença na deposição pulmonar do radioaerosol nos dois grupos estudados, foi observado aumento significativo dos parâmetros espirométricos (VEF_1, CVF, PFE, VC e CI) e redução significativa do VE e da FR no grupo VNI em comparação ao grupo controle. A tabela 1 resume os resultados obtidos dos principais estudos envolvendo o uso da VNI em pacientes asmáticos.

Tabela 1. Principais ensaios clínicos controlados e randomizados envolvendo asmático em crise.

Nome do primeiro autor	Ano de publicação	Amostra	Níveis de IPAP e EPAP	Principais desfechos
Holley [119]	2001	19 - BiPAP 16 – Controle (terapia convencional)	IPAP=10 cmH_2O EPAP=5 cmH_2O (grupo BiPAP)	Menor taxa de intubação. Menor tempo de permanência hospitalar.
Soroksky [17]	2003	15 – BiPAP 15 – Controle (terapia convencional)	IPAP=14 cmH_2O EPAP=4 cmH_2O (grupo BiPAP)	Elevado aumento do VEF_1. Menor taxa de hospitalização. Não houve necessidade de intubação.
Soma [20]	2008	16 – BiPAP (alta pressão) 14 – BiPAP (baixa pressão) 14 – Controle (terapia convencional)	Alta pressão: IPAP=8 cmH_2O EPAP=6cmH_2O Baixa pressão: IPAP=6 cmH_2O EPAP=4 cmH_2O	Grande aumento do VEF_1 no grupo com maior pressão. Redução da dispnéia e da sibilância nos grupos de alta e baixa pressões. Não houve necessidade de intubação.
Brandão [31]	2009	12 – Alto delta de pressão 12 – Baixo delta de pressão 12 – Controle (terapia convenciona)	Alto delta de pressão IPAP=15 cmH_2O EPAP=5 cmH_2O Baixo delta de pressão: IPAP=15 cmH_2O EPAP=10 cmH_2O	Melhora significante do PFE, VEF_1, da CVF no grupo de menor pressão. Não houve necessidade de intubação.
Gupta [21]	2010	28 – BiPAP 25 – Controle (terapia convencional)	IPAP=12 cmH_2O EPAP=5 cmH_2O (grupo BiPAP)	Melhora rápida do VEF_1. Menor taxa de hospitalização e tempo de permanência na UTI. Menores doses de broncodilatadores. Sem diferença entre os grupos quanto à taxa de intubação.
Galindo-Filho[32]	2013	10 – BiPAP+NJ 11 – NJ	IPAP=12 cmH_2O EPAP=5 cmH_2O (grupo BiPAP)	Não houve diferença na deposição do radioaerossol nos ambos os grupos. Melhora signifcativa do VEF_1, CVF, PFE e CI no grupo VNI. Redução da FR e do VM no grupo VNI.

BiPAP – Bi-level positive-end expiratory pressure; IPAP – Inspiratory positive airway pressure;
EPAP – Expiratory positive airway pressure; PFE – Pico de fluxo expiratório; VEF1 – Volume expiratório forçado no primeiro segundo; CVF – Capacidade vital forçada; CI – Capacidade inspiratória; FR – Frequência respiratória; VM – Volume minuto; NJ – Nebulizador de jato.

O sucesso obtido com o uso da VNI no tratamento da DPOC fez com que o seu uso fosse também encorajado na abordagem da exacerbação da asma[77]. Um dos aspectos que contribuiu para isto diz respeito às semelhanças fisiopatológicas entre estas duas patologias, pois ambas apresentam o aprisionamento aéreo em decorrência da limitação crônico do fluxo expiratório, desvantagem mecânica do músculo diafragma em gerar pressão, aumento do trabalho respiratório e fadiga dos músculos respiratórios[25,121,122].

Apesar do baixo nível de evidência científica, de acordo com o III Consenso Brasileiro de Ventilação Mecânica Não-Invasiva com Pressão Positiva, o grau de recomendação da VNI é “B”, podendo ser utilizada em conjunto com o tratamento medicamentoso convencional para o cuidado de pacientes selecionados com exacerbação aguda e grave da asma[77].

Dentre as principais condições que interferem na qualidade dos ensaios clínicos controlados e randomizados do uso da VNI durante as exacerbações da asma destacam-se: tamanho da amostra reduzida; viés de recrutamento do pacientes; ausência de mascaramento; doses ideais de drogas broncodilatadores e corticosteróides desde o início do estudo; diferenças metodológicas quanto à abordagem da nebulização em associação ou não com o BiPAP; diferenças quanto a gravidade da crise da asma; pressões muito baixas, semelhantemente aos níveis da CPAP e poder do estudo[123].

No tocante a gravidade da crise de asma, deve-se considerar na fisiopatologia da doença a presença de dois fenótipos clínico-biológico-funcionais diferentes. O primeiro é considerado o mais comum, designado tipo I e é responsável por 80-85% dos eventos fatais, caracterizado por inflamação

eosinofílica associada a gradual deterioração por dias e semanas, a qual ocorre em pacientes com asma severa e de pobre controle da doença. O segundo fenótipo é designado do tipo II, tem predomínio de uma reação inflamatória neutrofílica e tende a ser mais danoso, pois apesar da asma ser leve quando fora da crise, surge de forma insidiosa e com rápida progressão da obstrução brônquica, porém responde bem ao tratamento medicamentoso. Além disso, como a maioria dos asmáticos subestima a duração dos sintomas, tem sido difícil distinguir entre os subtipos apenas pela coleta da história clínica[14,123-125].

Desta forma, de acordo com Scala[123] o momento do início da VNI na crise de asma parece não estar bem estabelecido, sendo apontado como motivos o fato do paciente não perceber a gravidade do nível de dispnéia apresentada e subestimar a condição clínica. Somando-se a isto, devem ser levadas em consideração as poucas publicações sobre o uso da VNI, as quais não estão claras no tocante as recomendações deste suporte na asma e a pequena janela de tempo para que o suporte seja iniciado o mais precocemente possível quando iniciado os sintomas da crise.

Diferentemente da asma, nas exacerbações da DPOC os níveis de evidência científica quando ao uso da VNI alcançaram grau de recomendação "A"[77]. Isto se deve aos ensaios clínicos controlados e randomizados[25-29] publicados na literatura, inclusive com a realização de revisões sistemáticas[22-24]. Ainda, recomenda-se que nos pacientes com DPOC agudizados, a VNI seja introduzida precocemente, considerando-se acidose leve (pH < 7.35) e taquipnéia (FR > 23 ipm), logo após ter sido iniciado o tratamento medicamentoso[26,77].

A utilização da CPAP por máscara facial como primeira linha de tratamento nos pacientes com IRA hipercápnica e hipoxêmica, incluindo-se nesta amostra pacientes com DPOC, apresentou importantes benefícios clínicos e melhora hemogasimétrica dentro de um intervalo de 2 horas[33]. Da mesma forma, o uso da VNI com dois níveis pressóricos no tratamento da IRA, foi capaz de reverter o quadro clínico dos pacientes, evitando a intubação e a utilização da ventilação convencional[86]. Além disso, a comparação da VNI com a ventilação convencional na abordagem de pacientes com IRA evidenciou melhor eficácia nas trocas gasosas, redução das complicações pulmonares e menor tempo de estadia na Unidade de Terapia Intensiva[126].

Um dos estudos pioneiros quanto a aplicação da VNI em um amostra contendo apenas pacientes com DPOC foi realizado por Brochard et al[26], ao investigarem os benefícios clínicos deste suporte em 85 pacientes com DPOC exacerbada, os quais foram randomizados em dois grupos: tratamento convencional (n=42) e VNI (n=43). A modalidade ventilatória usada para a liberação da pressão positiva foi PSV ajustada até 20 cmH_2O, caso os pacientes apresentassem desconforto a pressão seria reduzida e a PEEP ficou a nível da pressão atmosférica. Observaram redução na necessidade de intubação, diminuição da frequência de complicações e decréscimo da mortalidade hospitalar no grupo que utilizou a VNI em comparação aquele que recebeu o tratamento convencional.

Plant et al[27] conduziram um estudo multicêntrico controlado e randomizado envolvendo 236 pacientes com DPOC leve a moderada para comparar o uso da VNI (n=118) com a terapia convencional (n=118) em 14

unidades hospitalares no Reino Unido durante um período de 22 meses. O nível da IPAP utilizada foi inicialmente de 10 cmH_2O, podendo chegar até 20 cmH_2O e a EPAP foi programada em 4 cmH_2O. O grupo VNI apresentou redução significativa da necessidade de intubação (15% versus 27% no grupo tratamento convencional) e também, redução na mortalidade hospitalar (10% no grupo VNI em 20% no grupo tratamento convencional). Ambos os grupos apresentaram melhoras no pH, $PaCO_2$ (pressão parcial de gás carbônico) e FR, porém o grupo VNI demonstrou melhora mais rápida do pH na primeira hora e significante redução da FR em até 4 horas de aplicação do suporte. Os autores concluíam que a VNI aplicada em pacientes com DPOC leve a moderada ocasionou rápida melhora das variáveis fisiológicas e redução da necessidade de intubação e da mortalidade hospitalar.

Ainda, Bardi et al[28] investigou os efeitos imediatos e após 1 ano de seguimento de aplicação da VNI durante as exacerbações da DPOC em um ensaio clínico controlado e randomizado. Estes autores avaliaram 30 pacientes, randomizados em dois grupos: grupo VNI (n=15) e grupo terapia medicamentosa (n=15). Apesar de verificarem baixa necessidade de intubação, da mortalidade hospitalar e do tempo de permanência no hospital, estes resultados não foram significantes em comparação ao grupo terapia medicamentosa. Houve aumento significativo da PaO_2 (pressão parcial de oxigênio), redução da $PaCO_2$ e $HCO3^-$ (bicarbonato) em ambos grupos na admissão e após o tratamento com VNI. Entretanto, ocorreu melhora do pH e aumento significativoaumento significativo do FEV_1 e VC apenas no grupo VNI. Com relação ao tempo de seguimento no estudo, verificaram que após 3, 6 e 12 meses as taxas de sobrevida foram

elevadas no grupo VNI e as novas admissões hospitalares durante 1 ano foram maiores no grupo que recebeu o tratamento medicamentoso. Por esta razão, os autores recomendam o uso da VNI em adição ao suporte medicamentoso como abordagem durante as exacerbações da DPOC.

Contrariamente, Keenan et al[127] realizaram um ensaio clínico controlado e randomizado em um hospital terciário envolvendo uma amostra com 52 pacientes DPOC agudizados, tendo 25 recebido o tratamento medicamentos e a VNI (grupo experimental) e 27 apenas realizaram o tratamento com drogas (grupo controle). O grupo VNI utilizou a pressão positiva por 8 horas no primeiro dia, 6 horas no segundo dia e 4 horas no terceiro dia, sendo obtidas medidas através da Escala de Borg, do tempo de permanência hospitalar, da necessidade de intubação e da mortalidade. Como resultado, observaram a baixa tolerância quanto ao uso da VNI e apenas 12 dos 25 pacientes conseguiram utilizar o suporte ventilatório durante os 3 dias preconizados no protocolo. Exceto a redução da dispneia após 1 horas de uso da VNI, não houve diferença significante entre as variáveis analisadas nos dois grupos. Os autores apontaram que a efetividade e relação custo-benefício do uso da VNI neste grupo de pacientes parece questionável.

Na tentativa de avaliar o melhor modo de ventilação durante a VNI em pacientes com DPOC estabilizados, Oscroft et al[128] conduziram um ensaio clínico *crossover* com uma amostra contendo 25 pacientes que usaram as modalidades VCV e PCV durante 8 semanas. Apontaram como desfechos primários do estudo a gasimetria arterial diurna e a SpO_2 noturna, sendo os desfechos secundários a função pulmonar, a capacidade de realizar exercícios,

os valores da $PaCO_2$ transcutânea noturna, o *status* de saúde e a aderência ao tratamento. Não evidenciaram diferença significante nos desfechos primários e secundários após 8 semanas de uso da VNI utilizando as modalidades ventilatórias acima descritas. Isto significa que independente da modalidade VCV ou PVC, o uso deste suporte traz efeitos clínicos para os pacientes com DPOC.

Recentemente, De Backer et al[129] analisaram os efeitos a longo prazo do uso da VNI na DPOC de pacientes hipercápnicos e para isto, randomizaram 15 pacientes em dois grupos (tratamento medicamentoso, n=5 e tratamento medicamentos + VNI, n=10) através do BiPAP com máscara facial (ajustes dos modos ventilatórios usados de forma a manter SpO2 > 90% e queda da $PaCO_2$ até 5% em 1 hora) durante 6 meses e os pacientes foram acompanhas por 1 ano. Não evidenciaram aumento significativo no VEF1 em ambos os grupos, mas houve queda significativa da $PaCO_2$ e aumento da PaO_2 no grupo VNI. Os autores justificaram estes resultados devido à melhora na relação ventilação-perfusão e no recrutamento das pequenas vias aéreas ocluídas.

No tocante a melhora da tolerância ao exercício obtidos com o uso da VNI em pacientes com DPOC, Borghi-Silva et al[130] analisaram os efeitos agudos da aplicação do BiPAP (IPAP = 14 cmH_2O e EPAP = 6 cmH_2O) em 27 pacientes com idade média de 68 ± 8.3 anos, VEF_1 < 50% do previsto e sintomas de dispneia aos esforços. Utilizaram como marcador o teste de caminhada de 6 minutos (TC6min) e verificaram aumento da distância percorrida no grupo que usou a VNI em comparação ao grupo controle (338 ± 72 m versus 300.5 ± 84 m), bem como aumento significativo da SpO_2 e menor valor na escala de dispneia

aplicada. Concluíram que o uso da VNI pode aumentar a tolerância ao exercício, manter a oxigenação e reduzir a dispnéia em pacientes com DPOC. Na tabela 2 estão representados os principais estudos envolvendo o uso da VNI em pacientes com DPOC.

Tabela 2. Principais ensaios clínicos controlados e randomizados durante as exacerbações da DPOC.

Nome do primeiro autor	Ano de publicação	Amostra	Níveis de IPAP e EPAP	Principais desfechos
Brochard [26]	1995	42 – Tratamento convencional 43 – VNI + tratamento convencional	PSV=20 cmH_2O (inicial) PEEP= pressão atmosférica	Redução da taxa de intubação. Redução de complicações. Diminuição da mortalidade hospitalar.
Plant [27]	2000	118 – Tratamento convencional 118 – Tratamento convencional + VNI	IPAP=10 cmH_2O (podendo aumentar até 20 cmH_2O) EPAP=4 cmH_2O	Redução da taxa de intubação. Melhora mias rápida do pH e da FR no grupo VNI.
Bardi[28]	2000	15 – Tratamento medicamentoso 15 – Tratamento medicamentoso + VNI	IPAP=máximo tolerado pelo paciente EPAP=2 – 4 cmH_2O	Melhora da gasimetria nos dois grupos. Aumento significativo do pH, VEF_1 e VC no grupo VNI. Aumento da sobrevida no grupo VNI. Diminuição nas hospitalizações no grupo VNI.
keenan[127]	2005	25 –Tratamento convencional + VNI 12 – Tratamento convencional	Iniciou com IPAP=9 cmH_2O e EPAP=4 cmH_2O e aumentou de acordo com a adaptação de cada paciente	Redução do tempo de permanência no hospital. Redução da taxa de intubação. Redução da mortalidade.
Borghi-Silva[130]	2005	28 – BiPAP 25 – Controle (terapia convencional	IPAP=14 cmH_2O EPAP=6 cmH_2O	Aumenta da distância percorrida no grupo BiPAP. Aumento da SpO_2 e da tolerância ao exercício. no grupo BiPAP.
Oscroft[128]	2010	25 pacientes DPOC *crossover*	IPAP e EPAP programado de acordo com a adaptação dos pacientes	Não houve diferença quanto nos parâmetros analisados.
De Backer[129]	2011	5 – Contole 10 – VNI	Ajustes feitos em ambos os modos de forma a evitar SpO_2 abaixo de 90% e permitir queda da $PaCO_2$ em 5% até 1 hora	Diminuição da $PaCO_2$ e aumento da $PaCO_2$ no grupo VNI. Sem diferença no VEF_1 nos dois grupos.

BiPAP – Bi-level positive-end expiratory pressure; IPAP – Inspiratory positive airway pressure;
EPAP – Expiratory positive airway pressure; PFE – Pico de fluxo expiratório; VEF_1 – Volume expiratório forçado no primeiro segundo; FR – Frequência respiratória; VC - Volume corrente; SpO2 – Saturação periférica de oxigênio.

Somando-se a isto, alguns estudos de revisão sistemática foram realizados com base em ensaios clínicos controlados e randomizados, confirmando redução no risco de intubação e na mortalidade hospitalar devido ao uso da VNI na DPOC agudizada. A tabela 3 apresenta a redução do risco quanto à necessidade de intubação e na mortalidade hospitalar, observados nas três principais meta-análises realizadas em pacientes com DPOC.

Tabela 3. Estudos de revisão sistemática com meta-análise envolvendo o uso da VNI em pacientes com DPOC.

Autor/Ano	Estudos	Intubação	Mortalidade
Lightowler, 2003	8	RR = 0.42 IC95% = 0.31 a 0.59	RR = 0.41 IC95% = 0.26 a 0.64
Keenan, 2003	15	Exacerbação grave* Redução do risco = 34% IC95% = 22% a 46% Exacerbação não grave Redução do risco = 0% IC95% = -11% a 11%	Exacerbação grave* Redução do risco = 12% IC95% = 6% a 18% Exacerbação não grave Redução do risco = 2% IC95% = -8% a 12%
Ram, 2004	14	RR = 0.41 IC95% = 0.33 a 0.53	RR = 0.52 IC95% = 0.35 a 0.76

RR = risco relativo; IC = intervalo de confiança.
*Exacerbação grave: definida como acidose respiratória (pH < 7.30) ou mortalidade hospitalar observada no grupo controle > 10%. O RR < 1 indica proteção.
Adaptado de III Consenso Brasileiro de Ventilação Mecânica – Ventilação mecânica não invasiva com pressão positiva. J Bras Pneum 2007;33(Supl 2):S92-S5.

Apesar dos resultados acima descritos quanto as revisões sistemáticas com meta-análise publicadas, Keenan et al[23] não encontrou os mesmos benefícios da VNI nas exacerbações leves da DPOC e sugere que a VNI seja aplicada em pacientes com hipercapnia e acidose respiratória. Por outro lado, foi realizado um estudo multicêntrico controlado e randomizado demosntrando que o uso precoce da VNI (em um interval de 24 a 48 horas) na DPOC aguda demonstrou benefícios clínicos, com menos alterações no pH e

PaCO2. Apesar dos autores encontrarem uma baixa taxa de intubação na ordem de 4.7% em comparação a 15.2% obtida no grupo controle, a taxa de mortalidade não diferiu em ambos os grupos.

No tocante ao uso da nebulização e da VNI, foi encontrado nas bases de dados pesquisadas apenas um estudo realizado por Mukhopadhway et al[33] analisou os efeitos da aplicação da nebulização durante à VNI em 19 pacientes com DPOC nos parâmetros fisiológicos (FR, FC, SpO_2, pH, $PaCO_2$ e Escala de Borg) e na sensação de dispneia. Não foram evidenciadas mudanças nos parâmetros fisiológicos e na oxigenação entre o uso da VNI ou durante os períodos de nebulização. Entretanto, observou-se aumento na PAS e FC após a inalação, provavelmente devido a resposta adrenérgica do broncodilatador e redução da SpO_2 em ambas as fases dos estudo. Como conclusão, os autores observaram que a retirada da VNI para a realização da nebulização não trouxe desconforto respiratório ou alteração das variáveis fisiológicas mensuradas no estudo.

No que diz respeito à análise da deposição de radioaerosol através de cintilografia pulmonar usando o NM durante o uso da VNI *in vivo*, também não foram encontrados estudos nas bases de dados pesquisadas. Entretanto, os estudos envolvendo estas duas formas terapêuticas foram realizados em modelos animais ou *in vitro*, neste último caso dispondo de simuladores respiratórios na tentativa de predizer o comportamento e padrão de deposição das partículas marcadas com radioisótopos[53,126-129].

Dubus et al[53], analisou a deposição do radioaerool marcado com tecnécio-99 em um modelo de ventilação mecânica neonatal em 4 macacos

(peso de 2,6 kg), objetivando comparar o NJ convencional (Misty-neb) e duas marcas do NM (*"Aeroneb Professional Nebulizer"*, APN-C e *"Aeroneb Professional Nebulizer Synchronized"*, APN-S) durante o uso de VNI. Como resultados, verificaram aumento de mais de 20 vezes no aerossol liberado para o trato respiratório inferior usando o NM com os dois NM testados, sendo o percentual nominal da dose de 12.6% (APN-C), 14.0% (APN-S) e 0.5% (NJ). Além disso, ambos os NM apresentaram VR em comparação ao NJ (9.9% - APN-C e 2.7% - APN *versus* 22.4% - NJ). Ainda, os autores observaram menor tempo de nebulização no dispositivo APN-C em comparação aos outros dois nebulizadores (2 minutos *versus* 6 e 10 minutos). Desta forma, concluíram que os NMs foram mais eficazes na administração dos aerossóis em modelos animais de ventilação neonatal.

Abdelrahim et al[131], analisaram os efeitos do posicionamento observados nos dispositivos de inalação *Sidestream nebulizer* (NJ) e *Aeroneb Pro* (NM) durante o uso da VNI através de um simulador respiratório, cujos parâmetros utilizados foram: IPAP = 20 cmH2O, EPAP = 5 cmH2O, relação inspiração:expiração (Ri:e) = 1:3, FR = 15 ipm e VC = 500ml. As posições adotadas para testar as duas marcas de nebulizadores foram: proximal ao dispositivo de inalação (posição A) e distalmente do dispositivo de inalação (posição). A determinação da contagem do aerossol depositado foi coletado em um filtro inspiratório. Ambos os nebulizadores colocados na posição A captaram maior quantidade das partículas quando comparado à posição B, mas o dispositivo com maior deposição foi o NM na posição A. Somando-se a estes achados, verificou-se menor VR no NM em ambas as posições testadas em

comparação ao NJ. Entretanto, vale ressaltar que neste modelo de inalação com pressão positiva, utilizou-se um filtro, o qual pode superestimar a dose do aerossol inalado, pois não foi utilizada uma máscara ou outra superfície para coletar o material depositado.

McPeck et al[132], usou um modelo de filtro acoplado a um simulador respiratório, cuja pressão positiva não invasiva foi liberada através de máscara orofacial em associação a inalação com um NJ convencional e NM através de cintilografia pulmonar, com três tipos de modalidades ventilatórias: CPAP, *Bilevel* 1 (IPAP = 10 cmH_2O e EPAP = 5 cmH_2O) e Bilevel 2 (IPAP = 15 cmH_2O e EPAP = 8 cmH_2O). Observaram significante percentual do radiaoerossol inalado usando o NM nos três tipos de modalidades ventilatórias em comparação ao NJ da seguinte forma: 14.6% *versus* 7.2% no modo CPAP, p=0.061; 14.3% *versus* 6.4% na modalidade *Bilevel* 1 (p=0.094) e 15.4% *versus* 3.6% no modo *Bilevel* 2 (p=0.004). Concluiu-se que a parte do NJ, a dose inalada não diferiu nas diferentes modalidades ventilatórias utilizando-se o NM.

Estudo conduzido por Alquami et al[133], coletou a droga inalada em um filtro distal a traquéia de um modelo de ventilação mecânica acoplado a um pulmão de teste passivo e verificou um percentual da massa do aerossol depositada de 13.2% no NJ, 28.83% no NM e 23.5% no MDI com espaçador.

Recentemente, Michote et al[134] comparou a dose de aerossol emitida por três tipos de nebulizadores (*Sidestream* - JN, *Aeroneb®Pro* e *Aeroneb®Solo* – ambos NMs) através de um circuito único conectado a um dispositivo de VNI gerador de dois níveis de pressão (BiPAP), bem como a influência do posicionamento dos dispositivos no circuito de ventilação, adotando-se para tal a

posição A (nebulizador colocado antes da válvula de exalação) e posição B (nebulizador posicionado depois da válvula de exalação). Com relação aos parâmetros de ventilação, programou-se o ventilador de forma a simular a respiração um paciente com DPOC: FR = 16 ipm; R i:e = 1:3 e VC = 400 mL. Os três dispositivos de inalação apresentaram maior deposição quando se utilizou a posição B em comparação a posição A, mas ambos os NMs apresentaram um maior rendimento quanto comparado ao NJ.

De acordo com os dados acima expostos, a deposição com o NM parece demonstrar resultados promissores, pois garantiu uma maior deposição do radioaerossol, inclusive os dados publicados apontam para uma deposição pulmonar 2 vezes maior quando comparado ao NJ[45,46].

7. RESULTADOS

Artigo Original 1

RADIOAEROSSOL PULMONARY DEPOSTION USING MESH AND JET NEBULIZERS DURING NONINVASIVE VENTILATION IN NORMAL SUBJECTS: A RANDOMIZED CROSSOVER CLINICAL TRIAL

Este artigo foi submetido para publicação na Respiratory Physiology and Neurobiology. Fator de Impacto = 2.242

Artigo Original 2

QUANTIFYING DELIVERY OF RADIOLABELED AEROSOL DURING NONINVASIVE VENTILATION TO STABLE MODERATE AND SEVERE ASTHMATICS: A RANDOMIZED CROSSOVER CLINICAL TRIAL

Este artigo será submetido para publicação na Respiratory Medicine. Fator de Impacto = 2.475

Artigo Original 3

IN VIVO ASSESSMENT OF RADIOLABELED AEROSOL DURING NONINVASIVE VENTILATION IN STABLE COPD: A RANDOMIZED CROSSOVER CLINICAL TRIAL

Este artigo será submetido para publicação no COPD - Journal of Chronic Obstructive Pulmonary Disease. Fator de Impacto = 1.794

RADIOAEROSSOL PULMONARY DEPOSTION USING MESH AND JET NEBULIZERS DURING NONINVASIVE VENTILATION IN NORMAL SUBJECTS: A RANDOMIZED CROSSOVER CLINICAL TRIAL

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Abstract

In vivo deposition studies of aerosol administration during noninvasive ventilation are scarce in the current literature.

We assessed 10 normal subjects in a crossover study evaluated by pulmonary scintigraphy aiming to compare radiaoaerosol pulmonary index and radioaerosol mass balance in the different compartments (pulmonary and extrapulmonary) of radiotagged aerosol administered using vibrating mesh nebulizers (VMN) and conventional jet nebulizer (JN) during noninvasive ventilation (NIV).

VMN deposited 972013.50±214459.76 counts *vs* 386025.00±130363.09 counts (p=0.005) when compared to JN. Regarding to radioaerosol mass balance, VMN showed a higher deposition of radioaerosol inhaled in comparison to JN (34.49±7.72% vs 6.14±2.47%, p=0.005) and the proportion of radioaerosol deposited into the lungs of 5.49±0.96% *vs* 1.48%±0.55%, respectively, p=0.005). In addition to this, VMN demonstrated a significant lower residual volume remaining in the reservoir of 5.08±1.45% *vs* 41.29±4.16%, p=0.005.

Our results suggest that in normal subjects, VMN delivered more than 2 fold radiolabelled drug into the respiratory tract that conventional JN during NIV. Additional studies are recommended in subjects with asthma, COPD, bronchiectasis and cystic fibrosis to better understand differences in both aerosol delivery and response.

Keywords: nebulizers, noninvasive ventilation, residual volume, scintigraphy, aerosol.

1. Introduction

Nebulization aims to deposit drugs directly into the lungs in patients with acute and chronic pulmonary diseases, avoiding adverse systemic side effects associated with other routes of administration (Rau 2005). Noninvasive ventilation (NIV) is commonly employed to reduce work of breathing, and minimize respiratory discomfort in those patients whose severe exacerbations increase the work of breathing (Appendini et al, 1994; Soroksky et al, 2003; Fink, 2004; Soma et al., 2008). Many of the patients requiring NIV may benefit from effective inhaled medication delivery (Brandão et al., 2009; Galindo-Filho et al., 2013).

Many factors influence the efficacy of aerosol delivery during NIV (e.g., type of ventilator, mode of ventilation, circuits, gas density, humidity, interfaces, type of aerosol generator, particle size, position of the aerosol generator, and factors related to the patient (including type and severity of disease, respiratory pattern and ability to tolerate a facemask) (Kwok et al., 2003; Nava et al., 2009; Abdelrahim et al., 2010; Ari et al., 2012; Dhand, 2012).

Among the different types of nebulizers, jet nebulizer (JN) has been used frequently in emergency departments (Vilarinho et al., 2003; Brandão et al., 2009; Brandão et al., 2010; Galindo-Filho et al., 2013). In recent years, a new generation of electronic aerosol generated named vibrating mesh nebulizer (VMN) is available in the market, which consists of a membrane (or mesh) with thousands of funnel-shaped apertures that dictate the particles sizes according to the exit diameter of the apertures. A piezo element converts electricity to

mechanical vibration of the mesh at 128 kHz (1/10th frequency of ultrasonic nebulizers, creating a micropumping action that extrudes fluid through the small holes in the membrane, breaking fluid from the apertures into a stream of precisely droplets (Smart, 2002; Dhand, 2002; Knoch and Keller, 2005; Coates et al., 2011a; Ari et al., 2012).

The VMN has been associated with production of a precise particle sizes without adding gas flow into the ventilator circuit and a low residual volume of drug remaining after nebulization is complete (Smart, 2002; Ari et al., 2012). This category of nebulizer has been shown to promising and effective regarding to pulmonary deposition in comparison to jet nebulizers, according to both in vitro studies and in animal models published in the current literature (Fink et al., 2001; Fink et al., 2003; Dubus et al., 2005; Abdelrahim et al., 2010).

While pulmonary scintigraphy has been used to quantify radioaerosol pulmonary deposition generated by different types of inhalers under a number of conditions, we did not find any reports comparing aerosol deposition from VMN or JN during NIV in normal subjects. Based on previous in vitro and animal studies we hypothesized that VMN would deposits more aerosol than jet nebulizer during NIV.

The aims of the present study were to analyze radioaerosol deposition index (RDI) in horizontal and vertical gradients, and determine the mass balance of aerosol including the pulmonary and extrapulmonary compartments (deposition) of radiotagged aerosols generated by VMN and JN during NIV.

2. Materials and Methods

2.1 Study design and sample

A randomized crossover clinical trial (Clinical study phase 1) was performed in the Nuclear Medicine Department and Cardiorespiratory Laboratory at Physiotherapy Department from Universidade Federal de Pernambuco in association with Georgia State University. Normal healthy subjects were enrolled from both sexes with ages between 18 to 60 years and recruited from the Hospital das Clínicas de Pernambuco and Cardiorespiratory Laboratory. This protocol was approved by Human Ethics Committee and all participants gave written informed consent after fully information about the protocol.

Inclusion criteria included: age between 18 - 60 years, from both sexes, with no history of lung disease and forced vital capacity (FVC) or forced expiratory volume in the first second (FEV_1) higher or equal to 80% from predicted values (Pereira et al., 1992), no history of smoking, without respiratory or cardiovascular disease, ability to understand verbal commands and willing to provide signed consent to participate in this study. On the other hand, subjects were excluded if they were pregnant or were unable to tolerate NIV (Metha and Hill, 2001).

2.2 Procedures and measurements

Initially, we collected anthropometric data from individuals (age, height, weight and body mass index – BMI) and cardiopulmonary parameters (respiratory rate – RR; peripheral oxygen saturation – SpO_2; systolic blood pressure – SBP and diastolic blood pressure–DBP) using pulse oxymetry (ACTIVE-Ecafix, São Paulo, Brazil) and a manual pressure manometer (Welch Allyn^{TM} DS 44-11 Beaverton, Oregon, USA). In addition to this, spirometry data (Micro Loop 8 / Cardinal Health, England, UK) was performed in accordance to the American Thoracic Society guidelines with a variance of < 0.2 L allowed between tests and the average of three measurements was recorded (American Thoracic Society, 1995).

Inhalation protocol was divided into two phases: Phase 1 – NIV+JN (control group) and Phase 2 – NIV+VMN (experimental group). The order in which nebulizers were to be tested was randomized for each patient and the second measurement was taken one week after to eliminate risk of trace radiation, avoiding the possibility of bias.

Inhalation was performed using diethilene triamine penta-acetic technetium (99mTc-DTPA) with radioactivity of 25 millicuries (Nobre et al., 2007). Both nebulizers were charged with 2.5 mg of salbutamol and 0.25 mg of ipratropium bromide and normal saline solution to complete a fill volume of 3 mL. The JN (Misty Max, Air Life, Yorba Linda, USA) with a particle MMAD of 5 µm (according to the manufacturer information) was positioned in the circuit using a “T” piece placed between the circuit leak and the mask, and operated with

oxygen flow at 8 L/min. VMN (NIVO, Respironics®, Murrysville, Pennsylvania, USA) with an MMAD of 3.0 µm was placed in the elbow adapter at the mask. Bilevel positive airway pressure (BiPAP Synchrony, Respironics®, Murrysville, Pennsylvania, USA) was applied through face mask (Comfort Full 2, Respironics®, Murrysville, Pennsylvania, USA) attached with straps and pressure adjusted to 12 cmH_2O peak inspiratory pressure and 5 cmH_2O of expiratory pressure at the beginning of the procedure. Patients were adapted to use NIV before starting measurements, pressures were titrated before reaching the established levels and just after this period masks were fitted using the straps. They were oriented to use a breathing pattern inspiring deeply and exhaling slowing to avoid ventilator-patient asynchrony (França et al., 2006; Galindo-Filho et al., 2013). Positioning nebulizers in the circuit for both groups are shown in figure 1.

Immediately after inhalation, participants sat in a chair with the back positioned in front to the gamma camera (STARCAM 3200 GE, California, USA) to obtain radioactives counts from the posterior thorax during a period of 300 seconds on a matrix of 256 X 256 matrix. After, participants were positioned sitting in front to the gamma camera to obtain imagems from face. Then, the same procedure was performed to analysis deposition in the nebulizer, circuits, inspiratory filter, expiratory filter and face mask. Counts representing stomach were obtained from posterior thorax and corrections for decay of technetium were used during extrapulmonary measurements. The analysis of deposition in pulmonary and extrapulmonary compartments was expressed as a percentage from the cumulative count in each compartment representing the total

radioaerosol mass. The inhaled radioaerosol was considered the sum of deposition into the upper airways, lungs and stomach (Dubus et al., 2005).

Regions of interest were delimited based on a previous protocol and RDI was expressed as absolute values and calculated according to the counts generated from each regions of interest (Nobre et al., 2007).

2.3 Statistical analysis

The sample size was calculated based on a pilot study involving 5 subjects to obtain standard deviation of repeated observations in the same individual and later is the standard deviation of the difference between two measurements in the same individual, considering percentage in lung deposition. A total of 10 healthy subjects entered in this two-treatment crossover study. The probability is 84% that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 1.190 units. It was based on the assumption that within-patient standard deviation of the response variable is 0.80. For the sample size calculation we used the software developed by David Schoenfeld, support from the MGH Mallinckrodt General Research Center. Javascript version developed by REMorse.

We considered as a primary outcome the radioaerosol deposition index into the lungs and the second outcomes were represented by the radioaerosol mass balance in pulmonary and extrapulmonary compartments. For statistical analysis the Shapiro-Wilk test was used to analyze normality, followed by Wilcoxon Test, Friedman Test and Dunn´s Multiple Comparison Test, considering

interval of confidence of 95% ($p<0.05$) through the software SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA) and GraphPad Prisma 4.0 (Graph Pad Software In., San Diego, Califórnia, USA).

3. Results

Fourteen individuals were enrolled and consented to participate in this study, but only 10 volunteers (6 males and 4 females) completed the protocol. One declined to perform phase 1, 2 complained of claustrophobia using facemask during NIV and one did not meet the inclusion criteria. Thus, 10 patients participated in this study and were randomly allocated to which type of nebulizer would be used first, as shown in Figure 2. Table 1 shows the anthropometric and spirometric data from subjects.

The total radioaerosol deposited into the lungs was higher in NIV+VMN group, in comparison to NIV+JN group (972013.50 ± 214459.76 counts *versus* 386025.00 ± 130363.09 counts, $p = 0.005$), as show in figure 3. Intergroup analysis of vertical and horizontal gradients demonstrated that NIV+VMN group increased the counts when compared to NIV+VMN group, as presented in figure 4. Table 2 shows the results of intragroup analysis of radioaerosol pulmonary index for each regions of interest in the vertical and horizontal gradients.

The percentage of radioaerosol inhaled was significantly higher in NIV+VMN group when compared to NIV+JN group, as shown in figure 5. We observed that VMN had a lower residual drug volume and more radiaerosol deposited in the face mask and upper airways, in comparison to jet nebulizer

during NIV. However, JN demonstrated greater deposition of radioaerosol in the expiratory filter than the mesh device. No differences were found regarding to radioaerosol deposited in the stomach, circuit and inspiratory filter for either group. Radioaerosol mass balance obtained in each compartment from both groups are shown in table 3.

Figure 6 shows representative scintigraphic images obtained from the deposition in the different compartments from each nebulizer tested coupled to NIV.

4. Discussion

This is the first *in vivo* study to quantify pulmonary deposition of radiotagged aerosol expressed in counts and a percent of nominal dose, and comparing deposition efficiency achieved with the JN and VMN during NIV, expressing deposition as the percent on the dose of radiation placed into the nebulizer.

With the JN, pulmonary deposition during NIV (1.6%) was lower than previously reported levels of lung deposition (8 – 12%) in spontaneously breathing patients (Newman et al., 2003; MacIntyre et al., 1985). França et al. (2006) examined pulmonary radioaerosol particles in the lungs with scintigraphy in 13 healthy subjects comparing JN during spontaneous breathing to nebulization during NIV. Substantially greater pulmonary aerosol deposition was observed in subjects using nebulization without NIV. The authors hypothesized

that high inspiratory flows associated with bi-level ventilation produced a large deposition of particles in the upper airways.

Soroksky et al. (2003) randomized patients presenting to the emergency room with acute severe asthma to receive bronchodilator via JN with up to 4 hours or conventional treatment (nebulization with bronchodilators). Pulmonary function was reported to improve, with greater FVC and FEV_1, relief of respiratory discomfort, and less need for hospitalization in patients using NIV. These results were attributed to effective direct bronchodilation, intrinsic PEEP compensation, recruitment of collapsed alveoli, improved ventilation perfusion matching and lower respiratory work associated with bi-level ventilation.

Brandão et al. (2010) randomized between NIV with JN and control (JN alone) and also reported improved bronchodilation with NIV. They found greater improvements in FVC, FEV_1 and $FEV_{25-75\%}$ with IPAP/EPAP of 15/5cmH_2O, than 15/10 cmH_2O, however both groups showed improvements in PEF *vs* control. Authors proposed that pulmonary volumes and capacities are improved in the group using nebulization with NIV and IPAP of 15 cmH_2O and EPAP of 10 cmH_2O, as a result of improved alveolar recruitment, which may reflect improved PEEP and patency of peripheral airways. They hypothesized that lower pressure delta with IPAP/EPAP of 15/5 cmH_2O (pressure difference between IPAP and EPAP), likely favored laminar air flow and greater drug deposition by sedimentation in peripheral airways. In this study, we found lower pulmonary deposition from the JN administered with NIV of 12/5cmH_2O than with JN alone.

Recently, Galindo-Filho et al. (2013) studied impact of administered radiotagged bronchodilator aerosols via NIV+JN *vs* JN alone to patients

presenting moderate to severe asthma reporting similar levels of radiation counts in the lungs for both groups, but a greater response to FEV_1, FVC, inspiratory capacity (IC) and PEF in the JN+NIV group. This difference in deposition may be associated with the tendency for a greater proportion of aerosol inhaled to deposit in the obstructed airways of asthmatics compared to normal subjects. If this was also true in the patients studied by those authors, it raises the possibility that even with less deposition NIV potentiates improved response to inhaled bronchodilators.

The low pulmonary deposition with JN during NIV is consistent with the 1-3% deposition from JN reported in intubated subjects during conventional mechanical ventilation (MacIntyre et al, 1985; Fuller et al, 1990.). In one of the few scintigraphy studies comparing jet and mesh nebulizers, Dubus et al. (2005) reported the amount of radiotagged aerosol deposited using VMN and JN (Misty Neb) in a macaque model of neonatal mechanical ventilation. In this case, the authors reported up to a 20 fold increase in lung dose with the MN. They identified the difference in drug residual in the nebulizer at the end of nebulization (1.2 mL *vs* 0.1 mL, for JN and VMN, respectively), difference in particle size and gas flow added to the circuit (JN) as factors contributing to the large difference in delivery efficiency. In our study, VMN generated particles size of 3.4 µm and Misty Max in a range of 5 µm MMAD.

Prior to the advent of modern bilevel noninvasive ventilation, Intermittent Positive Pressure Breathing (IPPB) was applied in the acute care setting to administer noninvasive ventilatory support and medical aerossol. Dolovich et al. (1977) compared lung deposition from a JN with spontaneous breathing and the

same nebulizer with IPPB with an inspiration pressure of 15 cmH_2O in nine individuals with stable chronic bronchitis. The authors reported approximately 30% lower deposition of radioaerosol throughout the lungs with IPPB than with the nebulizer alone. This was attributed to the flow rate at the onset of inspiration that strongly affects the deposition of aerosol particles in the oropharynx, trachea, and large airways. It was thought that this reduction in lung dose of bronchodilators with IPPB would reduce bronchodilator efficacy in relieving bronchial obstruction.

While *in vivo* reports of pulmonary deposition of radiotagged aerosol via scintigraphy using JN and/or VMN during NIV are limited, *in vitro* studies have provided valuable guidance. Our results demonstrated that VMN was more efficient than JN, with counts higher in NIV+VMN group compared to NIV+JN group for both lungs, and the results are consistent with *in vitro* studies reporting > 2 fold inhaled dose with VMN *vs* JN during NIV. The inhaled mass (calculated with deposition in the lungs, upper airway and stomach) was 34.49% with VMN and 6.14% with the JN, correlating to the lung dose of 5.49% and 1.48%, respectively. Abdelrahim et al. (2010) used a breath simulator and measure inhaled dose on a filter, reporting an inhaled dose of 24% (JN) and 51% (VMN). This method would likely over-estimate inhaled dose, as there is no mask or face surface collecting aerosol. Using a bilevel ventilator with single limb circuit and oropharyngeal mask attached to the face of anatomical adult upper airway, AlQuami et al. (2011), collected drug on a filter distal to the trachea of the model, attached to a passive test lung and reported inhaled mass of 13.2% (JN) and 28.83% (VMN) and 23.5% with pMDI and spacer.

Mc Peck et al. (2012) used a face model with filter attached to a respiration simulator via oro-nasal mask to compare JN and VMN with three different noninvasive ventilator settings assessed through pulmonary scintigraphy. They observed a significant radiaoerosol inhaled using VMN in all three ventilation settings in comparison to JN. Significantly more albuterol was delivered to the filter with the NIVO mesh nebulizer than the small JN: 14.6% *vs* 7.2% for CPAP 5 cmH2O (p=0.061), 14.3% *vs* 6.4% for Bi-Level of 10/5 cmH2O (p=0.094), and 15.4% *vs* 3.6% for Bi-Level of 15/8 cmH2O (p=0.004). Unlike the JN, inhaled dose did not vary across setting with the VMN.

Our results showed only 5.08% from the total radioaerosol mass balance remaining into the VMN reservoir against 41.29% obtained into the JN. Similarly, in the animal model reported by Dubus et al (2005), both VMN tested presented a lower residual volume in comparison to JN, as well in the *in vitro* study performed by Mc Peck (2012), which residual from 3.0 mL doses were 3.49% and 54.9%, for VMN and JN, respectively.

Pulmonary scintigraphy has been an important tool to quantify aerosol drug deposition into the respiratory tract with a variety of aerosol generating devices both on and off the ventilator (Macintyre et al., 1985; Fuller et al., 1990; Fok et al., 1996; Saari et al., 2003; Dubus et al., 2005; França et al., 2006; Galindo-Filho et al., 2013). Thus, this is a well-established approach with published studies demonstrating that radiolabelling of solutions with Technesium 99 does not alter particles size generated by nebulizers and inhalers (Newman et al., 2003; Drollman et al., 2004).

Many factors could alter radiaerosol distribution including: interfaces, respiratory pattern, humidification, aerosol apparatus, particle size, nebulizer positioning, type of circuit, parameters set and synchrony with the patient (Kwok et al., 2003; Nava et al., 2009; Abdelrahim et al., 2010; Ari et al., 2012; Dhand, 2012). To minimize confounding variable, subjects were fitted with masks, adapted to pressure application with NIV, and parameters were adjusted in the same level, as our previous study involving normal subjects (França et al., 2006). Subjects were instructed to relax and let the machine do the work of breathing as much as possible.

The radioaerosol pulmonary index increased in all regions of interest using VMN compared to JN. Intragroup analysis of vertical gradient demonstrated higher counts in the lower third than upper third in both lungs for each group. This might be explained by greater volumetric variation in alveolus of the lung base than in those located in the lung apex during NIV. On the other hand, counts registered in the horizontal gradient showed that intragroup deposition of radiaoerosol was more significant when comparing central to peripheral regions in both lungs for each group, demonstrating substantial deposition of aerosol reached central areas, which should be relevant during inhalation of bronchodilators with a higher concentration of bronchodilator receptors in the central airways.

According to Branconnier and Hess (2005), positioning inhalers between leak port and mask is more effective delivering a higher amount of aerosol into the lungs. This has been confirmed with both JN and VMN by Abdelrahim et al. In our study both types of nebulizers were positioned between the circuit leak and

the patient, although JN was placed in the circuit using a “T” piece, and the VMN was positioned directly in the elbow of the mask. This was the same placement as reported by McPeck (2012).

Regarding the fact that we administered bronchodilator drugs in healthy subjects, we did found at the end of the experiments, any problem or sign of side effects promoted by these drugs.

Some limitations should be considered when interpreting the results of this study. First, there are not any validated protocols in the literature regarding the levels of inspiratory and expiratory pressures to apply during NIV. Second, we tested the efficacy of nebulization coupled to NIV in normal subjects, limiting the ability to demonstrate a differential response to inhaled medication. Further studies should be performed in asthmatic, COPD, bronchiectasis and cystic fibrosis in which differences in clinical outcomes could be assessed.

In conclusion, this study showed that VMN delivered more than 2 fold radiolabelled drug into the respiratory tract when compared to JN during NIV and a substantial difference in both inhaled mass and lung dose with use of VMN *vs* JN during NIV with healthy subjects. As improved bronchodilator response has previously been shown with JN and NIV, despite low lung doses, future studies will be required to demonstrate the clinical benefit of the higher deposition efficiency demonstrated with VMN.

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Legends to Figures

Figure 1. Positions of VMN and JN in the NIV circuit during inhalation. Observed that VMN was coupled in the NIV mask through an elbow kit (Panel A) and for attaching JN was necessary an adaptation using a “T” piece (Panel B).

Figure 2. Flow diagram of the study.

Figure 3. Total pulmonary depositing reached by each nebulizer tested in this study. Wilcoxon Test. * p=0.005.

Figure 4. Intergroup comparison between groups according to the vertical gradients: upper, middle third and lower thirds (Panel A), and horizontal gradients: central, intermediate and peripheral regions (Panel B). Wilcoxon Test. *p=0.005.

Figure 5. Representation of radioaerosol inhaled deposited in each group. Wilcoxon Test. *p=0.05.

Figure 6. The pictures above represent the scintigraphic images obtained during nebulization associated to NIV using VMN (on the left) and JN (on the right).

Table 1.

Anthropometric and cardiopulmonary characteristics form individuals involved in this study (n = 10).

Variables	Values
Age (years)	33.7 ± 10.04
Weight (Kg)	78.1 ± 17.50
Heigth (m)	1.70 ± 0.09
BMI (Kg/m^2)	26.6 ± 2.70
BR (BPM)	15,5 ± 1,41
HR (bpm)	78,1 ± 5,65
SBP (mmHg)	122,0 ± 10,6
DBP (mmHg)	78,5 ± 3,53
SpO_2 (%)	97,1 ± 0,70
FEV_1 (L)	3,94 ± 0.69
FEV1 (% predicted)	100.7 ± 3.36
FVC (L)	4.47 ± 0.67
FVC (% predicted)	95.3 ± 0.85
FEV_1/FVC	87.0 ± 2.23
FEV_1/FVC (% predicted)	104.2 ± 5.21
PEF (L)	9.15 ± 1.53
PEF (% predicted)	92.3 ± 1.50

Values are mean ± SD. BMI, body mass index; BR, Breathing rate; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, peripheral oxygen saturation; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; FEV_1/FVC, ratio forced expiratory volume in the first second and forced vital capacity; PEF, peak expiratory flow.

Table 2.

Radioaerosol deposition index according to the vertical and horizontal gradients for each pulmonary region in both phases of the study.

		Vertical Gradient		Horizontal Gradient	
	Group	Lung Region	p-value	Lung Region	p-value
Right lung	NIV+JN (n=10)	UT < MT	> 0.05	CT > IT	> 0.05
		UT < LT	< 0.001*	CT > PT	< 0.001*
		MT < LT	> 0.05	IT > PT	> 0.05
	NIV+VMN (n=10)	UT < MT	> 0.05	CT > IT	> 0.05
		UT < LT	< 0.001*	CT > PT	< 0.001*
		MT < LT	> 0.05	IT > PT	> 0.05
Left lung	NIV+JN (n=10)	UT < MT	> 0.05	CT > IT	> 0.05
		UT < LT	< 0.001	CT > PT	< 0.001*
		MT < LT	> 0.05	IT > PT	> 0.05
	NIV+VJN (n=10)	UT < MT	> 0.05	CT > IT	> 0.05
		UT < LT	< 0.001*	CT > PT	< 0.01*
		MT < LT	> 0.05	IT > PT	> 0.05

Values are mean ± SD.NIV, noninvasive ventilation; JN, jet nebulizer; VMN, vibrating mesh nebulizer; UT, upper third; MT, middle third; LT, lower third; CT, central third; IT, intermediate third; PT, peripheral third.
Friedman Test and Dunn´s Multiple Comparison Test, *p<0.05.

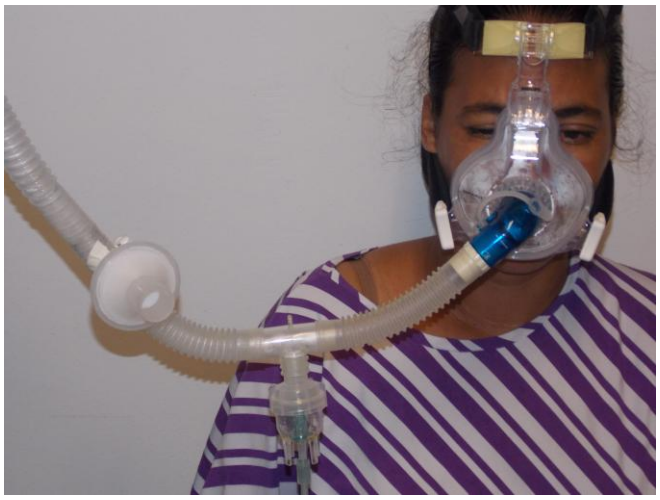
Table 3.

Mass aerosol balance presented in pulmonary and extrapulmonary deposition in each group of the study as a percentage.

COMPARTMENTS	VNI+MN (n=10)	VNI+JN (n=10)	p valor
Lungs (%)	5.49±0.96	1.48±0.55	0.005*
Upper airways (%)	16.20±4.23	4.28±1.97	0.005*
Stomach (%)	1.38±1.75	0.37±0.70	0.047
Nebulizer (%)	5.08±1,45	41.29±4.16	0.005*
Face mask	20.01±3.48	9,93±6.23	0.005*
Circuit (%)	8.72±9.89	12.5±4.03	0.093
Inspiratory filter (%)	0.15±0,17	0.08±0.05	0.400
Expiratory filter (%)	43.03±6.42	30.26±12,80	0.005*

Values are mean ± SD. Wilcoxon test, *p<0.05.

Figure 1.



Panel A

Panel B

Figure 2.

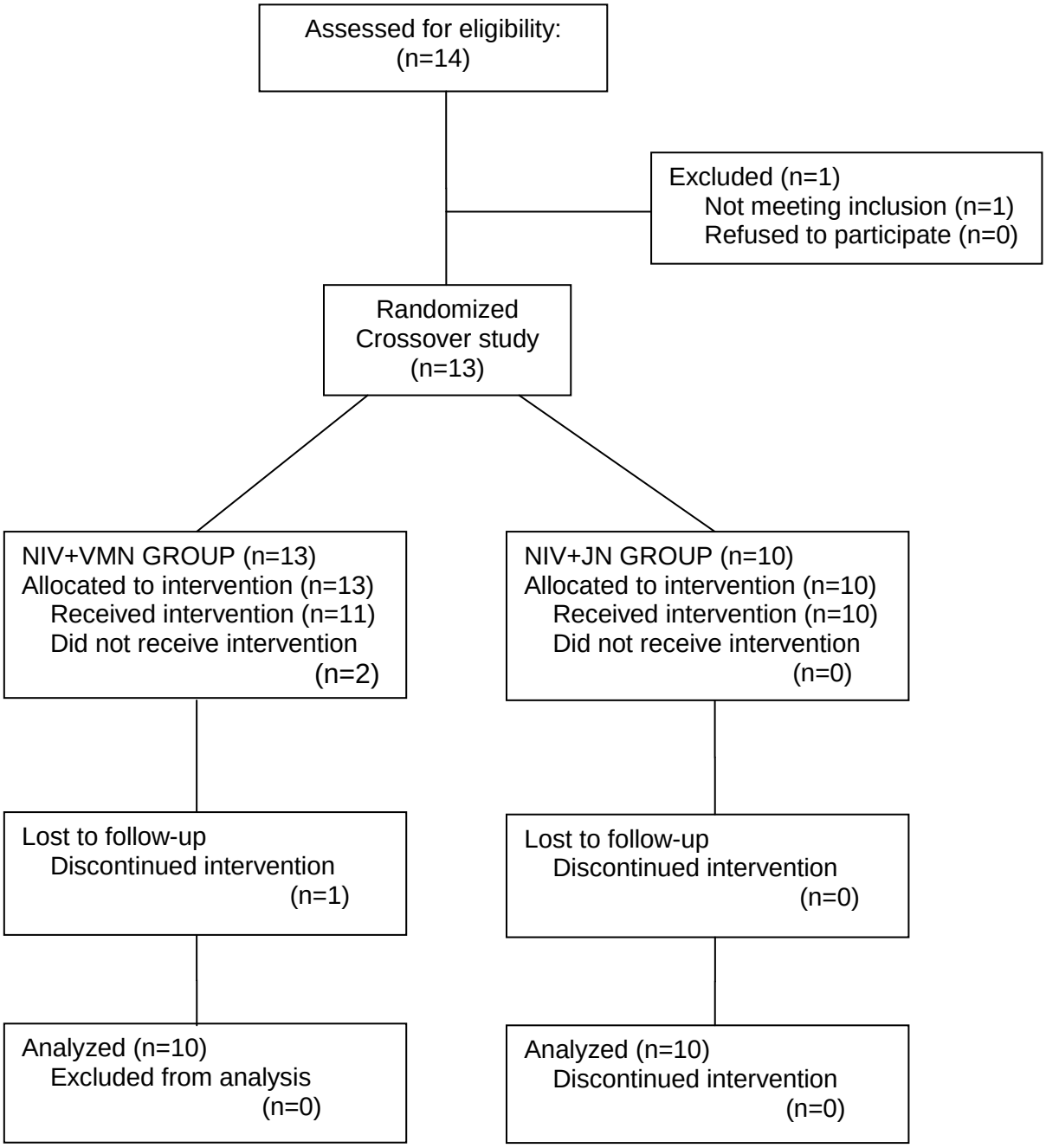

Assessed for eligibility:
(n=14)
Excluded (n=1)
Not meeting inclusion (n=1)
Refused to participate (n=0)
Randomized
Crossover study
(n=13)
NIV+VMN GROUP (n=13)
Allocated to intervention (n=13)
Received intervention (n=11)
Did not receive intervention
(n=2)
NIV+JN GROUP (n=10)
Allocated to intervention (n=10)
Received intervention (n=10)
Did not receive intervention
(n=0)
Lost to follow-up
Discontinued intervention
(n=1)
Lost to follow-up
Discontinued intervention
(n=0)
Analyzed (n=10)
Excluded from analysis
(n=0)
Analyzed (n=10)
Discontinued intervention
(n=0)

Figure 3.

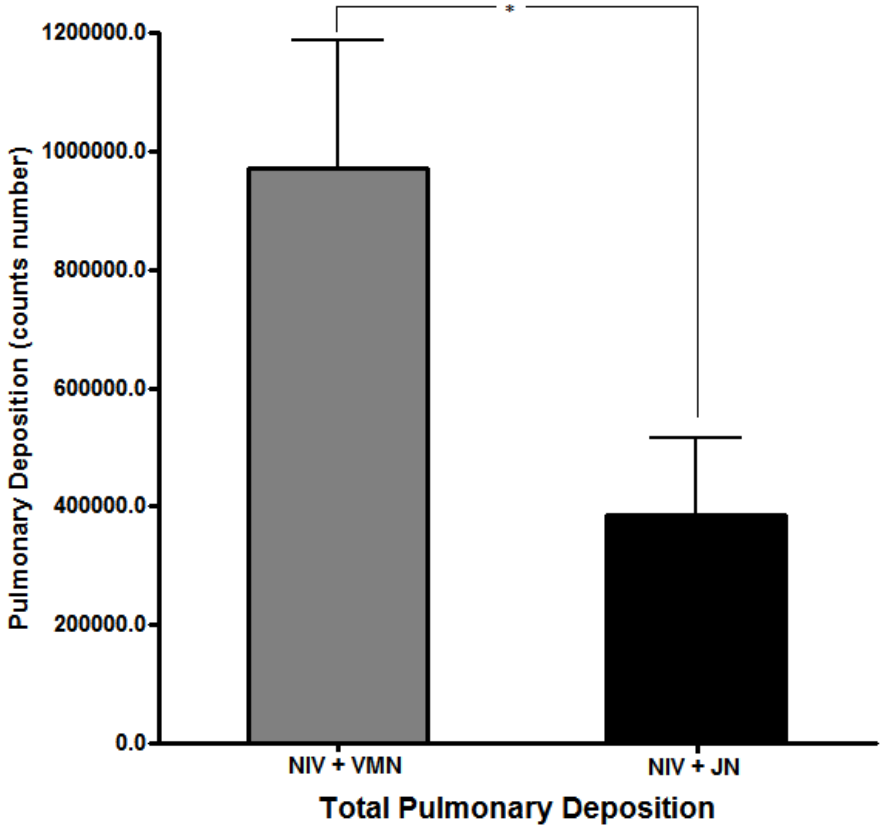
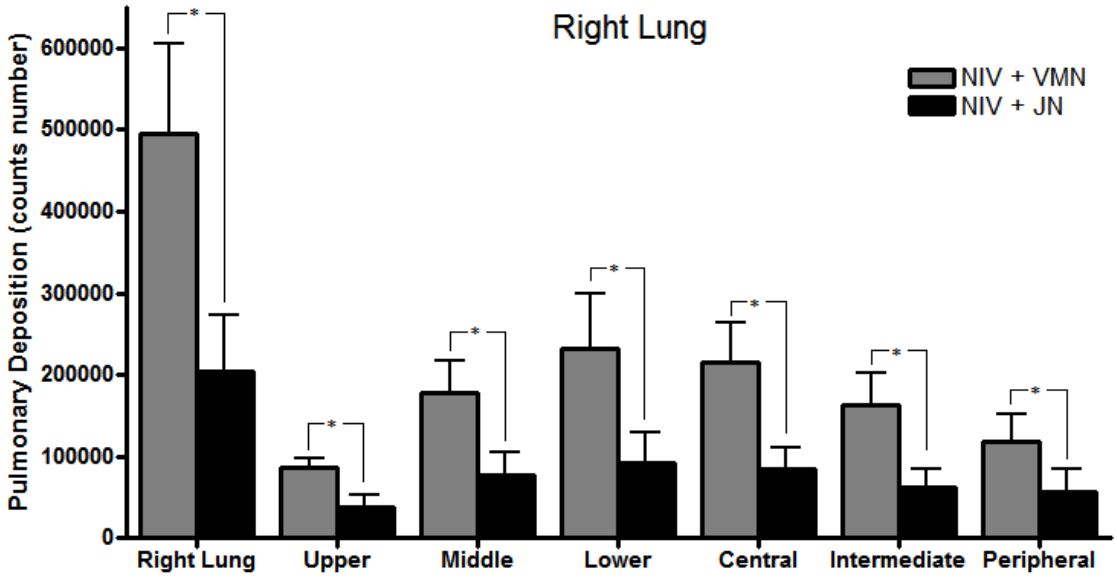

*
1200000.0
1000000.0
800000.0
600000.0
400000.0
200000.0
0.0
Pulmonary Deposition (counts number)
NIV + VMN
NIV + JN
Total Pulmonary Deposition

Figure 4.

Panel A



Panel B

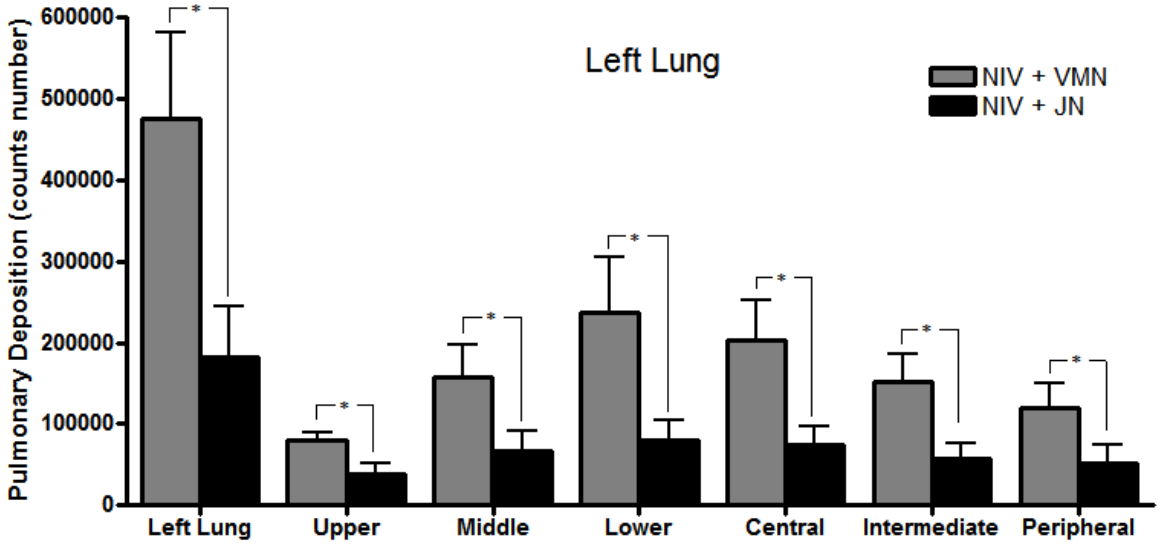


Figure 5.

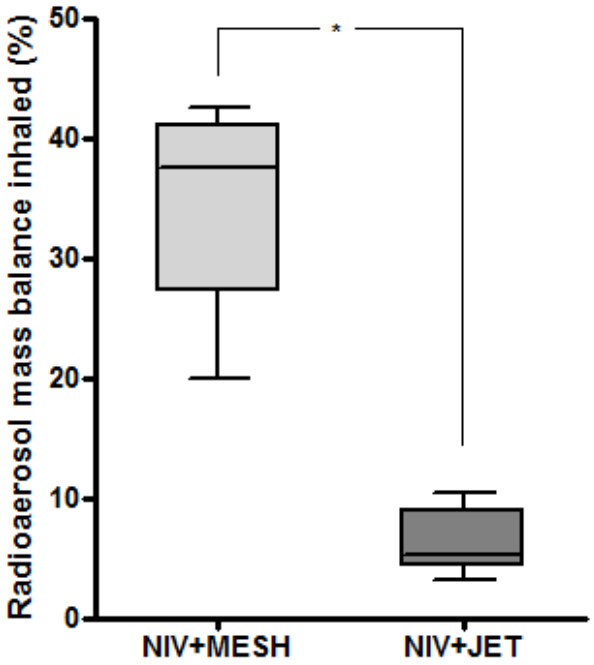
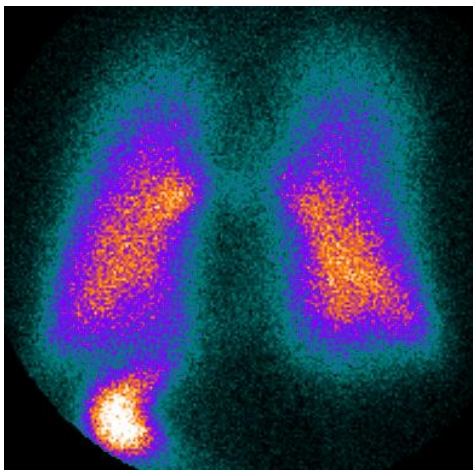
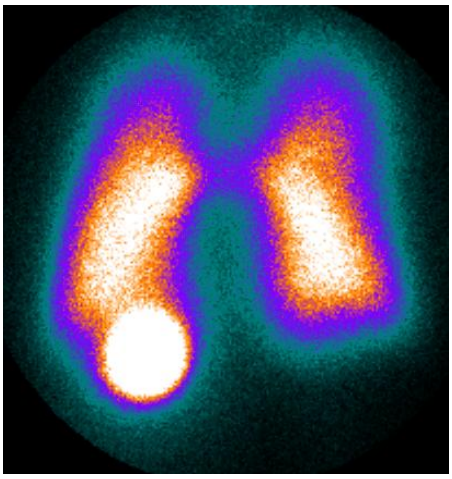

Radioaerosol mass balance inhaled (%)
50
40
30
20
10
0
*
NIV+MESH
NIV+JET

Figure 6.





QUANTIFING DELIVERY OF RADIOLABELED AEROSOL DURING NONINVASIVE VENTILATION TO STABLE MODERATE TO SEVERE ASTHMATICS: A RANDOMIZED CROSSOVER CLINICAL TRIAL

Coupling mesh devices to noninvasive ventilation in stable asthma

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Summary

Introduction: Inhalation therapy has been established as an efficient route to treat asthma exacerbations, but coupled to noninvasive ventilation(NIV) remains quite challenging. The aim of this study were to compare radiaoaerosol pulmonary deposition and radioaerosol mass balance in the different compartments (pulmonary and extrapulmonary) using vibrating mesh nebulizers (VMN) and jet nebulizer (JN) coupled NIV.

Methods: It was a crossover study involving 10 stable moderate to severe asthmatics randomly assigned for both phases of the study: Phase 1(NIV+MN,n=10) and phase 2(NIV+JN,n=10). Patients inhaled during NIV through a facemask attached with straps and pressures of 12 cmH_2O and 5 cmH_2O(inspiratory and expiratory, respectively). Radioactivity counts were performed using a gama camera and regions of interest(ROIs) were delimited. We determine aerosol mass balance from the lungs, upper airways, stomach, nebulizer, circuit, inspiratory and expiratory filters, and mask as a percentage.

Results: VMN showed a higher deposition of radioaerosol mass balance inhaled in comparison to JN (22.75±7.89% v*s* 7.27±1.59%, p=0.005) and the amount of radiaoaerosol deposited into the lungs was 5.77±0.96% *vs* 1.71±0.05%, p=0.005). VMN demonstrated a significant lower residual volume remaining in the reservoir of 4.17±0.85% *vs* 41.47±12.66%, p=0.005.In addition to this, great amount of radiotaged aerosol delivered by Mesh was deposited centrally.

Conclusions: Our results suggest that VMN delivery more than 2.5 fold of radioaerosol into the lungs and it may help guide clinician in selection of aerosol device option to optimize pulmonary deposition during moderate to severe asthmatic in treatment of exacerbations.

Keywords: nebulizers, noninvasive ventilation, asthma, scintigraphy, aerosol.

Introduction

Asthma is an inflammatory and chronic respiratory disease responsible for clinical alterations, with increased prevalence worldwide[1-3]. Inhalation therapy has been established as an effective route to deposit drugs directly into the lungs to treat asthma exacerbations[4-6], but aerosol administration during noninvasive (NIV) ventilation remains challenging and has not been well described in asthmatics[7-10].

Our group recently published a randomized controlled trial[10] focusing on administration of radiolabeled bronchodilator via jet nebulizers (JN) alone and with NIV during asthma exacerbation in the emergency department. Although cardiopulmonary and spirometric parameters showed significant clinical improvements in the NIV group, no difference was observed between groups regarding to radioaerosol pulmonary deposition. Other studies have reported clinical improvements using bronchodilators in association to NIV[7-9] or applying NIV without bronchodilators[11] or not concomitantly to positive pressure in asthmatic adults[12].

Despite the extensive use of JN in the clinical practice, a new generation of electronic nebulizer has been introduced which uses a vibrating mesh composed consisting of a thousand funnel shaped aperture. The vibrating mesh nebulizer (VMN) has been reported to produce aerosol without adding gas into the ventilator circuit with very little medication remaining in the reservoir at end of nebulization.[13-16].

The VMN has been shown to be more efficient than JN in animal and *in vitro* models of mechanical ventilation[17-21], and early *in vitro* work with NIV. In a pilot study[22] of normal subjects receiving radiotagged aerosol via NIV we observed greater than 2 fold inhaled mass and > 3fold lung deposition with VMN *vs* JN. However, we did not find in the literature studies involving the use of these devices coupled to NIV in stable or exacerbated asthma evaluated through scintigraphy. For this reason, we wanted to determine aerosol deposition of aerosol delivery in stable moderate to severe asthmatics with VMN and JN during NIV. Our hypothesis is that VMN will deliver a greater proportion of dose with a different pulmonary distribution than JN during NIV.

The aims of this study were: 1) to compare inhaled dose of radioaerosol into the lungs and determine distribution across horizontal and vertical gradients, and 2) to quantify mass balance of the delivery system and different compartments, including intrapulmonary and extrapulmonary deposition.

Materials and Methods

Study design and subjects

It was a crossover study involved 13 stable moderate to severe asthmatics, from both sexes, age between 18 to 60 years and was performed in the Department of Nuclear Medicine and Cardiorespiratory Laboratory at Physiotherapy Department from Universidade Federal de Pernambuco in association to Georgia State University between. Data collection was performed

after approved protocol by Human Ethics Institutional Committee and all participants gave written informed consent to participate. This trial was registered in ClinicalTrial.gov according to the number NCT01823926.

Inclusion and exclusion criteria

Inclusion criteria were considered as follows: moderate to severe stable asthma (FEV_1 > 60% and < 80% or FEV_1 < 60%, and PEF with a variation of 30% from the predicted values)[23]; more than one year elapsed since the diagnosis of asthma; none exacerbation in the last six months; age between 18 - 60 years; both sexes; no smoking history; able to understand verbal commands, and consent to participate in this protocol. On the other hand, exclusion criteria were: presence of dyspnea; cardiopulmonary diseases (chronic obstructive pulmonary disease, pneumonia, cardiac failure, myocardial infarction, pneumothorax); hyperthermia; hemodynamic instability (heart rate > 150 bpm and systolic blood pressure < 90 mmHg); arrhythmia absence; pregnancy; and contraindications for use of NIV[24].

Cardiopulmonary measurements

Anthropometric data was the first step in the initial assessment from the patients, consisting of age, height, weight and body mass index (BMI). For cardiopulmonary parameters we considered: respiratory rate (RR); peripheral oxygen saturation (SpO_2); systolic blood pressure (SBP) and diastolic blood

pressure (DBP) using pulse oxymetry (ACTIVE -Ecafix, São Paulo, Brazil) and a manual pressure manometer (Welch Allyn^{TM} DS 44-11 Beaverton, Oregon, USA). Then, to conclude respiratory assessment, spirometry was performed (Micro Loop 8 / Cardinal Health, England, UK), based on American Thoracic Society, which considered a variance of 0.2 L allowed between tests and the average of three measurements was recorded[25].

Inhalation protocol

Inhalation protocol was divided into two phases: Phase 1 – NIV+JN (control group) and Phase 2 – NIV+VMN (experimental group). The order nebulizers to be tested was randomized for each patient and the second measurement was taken one week before, to avoid radioactive waste into the respiratory tract between using one and another nebulizer, thereby avoiding possible bias.

Inhalation was performed using diethilene triamine penta-acetic technetium (99mTc-DTPA) with radioactivity of 25 millicuries[26]. Both nebulizers were charged with 2.5 mg of salbutamol and 0.25 mg of ipratropium bromide and 3 mL of saline solution was added to complete 3 Ml. JN (Mist yMax, Air Life, Yorba Linda, USA) was positioned in the circuit using a “T” piece, particle size generation in a 5 µm range (according to the manufacturer information) and flow oxygen tritated at 8 L/min. VMN (Aeroneb Solo, Galway, Ireland) was positioned in the mask using an elbow (Elbow Kit, Respironics®, Murrysville, Pennsylvania, USA), particle size generation in a 1 µm and connected to electrical energy.

Bilevel positive pressure (BiPAP Synchrony, Respironics®, Murrysville, Pennsylvania, USA) was applied through face mask (Comfort Full 2, Respironics®, Murrysville, Pennsylvania, USA) attached with straps and pressure adjusted were 12 cmH_2O of inspiratory pressure and 5 cmH_2O of expiratory pressure after a period of adaptation before beginning the procedure to avoid ventilator-patient asynchrony[27].

Immediately after inhalation, participants sat in a chair with the back positioned in front to the gamma camera (STARCAM 3200 GE, California, USA) to obtain radioactivity counts from the posterior thorax during a period of 300 seconds on a matrix of 256 X 256. After, participants were positioned sitting in front to the gamma camera to obtain images from face. Then, the same procedure was performed to analysis deposition in the nebulizer, circuits, inspiratory filter, expiratory filter and face mask. Counts representing stomach were obtained from posterior thorax and corrections for decay of technetium were used to during extrapulmonary measurements. The analysis of deposition in pulmonary and extrapulmonary compartments was expressed as a percentage from the count in each compartment to the total radioaerosol mass generated by nebulizers. The inhaled radioaerosol was considered the sum of deposition into the upper airways, lungs and stomach[17].

Regions of interest were delimited based on a previous protocol and RDI was expressed as absolute values and was calculated according to the counts generated from each regions of interest[26].

Statistical analysis

The sample size was calculated based on a pilot study involving 5 subjects to obtain standard deviation of repeated observations in the same individual and later is the standard deviation of the difference between two measurements in the same individual. A total of 10 asthmatics patients entered in this two-treatment crossover study. The probability is 82% that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 11.89 units. It was based on the assumption that within-patient standard deviation of the response variable is 8.16. For the sample size calculation we used the software developed by David Schoenfeld, support from the MGH Mallinckrodt General Research Center. Javascript version developed by REMorse.

Primary outcomes consisted of radioaerosol deposition index into the lungs and we considered as secondary outcomes, radioaerosol mass balance that reached pulmonary and extrapulmonary compartments.

For statistical analysis were used Shapiro-Wilk Test to analysis normality and after was applied Wilcoxon Test, Friedman Test and Dunn´s Multiple Comparison Test, considering as an interval of confidence 95% ($p<0.05$) through the software SPSS 20.0(SPSS Inc., Chicago, Illinois, USA) and GraphPad Prisma 4.0(Graph Pad Software In., San Diego, California, USA).

Results

Anthropometric and cardiopulmonary variables

Although 13 asthmatics patients were admitted to participate in this protocol, only 10 concluded all measurements (6 moderate and 4 severe). Reasons to be excluded to this protocol after enrollment were: one presented claustrophobia during application of NIV, one did not meet the inclusion criteria and the last one did not attend in the phase 1 to complete protocol (Figure 1). Finally, 10 patients were randomly assigned to indicate which nebulizer will be assessed first. Anthropometric, cardiorespiratory and spirometric data are shown in table 1.

Radioaerosol pulmonary index

The amount of radiaoaerosol deposited in both lungs was higher in NIV+VMN group when compared to NIV+JN group (1198479.20±434174.12 counts *vs* 426803.30±151758.68 counts, p = 0.005). Deposition in right and left lungs was higher when using mesh device coupled to NIV (right lung: 616641.40±223027.11 counts *vs* 218287.40±76311.49 counts, p = 0.005 and left lung: 580063.70±202894.04 counts *vs* 208515.90±76374.08 counts), as shown in figures 2 and 3.

Intergroup analysis across vertical and horizontal gradients demonstrated that NIV+VMN group had higher counts when compared to NIV+VMN group, as

shown in table 2. Table 3 shows the results of intragroup analysis of radioaerosol pulmonary index for each regions of interest across vertical and horizontal gradients.

Intrapulmonary and extrapulmonary depositions

The percentage of radiaerosol inhaled was significantly higher in NIV+VMN group when compared to NIV+JN group (22.75 ± 7.89% vs 7.27 ± 1.59%). We observed that mesh nebulizer reached a lower residual volume and more radiaerosol deposited in the face mask and upper airways, in comparison to jet nebulizer during NIV. However, jet nebulizer demonstrated a significant deposition of radioaerosol in the expiratory filter than mesh device. None differences were found regarding to radioaerosol mass balance found in the stomach, circuit and inspiratory filter for both groups. Radiaerosol mass balance obtained in each compartment from both groups are show in table 4.

Figure 4 represent the scintigraphic images obtained from the deposition in the different compartments from each nebulizers tested couple to NIV.

Discussion

This is the first crossover study comparing pulmonary delivery of medical aerosols administered with VMN and JN during NIV assessed by scintigraphy in moderate to severe asthma subjects. Our results demonstrate both greater deposition and distribution of radiolabeled aerosol in the lungs using VMN in

comparison to JN. We observed higher values in deposition across horizontal gradient reached in central regions for both lungs in comparison to intermediate and peripheral regions using the mesh device.

Many studies published in the current literature demonstrate the benefits of NIV in asthma exacerbations, some of them coupling nebulization to NIV[8-12]. However, while there are multiple comparisons of relatively efficiency of JN and VMN in conventional mechanical ventilation, most of it is *in vitro*[17,18,20,2127,28], and nothing reported *in vivo* during NIV.

The preliminary results from coupling NIV and nebulization was presented by Pollack et al[7] studying moderate to severe asthmatics reporting an increased PEF after delivering β agonists through two levels of positive pressure (IPAP/EPAP of 10/5 cmH_2O) in comparison to nebulization of the same drugs without NIV. They attributed the improvement in PEF to possible higher deposition of drugs into the respiratory tract as a result of applying positive pressure by BiPAP.

Soroksky et al[12] demonstrated improvement in spirometric data, relief in repiratory discomfort and reduction in the rate of intubation after administering NIV in a group of severe asthmatics in the emergency department. They attributed those results due to mechanical dilatation of the airways produced by NIV. Similarly, in a previous study performed from our group[8] used NIV to deliver bronchodilators in the emergency department in asthmatics compared to nebulization alone and found significant improvement in spirometric parameters as such FVC, FEV_1 and PEF using positive pressures 15-5 cmH_2O and 15-10 cmH_2O. They reported that PEF was higher using a pressure delta of 10 cmH2O

and the authors attributed suggested that this might be due to alveolar recruitment through collateral pulmonary ventilation. In addition to these studies, Soma et al[11] demonstrated the effects of higher and lower levels of pressure through BiPAP applied alone, without the use of bronchodilators, during asthma exacerbations to improve spirometric parameters, reducing respiratory rate, a reduction of hospitalization and faster alleviation of symptoms. Gupta et al[9] used NIV in asthma exacerbations and found increased FEV_1, reduction in hospital stay with decrease in the dose of bronchodilators necessary to relief respiratory symptoms.

Although those results presented above showed clinical improvements in asthmatic patients, it remains unclear whether the main effect of NIV coupled to nebulization is primarily a mechanical bronchodilatory effect or a higher deposition of aerosol into the airways. To address this, our group performed a randomized controlled trial[10] to quantify the deposition of radiolabeled bronchodilators administered via jet nebulizer alone or with NIV in 10 exacerbated asthmatics in the emergency department and found reduction in respiratory rate, increased tidal volume, reduction in minute ventilation and improvement of FEV_1, FVC, PEF and IC in the group that inhaled using BiPAP. Although we found clinical improvement with NIV, deposition did not differ between groups, which led us to suspect that the mechanical effects as an important factor potentiating bronchodilator response by inhalation during NIV.

Reports of *in vitro* studies[17,18,28,29] VMN have been demonstrating promising results from in vitro studies and radioaerosol deposits >2 fold more particles into the respiratory system than JN. Our results showed that aerosol

administered in association to NIV deposited 2.8 fold in comparison to JN in moderate to severe stable asthmatics. Regarding to the inhaled percentage from the nominal dose, VMN reached 22.7%5 vs 7.27% in JN correlating to a lung dose percentage of 5.77 with VMN vs 1.71 with the JN. These results are consistent with those presented by Dubus et al[17], which analyzed the deposition of radiotagged aerosol through an endotracheal tube (3 mm ID) to compare VMN and JN in a macaque model of neonatal ventilation. They reported more than 20 fold from the initial dose deposited into the lungs.

In a study of NIV, Abdelrahim et al[18], performed *in vitro* assessment using a breath simulator with the aerosol generators placed between the circuit leak and the patient airway reported an inhaled dose of 51% in VMN and 24% in JN. However, our method to measure particles deposition differs from those authors, which used a filter to measure inhaled dose which does not simulate exhalation of aerosol. In our experiment we used a facemask attached to the patient and inspiratory and expiratory filters in the single limb circuit to collect radioaerosol. Corroborating to our results, AlQuami et al[30] obtained an inhaled mass as percent of dose analyzing different devices to delivery aerosols in a range of 13.2% (JN), 28.83% (VMN) and 23.5% using a metered dose inhaler with spacer.

The parameters of ventilaton seem to influence deposition of aerosol with JN as demonstrated by Mc Peck et al[20]. They compared different pressure levels in BiPAP (10-5 cmH_2O and 15-8 cmH_2O) and continuous positive airway pressure (CPAP of 5 cmH_2O) using VMN and JN. They reported an inhaled mass values o14.3% *vs* 6.4%, 15.4% *vs* 3.6% and 14.6% *vs* 7.2%, respectively. While there was substantial variability with the JN (3.6 – 7.2% with differences in mode

and pressure, the difference with VMN (14.3 – 15.4% was not significant. These results suggest that with JN there is a difference in delivered dose that may provide insight into the impact of different pressures in the Brandão study[8], in which PEF increase with EPAP of 10 cm H_2O *vs* 5 cm H_2O, with the improved response being secondary to increase bronchodilator delivery. This raises the question of whether improved delivery of bronchodilator to the lung during NIV will improve patient response.

One key to increased delivery with VMN over JN appears to be the residual drug remaining in the reservoir at the end of aerosol generation, because more aerosolized drugs could reached the lungs and result in clinical benefits during asthma exacerbations. From a total dose of 3 mL, a lower residual volume representing 4.17% of dose with VMN compared to 41.43% with the JN. Dubus et al[17], in their *in vivo* macaque study of infant ventilation, noted a large difference in residual volume at the end of aerosol between VMN (2.7 % in APN-S and 9.9% in APN-C) and 22.4% in a JN. While Mc Peck et al[20], using a similar NIV setup to our reported residual drug volumes for VMN of 3.49% and JN of 54.9%.

A second difference in efficiency is likely the addition of flow to the circuit of 8 L/min with the jet nebulizer. The additional flow has a tendency to dilute the aerosol produced, so that a smaller proportion is inhaled. The VMN does not require additional gas flow, so that there is less flow blowing aerosol away from the patient between inspirations.

Regarding the others extrapulmonary compartiments, we found a significant deposition of VMN to the upper airways and face in comparison to JN.

It should be due to a combination of the greater percent of dose available to the airway by VMN and the position of nebulizer was attached directly at the elbow of the facemask, which is more affected by the high flows generated by BiPAP in comparison to JN positioned in the circuit.

Placement of the nebulizers differed in our study, but in both cases the aerosol generator was placed between the leak and the mask. Branconnier and Hess[31] used a simulator to deliver albuterol through bi-level ventilation of 20-5 cmH_2O and showed that devices should be positioned between leak port and mask. This was confirmed by Abdelrahim et al[18] in their *in vitro* comparison of inhaled dose from a JN and VMN, reporting 2 – 3 fold greater deposition with placement between the leak and mask. Analyzing across the vertical gradient showed a distribution pattern with higher deposition of radioaerosol in the middle and lower thirds of both lungs with both devices. This is consistent with findings in normal subjects, were deposition was greater in lower third of the lung in comparison to upper and middle thirds. This was associated with the variation in pleural pressure influencing the amount of volumetric variation into the alveoli from apex to the base of the lungs. The alveoli located in the apex are more distended and less compliant than those in the dependent bases which are more compliant allowing for greater volume variation from the residual capacity to total pulmonary capacity. Although images obtained from stable asthmatics presented a homogeneous deposition pattern similarly to normal subjects, the amount of deposition in different ROIs could differ from one asthmatic to another. In another report assessing asthmatic during exacerbation we found a pattern of deposition representing hot spots[10].

On the other hand, deposition across horizontal gradient showed a higher distribution in central areas than in intermediate and peripheral regions. This may be advantageous in that the primary receptors for beta agonists are located more centrally.

Some limitations should be considered when interpreting our findings. First, there are different levels of pressure applied by BiPAP and none protocol have been validated to assume the best results regarding to clinical findings and the amount of deposition. Second, our sample was composed by stable moderate to severe asthmatics, in which spirometry was performed before but not after the experimental protocol.

Conclusion

In conclusion, according to the research literature, this is the first crossover study involving the analysis of radiotagged aerosol delivery coupled to NIV in moderate to severe stable asthmatics comparing VMN and JN. VNM was more effective to delivering a higher percentage of radioaerosol to the lung. These finding may help guide clinician in selection of aerosol device option to optimize pulmonary deposition during moderate to severe asthmatic in treatment of exacerbations. Further clinical studies are required to determine if the > 2.8 fold lung deposition has an impact on clinical response or outcomes.

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Conflict of interest statement

Valdecir Castor Galindo-Filho has no conflict of interest. Maria Eveline Ramos has no conflict of interest. Catarina Souza Ferreira Rattes Lima has no conflict of interest. Antônio Konrado Barbosa has no conflict of interest. Simone Cristina Soares Brandão has no conflict of interest. James B. Fink has no conflict of interest. Armèle Dornelas de Andrade has no conflict of interest.

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Legends to Figures

Fig. 1. Flow chart diagram of the study.

Fig. 2. Total pulmonary depositing reached by each nebulizer tested in this study. Wilcoxon Test. * p=0.005.

Fig. 3. Comparison of pulmonary deposition in the right lung (4A) and left lung (4B) for both groups.Wilcoxon Test. *p=0.005.

Fig. 4. The pictures above represent the scintigraphic images obtained during experiments in the different compartmens. 5A represents JN and 5B illustrates VMN. From the right to the left are presented: lungs and stomach; upper airways; circuit and nebulizer; mask, inspiratory and expiratory filters.

Table 1.

Anthropometric and cardiopulmonary characteristics from asthmatics enrolled to participate in this study (n = 10).

Variables	Values
Age (years)	33.50 ± 13.46
Weight (Kg)	64.40 ± 9.57
Heigth (m)	1.61 ± 0.06
BMI (Kg/m^2)	24.82 ± 4.58
BR (BPM)	19.9 ± 4.88
HR (bpm)	78.9 ± 5.66
SBP (mmHg)	124.0 ± 9.66
DBP (mmHg)	78.5 ± 7.07
SpO_2 (%)	95.2 ± 1.41
FEV_1 (L)	2.14 ± 0.56
FEV1 (% predicted)	61.01 ± 13.16
FVC (L)	3.23 ± 0.53
FVC (% predicted)	70.89 ± 13.16
FEV_1/FVC	66.28 ± 11.20
FEV_1/FVC (% predicted)	74.71 ± 7.55
PEF (L)	390.6 ± 114.7
PEF (% predicted)	60.02 ± 18.03

Values are mean ± SD. BMI, body mass index; BR, Breathing rate; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, peripheral oxygen saturation; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; FEV_1/FVC, ratio forced expiratory volume in the first second and forced vital capacity; PEF, peak expiratory flow.

Table 2

Intergroup analysis across the vertical and horizontal gradients presented by counts for both groups studied.

Vertical gradient	Regions of interest	NIV+VMN Group (n=10)	NIV+JN Group (n=10)	p value
	Right upper third	116936 ± 72310	44405 ± 18856	0.005*
	Left upper third	105341 ± 59709	44270 ± 19042	0.005*
	Right middle third	260002 ± 122445	84314 ± 38435	0.005*
	Left middle third	235167 ± 110383	81385 ± 38881	0.005*
	Right lower third	239703 ± 76164	89570 ± 27614	0.005*
	Left lower third	239555 ± 60371	82859 ± 27416	0.005*
Vertical gradient	Regions of interest	NIV+VMN (n=10)	NIV+JN (n=10)	p value
	Right central	288849 ± 104643	98960 ± 30089	0.005*
	Left central	227093 ± 112459	99394 ± 37645	0.005*
	Right intermediate	169924 ± 67850	60631 ± 20925	0.005*
	Left intermediate	166257 ± 79252	56865 ± 21371	0.005*
	Right peripheral	159704 ± 83839	59008 ±28646	0.005*
	Left peripheral	142713 ±47940	54921± 22518	0.005*

Values are mean ± SD. Wilcoxon test, *p<0.05.

Table 3.

Radioaerosol deposition index according to the vertical and horizontal gradients for each pulmonary region in both phases of the study.

		Vertical Gradient		Horizontal Gradient	
	Group	Lung Region	p-value	Lung Region	p-value
Right lung	NIV+JN	UT = MT	> 0.05	CT = IT	> 0.05
	(n = 10)	UT < LT	< 0.001*	CT > PT	< 0.001*
		MT = LT	> 0.05	IT = PT	> 0.05
	NIV+VMN	UT = MT	> 0.05	CT = IT	> 0.05
	(n = 10)	UT < LT	< 0.001*	CT > PT	< 0.001*
		MT = LT	> 0.05	IT = PT	> 0.05
Left lung	NIV+JN	UT < MT	<0.05*	CT > IT	< 0.05*
	(n = 10)	UT < LT	< 0.001*	CT > PT	< 0.001*
		MT = LT	> 0.05	IT = PT	> 0.05
	NIV+VJN	UT < MT	> 0.01	CT > IT	> 0.05
	(n = 10)	UT < LT	< 0.05*	CT > PT	< 0.001*
		MT = LT	> 0.05	IT = PT	> 0.05

Values are mean ± SD.NIV, noninvasive ventilation; JN, jet nebulizer; VMN, vibrating mesh nebulizer; UT, upper third; MT, middle third; LT, lower third; CT, central third; IT, intermediate third; PT, peripheral third.
Friedman Test and Dunn´s Multiple Comparison Test, *p<0.05.

Table 4.

Mass aerosol balance obtained in different compartments (pulmonary and extrapulmonary) for each group of the study as a percentage.

COMPARTMENTS	**VNI+MN** (n = 10)	**VNI+JN** (n = 10)	**p valor**
Lungs (%)	5.77±2.00	1.71±0.05	0.005*
Upper airways (%)	14.08±7.60	4.79±1.65	0.005*
Stomach (%)	2.89±0.91	0.77±058	0.005*
Inhaled dose	22.75±7.89	7.27±1.59	0.005*
Nebulizer (%)	4.17±0.85	41.43±12.66	0.005*
Face mask	16.66±6.21	6.69±1.61	0.005*
Circuit (%)	16.80±6.21	15.88±5.31	0.386
Inspiratory filter (%)	0.73±0.76	0.61±0.86	0.342
Expiratory filter (%)	38.57±7.87	25.15±5.56	0.007*

Values are mean ± SD. Wilcoxon test, *p<0.05.

Figure1.

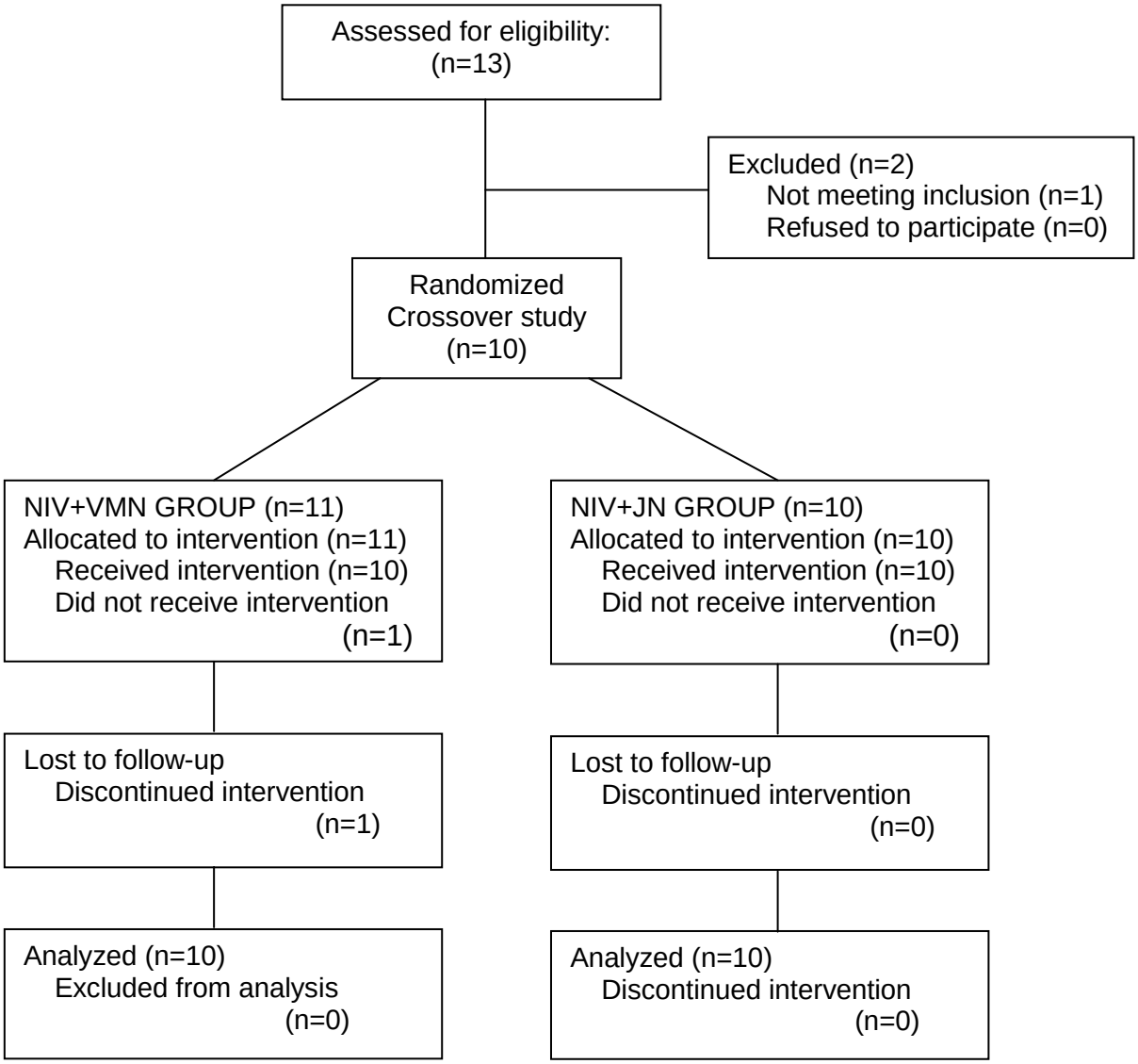

Assessed for eligibility:
(n=13)
Excluded (n=2)
Not meeting inclusion (n=1)
Refused to participate (n=0)
Randomized
Crossover study
(n=10)
NIV+VMN GROUP (n=11)
Allocated to intervention (n=11)
Received intervention (n=10)
Did not receive intervention
(n=1)
NIV+JN GROUP (n=10)
Allocated to intervention (n=10)
Received intervention (n=10)
Did not receive intervention
(n=0)
Lost to follow-up
Discontinued intervention
(n=1)
Lost to follow-up
Discontinued intervention
(n=0)
Analyzed (n=10)
Excluded from analysis
(n=0)
Analyzed (n=10)
Discontinued intervention
(n=0)

Figure 2.

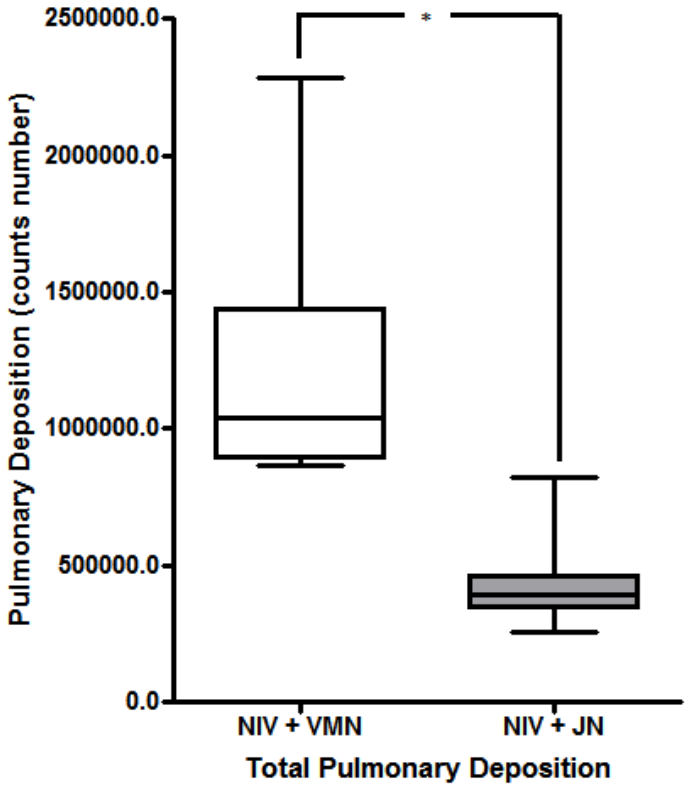
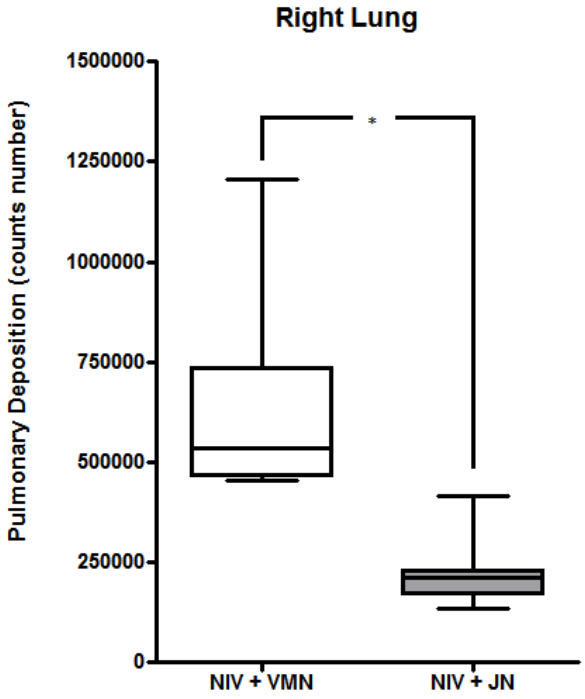
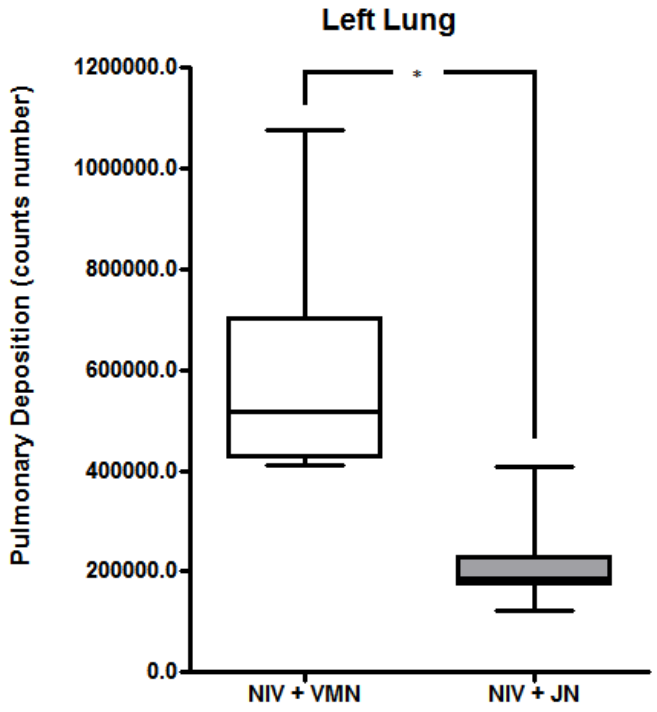

2500000.0
2000000.0
1500000.0
1000000.0
500000.0
0.0
Pulmonary Deposition (counts number)
*
NIV + VMN
NIV + JN
Total Pulmonary Deposition

Figure 3.

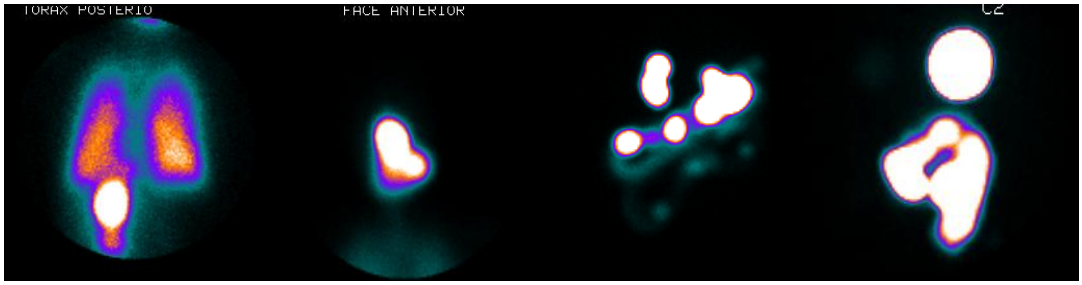


3A

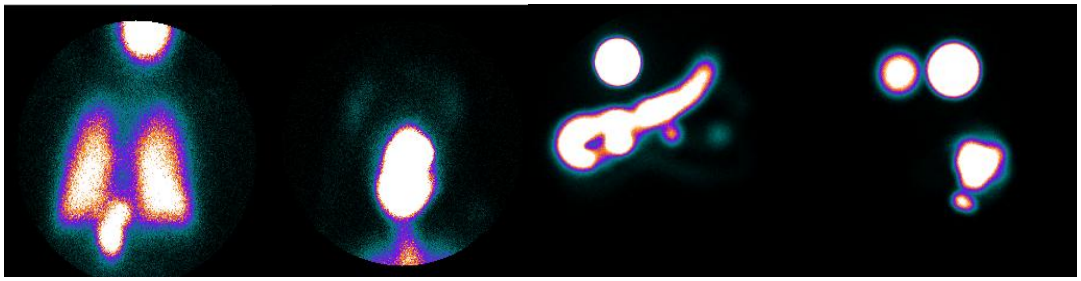


3B

Figure 4.



4A



4B

IN VIVO ASSESSMENT OF RADIOLABELED AEROSOL DURING NONINVASIVE VENTILATION IN STABLE COPD: A RANDOMIZED CROSSOVER CLINICAL TRIAL

Noninvasive ventilation coupled to nebulization by scintigraphy in COPD

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Abstract

Background: Beneficial effects from noninvasive ventilation (NIV) in acute COPD are well-established, but couple to nebulization is still challenging. *Aim:* To compare radiaoaerosol pulmonary deposition and radioaerosol mass balance in the different compartments (pulmonary and extrapulmonary) using vibrating mesh nebulizer (VMN) and jet nebulizer (JN) coupled to NIV. *Methods:* It was a crossover study involving 9 stable moderate to severe COPD randomly allocated for both phases of the study: Phase 1(NIV+MN,n=9) and phase 2(NIV+JN,n=9). Bronchodilators were delivered during NIV using a facemask (pressures of 12 cmH_2O and 5 cmH_2O - inspiratory and expiratory, respectively). Radioactivity counts were performed using a gamma camera and regions of interest(ROIs) were delimited. We determine aerosol mass balance from the lungs, upper airways, stomach, nebulizer, circuit, inspiratory and expiratory filters, and mask as a percentage. *Results:* Radiolabelled aerosol was delivery in a higher amount using VMN in comparison to JN (1867044±456120 counts *vs* 579729±312261 counts, p = 0.008). Inhaled dose reached 19.90±3.18% in VMN against 7.03±2.97% from JN (p=0.008) in correlation to the percentage of lung deposition of 8.75±2.23% in VMN against 2.82±1.21% to JN (p=0.008). Residual volume was lower in VMN than in JN (3.20±1.33% *versus* 49.53±6.40%, p=0.008). Thus, peripheral deposition of radiaoerosol was significantly lower. *Conclusions:* According to our results VMN deposited more than 3 fold radiaoerosol into the lungs in comparison to JN and could be an alternative to ensure effective bronchodilators deposition in those COPD patients unable to perform other cathegories of inhaler devices.

Keywords: nebulizers, noninvasive ventilation, COPD, scintigraphy, aerosol.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and systemic inflammatory disease characterized by a variable airflow limitation, which presents a range of vary between individuals (1,2). It is considered the fourth cause of death in the world, consisting in a public health problem which lead to social, economic and quality of life repercussions worldwide (3,4).

Inhalation of short-acting beta-agonists are central to treat all stages of the disease and evidence from data published in the literature showed the long-term benefits of using inhalation therapy in COPD (4). However, particle size, velocity of the aerosol plume, different inhalers designs, ability to use correctly the inhaler device, and breathing patterns are some factors that directly affect the efficacy of pulmonary drug deposition (5-10). Studies involving different inhalers demonstrated a high deposition of aerosol in the oral pharynx and less than 20% of the nominal dose reaches the lungs (6,7,11).

Nowadays, there are evidences from the literature suggesting that many stable COPD are unable to use prescribed inhalers properly, recommending the use of jet nebulizers (JN) (4,12,13), mainly because those devices have some advantages as such: aerosol generated from water-soluble drugs, facilities to perform the technique (press and breathe) and the absence of propellants (4,12-14).

In addition to this, some studies in animal model and *in vitro* involving a new generation of nebulizers, named vibrating mesh nebulizers (VMN) have

demonstrated efficacy to deposit more than 2 fold from the nominal aerosol dose, less time to nebulize, lower particle size and residual volume(15-19).

Randomized controlled trials and meta-analysis have demonstrated some benefits obtained with the application of NIV in COPD patients. Those clinical benefits include reduction in work of breathing, respiratory discomfort, need of intubation, hospital stay and hospital mortality (20-27). Plant et al conducted a prospective multicenter randomized controlled trial involving 236 mild to moderate acute COPD to compare the use of NIV with standard therapy (24). They observed that NIV group presented significant reduction in the need of intubation (15% in NIV group versus 27% in standard therapy group) and in-hospital mortality (10% in NIV group versus 20% in standard therapy group).

However, there is a lack of information about the effects of coupling NIV to nebulizers in this population and one study involving NIV and delivery of bronchodilators in COPD did not found clinical benefits (28). In the literature researched, we did not find studies coupling NIV to nebulization and results using VMN in association to positive pressure seems to be very promising. For this reason, we hypothesis that delivery of bronchodilators using VMN will increase the amount of radiolabeled aerosol deposited into the lungs in COPD.

The aims of this study were: 1) to compare inhaled dose of radioaerosol into the lungs and determine distribution across horizontal and vertical gradients, and 2) to quantify mass balance of the delivery aerosol in different compartments (intrapulmonary and extrapulmonary).

Material and Methods

Study design and sample

It was a crossover study involved 9 moderate to severe stable COPD, from both sexes, age between 18 to 65 years and was performed in the Department of Nuclear Medicine and Cardiorespiratory Laboratory at Physiotherapy Department from Universidade Federal de Pernambuco in association to Georgia State University between. Data collection was performed after approved protocol by Human Ethics Institutional Committee and all participants gave written informed consent to participate.

Inclusion and exclusion criteria

Inclusion criteria were considered as follows: moderate to severe stable COPD (50% ≤ FEV_1 < 80% from predicted values or 30% ≤ FEV_1 < 50% from predicted values)(4); none exacerbation in the last six months; age between 18 - 60 years; both sexes; no smoking history; able to understand verbal commands, and consent to participate in this protocol. On the other hand, exclusion criteria were: presence of dyspnea; cardiopulmonary diseases (chronic obstructive pulmonary disease, pneumonia, cardiac failure, myocardial infarction, pneumothorax); hyperthermia; hemodynamic instability (heart rate > 150 bpm and systolic blood pressure < 90 mmHg); arrhythmia absence; pregnancy; and contraindications for use of NIV (29).

Anthropometric and Cardiopulmonary measurements

Anthropometric data was the first step in the initial assessment from the patients consisted of collecting anthropometric data (age, height, weight and body mass index - BMI). For cardiopulmonary parameters we considered: respiratory rate (RR); peripheral oxygen saturation (SpO_2); systolic blood pressure (SBP) and diastolic blood pressure (DBP) using pulse oxymetry (ACTIVE -Ecafix, São Paulo, Brazil) and a manual pressure manometer (Welch Allyn^{TM} DS 44-11 Beaverton, Oregon, USA). Then, to conclude respiratory assessment, spirometry was performed (Micro Loop 8 / Cardinal Health, England, UK), based on American Thoracic Society, which considered a variance of 0.2 L allowed between tests and the average of three measurements was recorded (30).

Inhalation protocol

Inhalation protocol was divided into two phases: Phase 1 – NIV+JN (control group) and Phase 2 – NIV+VMN (experimental group). The order nebulizers to be tested was randomized (Random Allocation Software – version 2.0) for each patient and the second measurement was taken one week before, to avoid radioactive waste into the respiratory tract between using one and another nebulizer, thereby avoiding possible bias.

Inhalation was performed using diethilene triamine penta-acetic technetium (99mTc-DTPA) with radioactivity of 25 millicuries (31). Both

nebulizers were charged with 2.5 mg of salbutamol and 0.25 mg of ipratropium bromide and 3 mL of saline solution was added to complete 3 Ml. JN (Mist yMax, Air Life, Yorba Linda, USA) was positioned in the circuit using a “T” piece, particle size generation in a 5 µm range (according to the manufacturer information) and flow oxygen tritated at 8 L/min. VMN (Aeroneb Solo, Galway, Ireland) was positioned in the mask using an elbow (Elbow Kit, Respironics®, Murrysville, Pennsylvania, USA), particle size generation in a 1 µm and connected to electrical energy. Bilevel positive pressure (BiPAP Synchrony, Respironics®, Murrysville, Pennsylvania, USA) was applied through face mask (Comfort Full 2, Respironics®, Murrysville, Pennsylvania, USA) attached with straps and pressure adjusted were 12 cmH_2O of inspiratory pressure and 5 cmH_2O of expiratory pressure after a period of adaptation before beginning the procedure to avoid ventilator-patient asynchrony (32,33).

Immediately after inhalation, participants sat in a chair with the back positioned in front to the gamma camera (STARCAM 3200 GE, California, USA) to obtain radioactivity counts from the posterior thorax during a period of 300 seconds on a matrix of 256 X 256. After, participants were positioned sitting in front to the gama camera to obtain images from face. Then, the same procedure was performed to analysis deposition in the nebulizer, circuits, inspiratory filter, expiratory filter and face mask. Counts representing stomach were obtained from posterior thorax and corrections for decay of technetium were used to during extrapulmonary measurements. The analysis of deposition in pulmonary and extrapulmonary compartments was expressed as a percentage from the count in each compartment to the total radioaerosol mass generated by nebulizers. The

inhaled radioaerosol was considered the sum of deposition into the upper airways, lungs and stomach (15).

Regions of interest were delimited based on a previous protocol and RDI was expressed as absolute values and was calculated according to the counts generated from each regions of interest (31).

Statistical analysis

The sample size was calculated based on a pilot study involving 5 subjects to obtain standard deviation of repeated observations in the same individual and later is the standard deviation of the difference between two measurements in the same individual, considering percentage in lung deposition. A total of 5 stable COPD patients entered in this two-treatment crossover study. The probability is 84% that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 1.830 units. It was based on the assumption that within-patient standard deviation of the response variable is 0.72. However, this study was carried out with 9 individuals, against the possibility of subjects not completing the protocol. For the sample size calculation we used the software developed by David Schoenfeld, support from the MGH Mallinckrodt General Research Center. Javascript version developed by REMorse.

Primary outcomes consisted of radioaerosol deposition index into the lungs and we considered as secondary outcomes, radioaerosol mass balance that reached pulmonary and extrapulmonary compartments. For statistical analysis were used Kolmogorov-Smirnov Test to analysis normality and after was

applied Wilcoxon Test, Friedman Test and Dunn´s Multiple Comparison Test, considering as an interval of confidence 95% ($p<0.05$) through the software SPSS 20.0(SPSS Inc., Chicago, Illinois, USA) and GraphPad Prisma 4.0(Graph Pad Software In., San Diego, California, USA).

Results

Despite 12 CPOD patients were enrolled in this study, only 9 completed the entire protocol. The reasons to be excluded from this protocol were: 1 presented claustrophobia during application of NIV and 2 did not meet the inclusion criteria, as demonstrated in the study flow chart (Figure1). Anthropometric, cardiorespiratory and spirometric data are shown in table 1.

NIV+VMN group reached higher radiolabelled aerosol in both lungs in comparison to NIV+JN group (1867044±456120 counts *versus* 579729±312261 counts, p = 0.008), as shown in figure 2. Deposition in right and left lungs was higher when using mesh device coupled to NIV (right lung: 971375±284808 counts *versus* 303657±172738 counts, p = 0.008 and left lung: 896779±205960 counts *vs* 276072±143392 counts), as shown in figure 3.

Intragroup analysis of radioaerosol pulmonary index for ROI across vertical and horizontal gradients is shown in table 2. When analyzing intergroup deposition in different ROI across vertical and horizontal gradients, we found that NIV+VMN group had higher counts in comparison to NIV+VMN group, as shown in table 3.

The percentage of radioaerosol inhaled was significantly higher in NIV+VMN group when compared to NIV+JN group (19.90 ± 3.18% *versus* 7.03 ± 2.97%, p=0.008). VMN presented a lower residual volume (3.20 ± 1.33% *versus* 48.53 ± 6.40%, p=0.008) and more radiaerosol deposited in the face mask and upper airways, in comparison to jet nebulizer during NIV. Our results showed that JN demonstrated a significant deposition of radioaerosol in the expiratory filter than mesh device. Thus, none differences were found regarding to radioaerosol mass balance found in the stomach, circuit and inspiratory filter for both groups. Table 4 represents the radiaerosol mass balance obtained in each compartment from both groups.

Figure 4 demonstrated the individual pattern deposition of radiolabelled aerosol using VMN and JN during application of NIV.

Discussion

This is the first study to compare deposition and distribution of aerosol during NIV to COPD patients. Our results showed a higher amount of radioaerosol deposited into the lungs and a higher percentage from nominal dose charged in the nebulizers. In addition to this, VMN presented a lower residual volume which possibly delivery more aerolized drugs to COPD patients.

Analysis of radiaoerosol using JN coupled to NIV demonstrated a lower amount of particles deposited into the lungs in comparison to spontaneously breathing in normal subjects (32). Although there many studies reporting the benefits obtained from NIV in COPD patients (20-27), we did not

found in the database researched, any study using VMN coupled to NIV evaluated through scintigraphy in COPD.

However, we found just one study involving the use of NIV and nebulization in COPD reported by Mukhopadhway et al, aiming to analysis the effects of withdrawing NIV in 19 exacerbated COPD to delivery medications on physiologic (RR, HR, BP, SpO2, pH, PaCO2 and Borg Score) and dyspnea sensation. Results from this assessment did not showed significant change in physiologic parameters and oxygenation between NIV and nebulization periods. They observed increase in SBP and HR after inhalation, probably due to the systemic adrenergic effects of bronchodilator and decrease in SpO2 between both phases in the study. As a conclusion, short-term cessation of NIV to nebulize did not demonstrated discomfort or physiologic alterations (28).

Our findings regarding the difference in deposition during NIV is consistent with reports of aerosol deposited in patients submitted to conventional mechanical ventilation (CMV). Fuller et al analyzed deposition of radiotagged aerosol via JN and metered dose inhaler (pMDI) during CMV and found similar levels of lung dose with JN (1 – 3%) and higher levels of deposition with pMDI coupled to spacer (6 – 8%) (34). Their findings using JN is consistent with our results, because percentage using JN was 2.82%.

In a vitro model of adult mechanical ventilation, Ari et al compared aerosol delivery with JN, pMDI, VMN and ultrasonic nebulizer (UN) (35). Under similar conditions as Fuller, deposition distal to endotracheal tube was 3.6%in JN, while pMDI, VMN and USN were similar at 17%. According to this results, the same relative deposition for pMDI and VMN *in vitro*, it is reasonable to expect that *in*

vivo deposition would be similar. Consequently, our reported deposition with JN and VMN appear to agree with reports with CMV.

Assessing the efficacy of VMN coupled to NIV has been very promising, because radioaerosol deposition reached more than two fold (15-19,36-39). In this study, our results observed a higher amount of radiolabelled aerolized bronchodilator counts in stable moderate to severe COPD more than three folds in the comparison between VMN and JN. Abdelrahim et al, applied NIV in association to nebulization in a breathing simulator using 20 cmH_2O (inspiratory pressure) and 5 cmH_2O (expiratory pressure) with parameters set to simulate COPD patients (tidal volume of 500 ml, 15 breaths/min and 1:3 as I:E ratio) to compare VMN and JN in different positions. They found that VMB reached much more radiolabelled aerosol than JN in both tested positions. Thus, Dubus et al, observed more than 20 fold deposited into the lungs after comparing VMN to JN in a macaque model of mechanical ventilation to neonates (16).

Another result from this study, concerned about the lung deposition of 8.75% to VMN *versus* 2.82% to JN in line with the values observed in the inhaled dose of 19.90% .to VMN *versus* 7.03% to JN. Our results corroborates to those found by Abdelrahim et al, after assessing *in vitro* radioaerosol deposition through a breath simulator using VMN and NIV and reported around 51% of inhaled dose in VMN against 24% to JN (16). Similarly, AlQuami et al analyzed the inhaled dose of radioaerosol that reached *in vitro* test breath simulator in three different inhalers and found a higher percentage of 28.83 in VMN, 23.5% delivered by pMDI attached to spacer and only 13.2% in JN (40).

Mc Peck et al compared different modes of ventilation and demonstrated that radioaerosol inhaled dose of vary among these parameters set using VMN and JN. They found 14.3% versus 6.4% (using 10-5 cmH_2O by BiPAP), 15.4% *versus* 3.6% (applying 15-8 cmH_2O by BiPAP) and 14.6% *versus* 7.2% (using 5 cmH_2O by CPAP) (18).

VMN has got three advantages, regarding to no need of gas during nebulization in a pressurized circuit, small particles sizes generated by device and a lower residual volume (15-19, 28, 29). Our results demonstrated, according to this last advantage, a lower residual volume using VMN of 3.20% versus 49.53% to JN. A lower residual volume means that much more aerolized drugs will be kept into the recipe at the end of nebulization and probably more generated particles will reach the respiratory tree, mainly in those COPD patients to reduce dynamic hyperinflation and avoid increase of functional residual capacity.

In accordance to our results, Dubus et al compared two VMN and one JN in the macaque model of pediatric ventilation and pointed out 2.7% (APN-S model of VMN) and 9.9% (APN-C model of VMN) against 22.4% (15). In addition to this, similarly to our results, Mc Peck et al, reported a lower residual volume of 3.49% (VMN) versus 54.9% (JN) (18).

Analyzing deposition across the vertical and horizontal gradients, we found that intergroup deposition was higher comparing VMN to JN in different regions of interest for both lungs. While there is 2 - 3 fold more aerosols in all regions of interest with VMN than JN, we found similar ratios of distribution. It appears that distribution of aerosol is different between subjects, and between

the two nebulizer groups that are not obvious from analysis of regions of interest. Although the images were taken at one week intervals for each subject, individual subjects appear to have similar areas of aerosol concentration between the two types of aerosol generator used. These concentrations of aerosols in the lung likely represent localized areas of obstruction in each lung.

Among the factors that influence aerosol deposition along the airways, the respiratory pattern seems to contribute reducing the amount of drugs reaching the site of action. We believe that respiratory pattern adopted by COPD patients during NIV delivery influenced the standard deposition of radiolabelled aerolized bronchodilators in this study. Probably, we should consider the level of obstruction represented by those patients in the different stage of the disease.

We found a lower deposition in peripheral areas in both groups when analyzing ROIs, it should be explained because this sample of COPD patients presented lower values of FEF 25-75% (0.71 L – around 31.35% from predicted values), which correlates to prominent destruction of small airways presented by physiophatology of this disease. We found more depositing in this group of patients, similarly to Abdelrahim et al, but those authors used a simulator in which respiratory parameter was set and did not differ during the time of using NIV. However, in our *in vivo* protocol, respiratory parameters changed in each respiratory duty cycle during NIV (16).

The scintigraphy images obtained in this study from COPD patients presented hot spots, which concentrates more aerosol in some areas due to pulmonary obstruction and similar areas of hot spots were reported by Dolovich

et al, which demonstrating that using aerosol generators with two different particle sizes, distribution of aerosol changes beyond the hot spots (41).

Another concerning is about the higher percentage of deposition in the upper airways and face mask using VMN in comparison to JN. Probably, it should be a result of inhaled dose available to breath offered by VMN, the position of this device in the face mask and high inspiratory flows generated by BiPAP. In a randomized controlled trial performed by our group to assess radiaoerosol deposition coupling NIV to JN and JN alone during asthma exacerbation, we observed that NIV generates higher inspiratory flows than using nebulization breathing spontaneously (33).

Positions of nebulizers during measurements differ in our protocol because VMN was placed using an elbow attached to the mask, while JN was placed between leak and the mask as recommended in two studies, which demonstrated a higher percentage of radioaerosol deposited using this positions through VMN during NIV (16,42).

Some limitations should be considered when interpreting our findings. First, despite the amount of publications involving NIV in COPD exacerbations, none established pressures protocol was validated in this population to indicate the best results in correlation to clinical benefits and the amount of bronchodilator deposited into the respiratory tract. Second, we did not use another type of assessment to confirm possible airway remodeling in COPD to correlate the pattern of deposition through high resolution computerized tomography. Finally, was not possible to measure the effects of the amount of drug deposited in the

lungs through NIV and the impact in functional residual capacity in this sample by optoelectronic pletismography.

Conclusion

In conclusion, this is the first crossover study involving the analysis of radiolabelled aerosol bronchodilator delivery coupled to NIV in moderate to severe stable COPD using VMN and JN. We found more than 3 fold aerolized particles from the total 3 mL of solution charged into the VMN in comparison to JN and a lower residual volume, which should explain the amount of radioaerosol that reached both lungs. These results confirm the effectiveness of nebulizing liquid solutions in a particular group of stable COPD unable to perform other types of inhalers due to personal difficult to actuated the device and breath at the same time. Further randomized controlled trials are necessary to evaluate clinical findings obtained from VMN to relieve respiratory discomfort and dynamic hyperinflation in COPD.

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Conflict of interest statement

All authors have no conflict of interest to be disclose.

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Legends to Figures

Figure 1. Flow chart diagram of this study protocol (n = 9).

Figure 2. Total pulmonary depositing reached by each nebulizer tested in this study. Wilcoxon Test. * p=0.005.

Figure 3. Comparison of pulmonary deposition in the right lung (Panel A) and left lung (Panel B) for both groups. Wilcoxon Test. *p=0.005.

Figure 4. Scintigraphic images obtained during inhalation coupled to NIV for both nebulizers in all COPD patients. See that the pattern deposition obtained from each patient in all regions of interest was higher with VMN than JN, with similar ratios of distribution, but patients 2 and 8 presented images suggesting penetration of radioaerosol withdifferent ratios distribution.
VMN = vibrating mesh nebulizer and JN = jet nebulizer.

Table 1.

Anthropometric and cardiopulmonary characteristics from asthmatics enrolled to participate in this study.

Variables	Values
Age (years)	60.14 ± 7.55
Weight (Kg)	70.64 ± 8.21
Heigth (m)	1.65 ± 0.08
BMI (Kg/m^2)	24.99 ± 5.12
BR (BPM)	21.86 ± 1.06
HR (bpm)	82,43 ± 3,40
SBP (mmHg)	131.43 ± 8.02
DBP (mmHg)	83.57 ± 5.56
SpO_2 (%)	95.2 ± 1.41
FEV_1 (L)	1.32 ± 0.36
FEV1 (% predicted)	42.49 ± 8.71
FVC (L)	2.42 ± 0.60
FVC (% predicted)	58.75 ± 9.21
$FEF_{25-75\%}$	0.79 ± 0.36
$FEF_{25-75\%}$ (% predicted)	31.35 ± 10.51
FEV_1/FVC	57.05 ± 5.52
FEV_1/FVC (% predicted)	71.10 ± 68.40
PEF (L)	321.10 ± 45.86
PEF (% predicted)	56.09 ± 11.29

Values are mean ± SD. BMI, body mass index; BR, Breathing rate; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, peripheral oxygen saturation; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow at 25-75%, FEV_1/FVC, ratio forced expiratory volum in the first second and forced vital capacity; PEF, peak expiratory flow.

Table 2

Intergroup analysis across the vertical and horizontal gradients presented by counts for both groups involved in this study.

Vertical gradient	Regions of interest	NIV+VMN Group (n=9)	NIV+JN Group (n=9)	p value
	Right upper third	163450 ± 160425	59741 ± 69910	0.008
	Left upper third	113078 ± 113889	34760 ± 51036	0.008
	Right middle third	367417 ± 141640	103154 ± 65495	0.008
	Left middle third	466516 ± 119100	126942 ± 38541	0.008
	Right lower third	440509 ± 150060	140762 ± 81849	0.008
	Left lower third	314188 ± 141436	114370 ± 66886	0.008
Vertical gradient	Regions of interest	NIV+VMN (n=9)	NIV+JN (n=9)	p value
	Right central	370525 ± 114841	107769 ± 73732	0.008
	Left central	398909 ± 164694	111697 ± 74751	0.008
	Right intermediate	375677 ± 104661	124254 ± 61864	0.008
	Left intermediate	331845 ± 111254	108186 ± 49121	0.008
	Right peripheral	225173 ± 124044	71634 ±52695	0.008
	Left peripheral	166025 ± 70121	56185 ± 36518	0.008

Values are mean ± SD. Wilcoxon test, *p<0.05.

Table 3.

Radioaerosol deposition index according to the vertical and horizontal gradients for each pulmonary region in both goups.

		Vertical Gradient		Horizontal Gradient	
	Group	Lung Region	p-value	Lung Region	p-value
Right lung	NIV+JN	UT = MT	> 0.05	CT = IT	> 0.05
	(n = 9)	UT < LT	< 0.05*	CT = PT	> 0.05
		MT = LT	> 0.05	IT > PT	< 0.05*
	NIV+VMN	UT < MT	< 0.05*	CT = IT	> 0.05
	(n = 9)	UT = LT	> 0.05	CT > PT	< 0.05*
		MT = LT	> 0.05	IT = PT	> 0.05
Left lung	NIV+JN	UT < MT	< 0.01*	CT = IT	> 0.05
	(n = 9)	UT < LT	< 0.01*	CT > PT	< 0.01*
		MT = LT	> 0.05	IT = PT	> 0.05
	NIV+VMN	UT < MT	< 0.01*	CT = IT	> 0.05
	(n = 9)	UT = LT	> 0.05	CT > PT	< 0.05*
		MT = LT	> 0.05	IT = PT	> 0.05

Values are mean ± SD.NIV, noninvasive ventilation; JN, jet nebulizer; VMN, vibrating mesh nebulizer; UT, upper third; MT, middle third; LT, lower third; CT, central third; IT, intermediate third; PT, peripheral third.
Friedman Test and Dunn´s Multiple Comparison Test, *p<0.05.

Table 4.

Mass aerosol balance obtained in different compartments (pulmonary and extrapulmonary) for each group of the study as a percentage.

COMPARTMENTS	**VNI + MN** (n = 9)	**VNI + JN** (n = 9)	**p valor**
Lungs (%)	8.75 ± 2.23	2.82 ± 1.21	0.008*
Upper airways (%)	10.46 ± 3.57	4.45 ± 3.29	0.008*
Stomach (%)	0.67 ± 0.26	0.77 ± 058	0.008*
Inhaled dose	19.90 ± 3.18	7.03 ± 2.97	0.008*
Nebulizer (%)	3.20 ± 1.33	49.53 ± 6.40	0.008*
Circuit (%)	14.06 ± 4.82	14.60 ± 5.13	0.575
Face mask (%)	19.38 ± 3.55	5.37 ± 1.62	0.008*
Inspiratory filter (%)	0.34 ± 0.28	0.50 ± 0.93	0.400
Expiratory filter (%)	43.25 ± 5.33	23.05 ± 5.63	0.008*

Values are mean ± SD. Wilcoxon test, *p<0.05.

Figure 1.

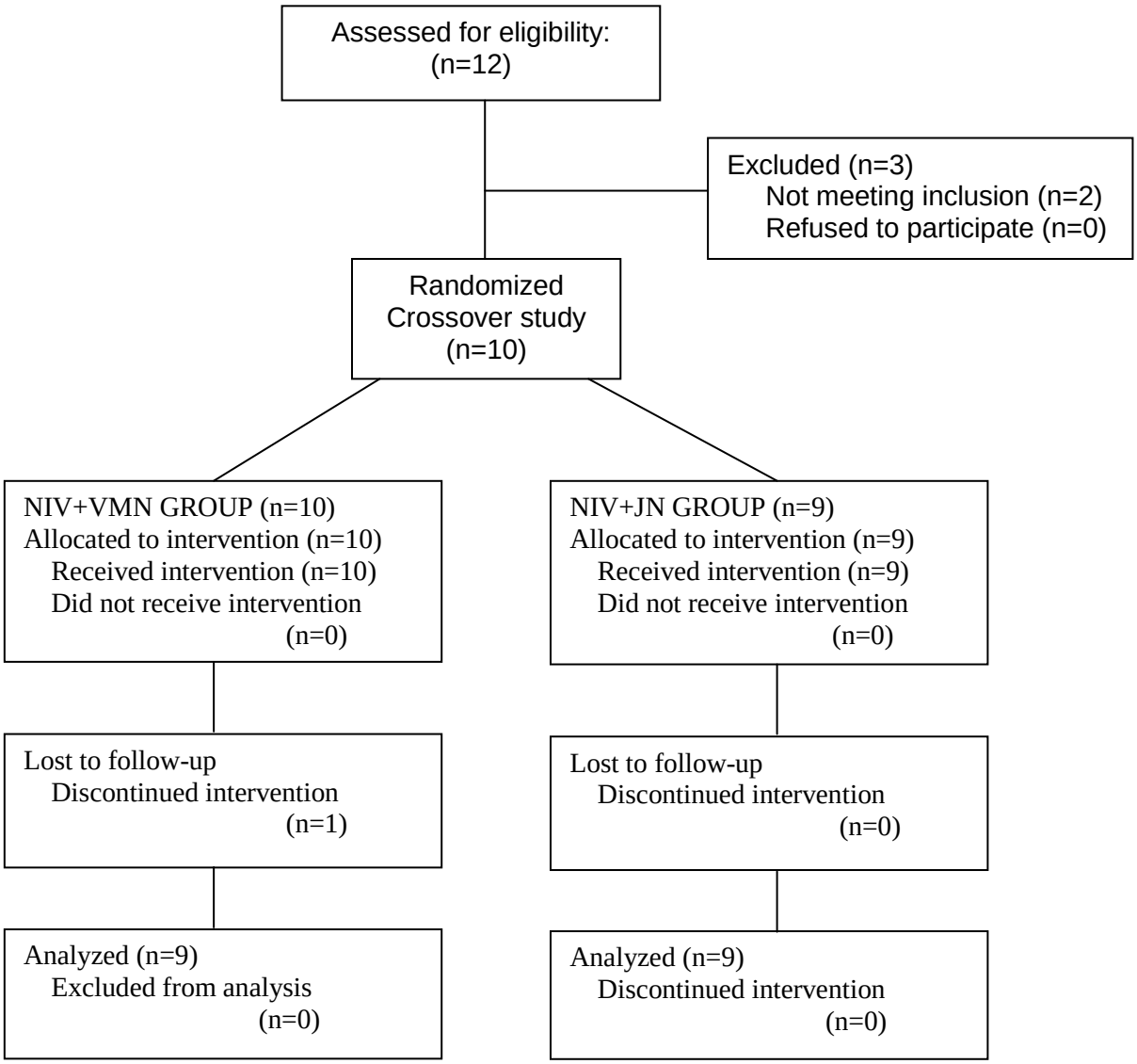

Assessed for eligibility:
(n=12)
Excluded (n=3)
Not meeting inclusion (n=2)
Refused to participate (n=0)
Randomized
Crossover study
(n=10)
NIV+VMN GROUP (n=10)
Allocated to intervention (n=10)
Received intervention (n=10)
Did not receive intervention
(n=0)
NIV+JN GROUP (n=9)
Allocated to intervention (n=9)
Received intervention (n=9)
Did not receive intervention
(n=0)
Lost to follow-up
Discontinued intervention
(n=1)
Lost to follow-up
Discontinued intervention
(n=0)
Analyzed (n=9)
Excluded from analysis
(n=0)
Analyzed (n=9)
Discontinued intervention
(n=0)

Figure 2.

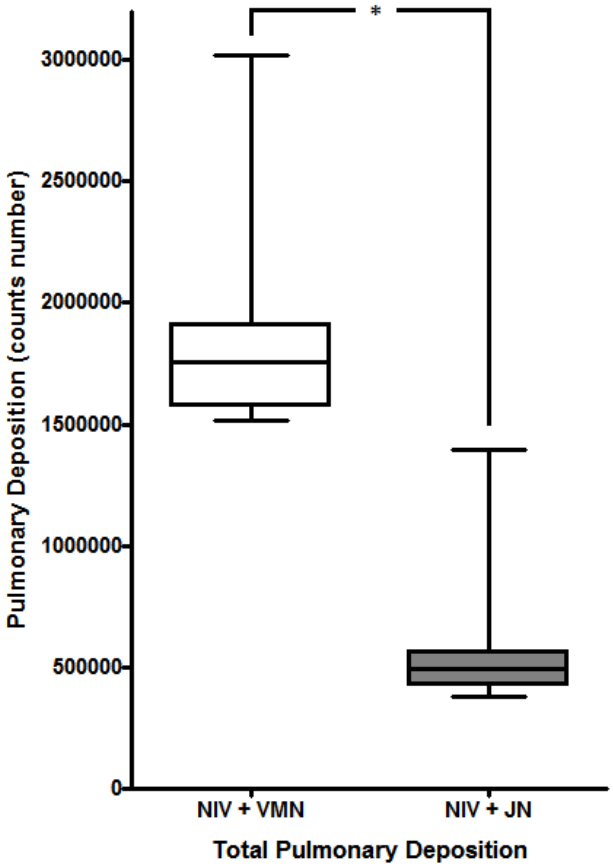
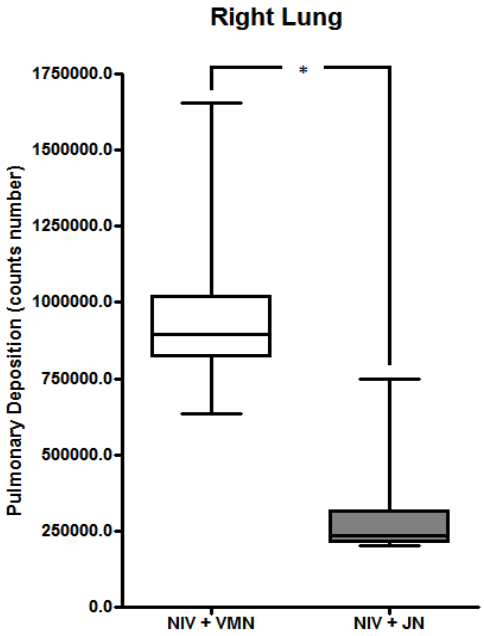
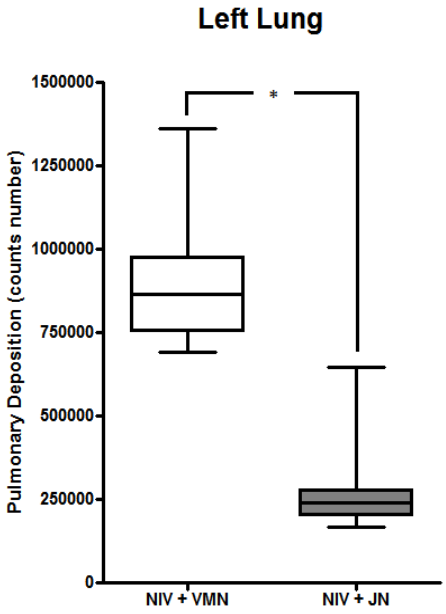

*
3000000
2500000
2000000
1500000
1000000
500000
0
Pulmonary Deposition (counts number)
NIV + VMN
NIV + JN
Total Pulmonary Deposition

Figure 3.

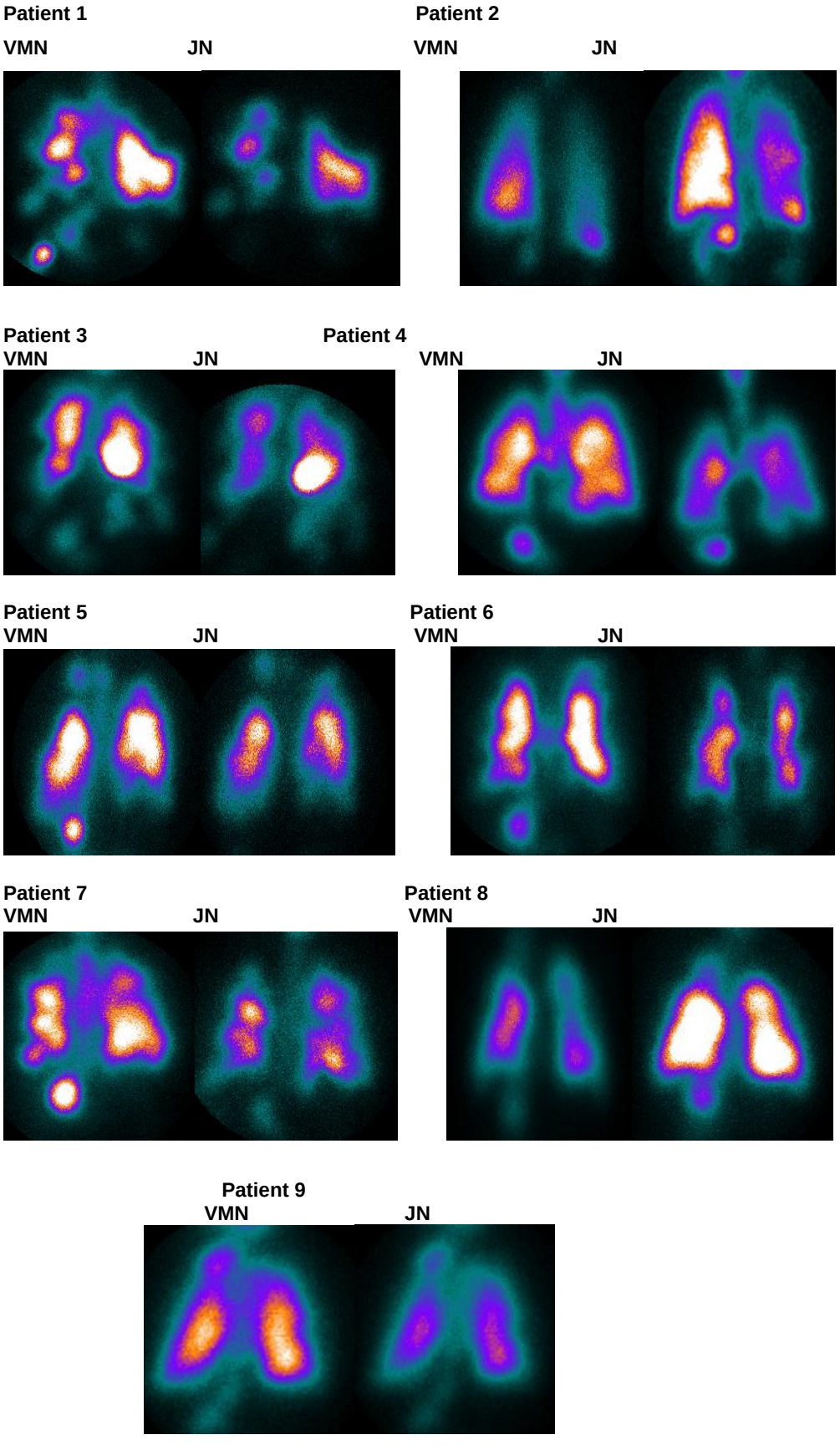


Panel A



Panel B

Figura 4


Patient 1
VMN
JN
Patient 2
VMN
JN
Patient 3
VMN
JN
Patient 4
VMN
JN
Patient 5
VMN
JN
Patient 6
VMN
JN
Patient 7
VMN
JN
Patient 8
VMN
JN
Patient 9
VMN
JN

8. COMENTÁRIOS, CRÍTICAS E SUGESTÕES

A ideia original deste projeto de pesquisa surgiu a partir da observação da literatura científica quanto à escassez de estudos envolvendo o uso das nebulizações durante a realização da VNI. Com o surgimento dos NM e a partir dos resultados obtidos de experimentos em modelos animais e *in vitro*, observou-se o aumento significativo do aerossol liberado a nível pulmonar quando feita a associação entre estas duas formas terapêuticas.

Partindo-se destes resultados, surgiu o interesse de comparar o NJ e o NM junto a VNI em indivíduos saudáveis, com asma e DPOC estabilizados, utilizando-se como marcador funcional os dados mensurados através da cintilografia pulmonar. Foi utilizado o tecnécio marcado com radioisótopo pelo fato de não alterar o tamanho das partículas produzidas pelos geradores de aerossóis.

Entretanto, pelo fato de utilizarmos radioisótopos, fez-se necessário ter cuidado e atenção nos passos realizados durante a cintilografia, pois qualquer alteração na organização do método poderia ocasionar o surgimento de viés e uma nova medida só iria ser tomada após uma semana, pois seria necessário aguardar o tempo de decaimento da radiação do material inalado pelo paciente. Outro aspecto importante, diz respeito à possibilidade de vazamentos ou desconexão do circuito de VNI durante o experimento, o qual irá promover a contaminação na sala de inalação pelo aerosol marcado com radioatividade.

Ainda, foi necessário observar durante a inalação, qualquer tipo de vazamento pelos dispositivos de inalação ou pela máscara de VNI durante ou erros, ao acionar a nebulização sem ligar o aparelho de VNI. Todas estas possibilidades poderiam contribuir no surgimento de viés de mensuração durante os experimentos.

Com relação aos objetivos deste projeto de pesquisa, além de analisarmos a distribuição da deposição nos diferentes ROIs, considerou-se também a ideia de verificar o percentual da massa de aerossol que seria depositado em outros compartimentos além dos pulmões. Assim, baseando-se em estudo prévio e com algumas adaptações, resolveu-se mensurar a massa de aerossol em cada um dos compartimentos em relação à dose nominal marcada com 25 mCi de atividade radioativa.

Ainda, no tocante aos objetivos, o percentual da massa inalada do radioaerossol foi determinado levando-se em consideração a soma do quantitativo depositado nos pulmões, no estômago e nas vias aéreas superiores. Este achado é importante, por quantificar a partir da dose nominal do aerosol que consegue ser inalada pelos pacientes e que devido a vários fatores, conforme discutido em uma das sessões da Revisão e Literatura, reduz a deposição dos aerossóis nos pulmões.

Como fator limitante do estudo podemos apontar o fato de não existir um protocolo validado quanto aos valores pressóricos utilizados na VNI, pois os estudos até então realizados, seja envolvendo pacientes com Asma ou DPOC, baseia-se em valores preestabelecidos aleatoriamente ou variação dos valores dentro da amostra analisada, pois o sistema de pressão positiva não invasiva é

pressurizado de acordo com a adaptação para cada paciente avaliado, sendo encontrado os níveis de IPAP e EPAP para cada participante.

Pelo fato de avaliarmos pacientes no período de estabilização da doença, não foram realizadas medidas espirométricas após os experimentos. Em se tratando dos pacientes com DPOC, sabe-se que a resposta espirométrica após uso do broncodilatador é reduzida, apesar da melhora do processo de hiperinsuflação após a nebulização. No caso dos asmáticos, não poderemos aventar a mesma possibilidade, pois não foram realizadas as medidas depois da nebulização, mesmo considerando que a maior parte dos asmáticos analisados não apresentavam sinais de desconforto respiratório ao participarem dos experimentos.

Como sugestões, pelo fato da escassez de estudos envolvendo a VNI junto às nebulizações com o NM, sugerimos a realização de mais estudos enfocando as respostas clínicas em asmáticos e DPOC durante as exacerbações. Pode-se dispor de análise através de pletismografia opto-eletrônica, com o intuito de analisar a ocorrência de assincronias e hiperisuflação nas doenças obstrutivas crônicas e finalmente, estudos que possam correlacionar a deposição dos aerossóis geradas pelo NM através de cintilografia pulmonar com o processo de remodelamento brônquico na Asma e na DPOC utilizando a Tomografia Computadoriza de Alta Resolução. Vale ressaltar, a possibilidade de enfocar outras doenças respiratórias, tais como os pacientes com fibrose cística e bronquiectásicos.

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APÊNDICE1

COMITÊ DE ÉTICA E PESQUISA

SERVIÇO PÚBLICO FEDERAL
UNIVERSIDADE FEDERAL DE PERNAMBUCO
Comitê de Ética em Pesquisa

Of. Nº. 140/2011 - CEP/CCS

Recife, 20 de abril de 2011

Registro do SISNEP FR – 406939
CAAE – 0069.0.172.000-11
Registro CEP/CCS/UFPE Nº 094/11
Titulo: **Análise da eficácia da nebulização associada á ventilação não invasiva através de pletismografia optoeletrônica e de deposição de radioaerossol em pacientes com doença pulmonar obstrutiva na intercrise.**
Pesquisador Responsável: Valdecir Castor Galindo Filho

Senhor (a) Pesquisador (a):

Informamos que o Comitê de Ética em Pesquisa Envolvendo Seres Humanos do Centro de Ciências da Saúde da Universidade Federal de Pernambuco (CEP/CCS/UFPE) registrou e analisou de acordo com a Resolução N.º 196/96 do Conselho Nacional de Saúde, o protocolo de pesquisa em epígrafe, liberando-o para início da coleta de dados em 20 de abril de 2011.

Ressaltamos que a aprovação definitiva do projeto será dada após a entrega do relatório final, conforme as seguintes orientações:

a) Projetos com, no máximo, 06 (seis) meses para conclusão: o pesquisador deverá enviar apenas um relatório final;
b) Projetos com períodos maiores de 06 (seis) meses: o pesquisador deverá enviar relatórios semestrais.

Dessa forma, o ofício de aprovação somente será entregue após a análise do relatório final.

Atenciosamente

Prof. Geraldo Bosco Lindoso Couto
Coordenador do CEP/CCS / UFPE

Ao
Doutorando Valdecir Castor Galindo Filho
Departamento de Fisioterapia- CCS/UFPE

Av. da Engenharia, s/n – 1º Andar, Cid. Universitária, CEP 50740-600, Recife - PE, Tel/fax: 81 2126 8588;
www.ufpe.br/ccs; e-mail: cepccs@ufpe.br

APÊNDICE 2

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO PARA PARTICIPAÇÃO EM ESTUDO CLÍNICO (Indivíduos Normais)

TÍTULO: ANÁLISE CINTILOGRÁFICA DA DEPOSIÇÃO PULMONAR DE RADIOAEROSSOL APÓS ASSOCIAÇÃO DA NEBULIZAÇÃO ATRAVÉS DOS DISPOSITIVOS *MESH* E JATO COM A VENTILAÇÃO NÃO INVASIVA EM INDIVÍDUOS NORMAIS E COM PNEUMOPATIAS OBSTRUTIVAS CRÔNICAS

INVESTIGADOR: Valdecir Castor Galindo Filho.
ORIENTADOR: Armèle Dornelas de Andrade.
Nome completo do local de estudo: Lab. Fisioterapia Cárdio respiratória, Departamento de Fisioterapia - UFPE.
Telefone: 2126-8492
CONTATO COM O CEP: Av. da Engenharia s/n – 10 andar, Cidade Universitária, Revife – PE, CEP: 50740-600, Telefone: 2126-8588.

Este termo de consentimento pode conter palavras que você não entenda. Por favor, pergunte à equipe que o acompanha no estudo a respeito de quaisquer palavras ou informações que você não entenda claramente. Você receberá uma cópia deste termo de consentimento para seu registro.

INTRODUÇÃO E OBJETIVOS:

O (A) Senhor(a) está sendo convidado a participar de um estudo de pesquisa, "ANÁLISE CINTILOGRÁFICA DA DEPOSIÇÃO PULMONAR DE RADIOAEROSSOL APÓS ASSOCIAÇÃO DA NEBULIZAÇÃO ATRAVÉS DOS DISPOSITIVOS *MESH* E JATO COM A VENTILAÇÃO NÃO INVASIVA EM INDIVÍDUOS NORMAIS E COM PNEUMOPATIAS OBSTRUTIVAS CRÔNICAS".

Nesse sentido, alguns estudos têm sido desenvolvidos a fim de melhorar à dificuldade respiratória das pessoas que apresentam doenças como Asma e DPOC (Doença Pulmonar Obstrutiva Crônica) e entre as formas de tratamento temos o uso de um aparelho chamado de ventilador (BIPAP), o qual funciona com a colocação de uma máscara no rosto do paciente e oferece a liberação de "ar" ajudando a melhorar a dificuldade em respirar. No entanto, necessa´rio se faz entender inicialmente como seria o comportamento desta inalação junto ao aparelho em indivíduos sem doença pulmonar.

Assim, você irá realizar a nebulização junto com o aparelho para que possamos avaliação a deposição dos aerossóis produzidos pelo nebulizador nos pulmões.

DURAÇÃO DO ESTUDO:

O estudo constará de apenas uma fase, onde os indivíduos serão selecionados para realizar a inalação com um dos tipos de nebulizadores associado com o aparelho.

DESCRIÇÃO DO ESTUDO:

Esta pesquisa tem como objetivo analisar como a névoa (“fumaçinha da nebulização”) consegue chegar até o interior dos pulmões através de um exame chamado de cintilografia pulmonar. Teremos 2 grupos: Grupo 1 (vai inalar com um nebulizador de jato) e o grupo 2 (vai inalar com um outro tipo de nebulizador, semelhante ao ultrassônico). Só poderão participar desta pesquisa: pessoas a partir dos 18 anos até 65 anos e de ambos os sexos com e sem uma das duas doenças já comentadas anteriormente. Os indivíduos serão triados no Laboratório de Fisioterapia Cardiorespiratória e encaminhados com a presença do pesquisador ao setor Medicina Nuclear do Hospital das Clínicas do estado de Pernambuco e ao chegar no local do exame fará uma avaliação rápida do sopro em um aparelho (espirometria) para verificar a função dos pulmões e em seguida receberão a nebulização de acordo com a colocação em um dos dois grupos comentado acima. Depois vão realizar o exame de cintilografia pulmonar. Após o exame será visto pelo visto pelo médico e o fisioterapeuta, para verificar se estão bem, confortáveis e se precisam de alguma assistência. Após serão liberados para retornar a sua residência.

RISCOS:

O uso do aparelho com a máscara pode relatar sufocação e pode ficar mal adaptado ao uso da máscara, a qual será prontamente retirada. Além disso, para realizar o exame de cintilografia irão inalar um radioisótopo, o qual será utilizado em baixa concentração e sendo eliminado do organismo de forma rápida e sem repercussões sistêmicas.

BENEFÍCIOS:

O estudo trará benefícios aos profissionais da Área de Saúde, inclusive aos fisioterapeutas que utilizam este aparelho (BiPAP) para entender o comportamento desta duas formas terapêuticas em pessoas sem doença pulmonar. Em se tratando de pessoas com Asma e DPOC poderá contribuir na melhora clínica da função pulmonar, a qual é alterada pelas exacerbações destas doenças.

CONFIDENCIALIDADE:

As informações obtidas através desse estudo serão sigilosas, não daremos informações sobre o nome ou outros dados das pessoas que participarem e os resultados do estudo serão divulgados publicamente, mas vale lembrar mais uma vez, a identidade do participante não é revelada.

PARTICIPAÇÃO VOLUNTÁRIA / RETIRADA:

A sua participação nesse estudo é voluntária. Você pode recusar-se a participar ou parar de participar a qualquer momento da pesquisa.

CONSENTIMENTO DO VOLUNTÁRIO

Li e entendi as informações procedentes descrevendo esse estudo, e todas as minhas dúvidas em relação ao estudo e a minha participação nele

foram respondidas satisfatoriamente. Dou livremente meu consentimento em participar do estudo até que decida pelo contrário.

Assinando este termo de consentimento, concordo em participar desse estudo e não abro mão, na condição de participante de um estudo de pesquisa, de nenhum dos direitos legais que eu teria de outra forma.

_____	_____	_____
Nome do Voluntário	Assinatura	Data
_____	_____	_____
Pesquisador responsável	Assinatura	Data
_____	_____	_____
Testemunha 1	Assinatura	Data
_____	_____	_____
Testemunha 2	Assinatura	Data

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO PARA PARTICIPAÇÃO EM ESTUDO CLÍNICO (Asma e DPOC))

TÍTULO: ANÁLISE CINTILOGRÁFICA DA DEPOSIÇÃO PULMONAR DE RADIOAEROSSOL APÓS ASSOCIAÇÃO DA NEBULIZAÇÃO ATRAVÉS DOS DISPOSITIVOS *MESH* E JATO COM A VENTILAÇÃO NÃO INVASIVA EM INDIVÍDUOS NORMAIS E COM PNEUMOPATIAS OBSTRUTIVAS CRÔNICAS

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Telefone: 2126-8492
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INTRODUÇÃO E OBJETIVOS:

O (A) Senhor(a) está sendo convidado a participar de um estudo de pesquisa, "ANÁLISE CINTILOGRÁFICA DA DEPOSIÇÃO PULMONAR DE RADIOAEROSSOL APÓS ASSOCIAÇÃO DA NEBULIZAÇÃO ATRAVÉS DOS DISPOSITIVOS *MESH* E JATO COM A VENTILAÇÃO NÃO INVASIVA EM INDIVÍDUOS NORMAIS E COM PNEUMOPATIAS OBSTRUTIVAS CRÔNICAS".

A Asma e a Doença Pulmonar Obstrutiva Crônica (enfisema e Bronquite Crônica) são caracterizadas como doenças, na quais ocorrem dificuldades durante a respiração, trazendo a "sensação de falta de ar", "aperto no peito" e "respiração pesada". Além disso, o paciente apresenta tosse, "chieira no peito", produção de "catarro", sem falar no esforço apresentado ao respirar, podendo vir a piorar cada vez mais e desenvolver uma condição chamada de "insuficiência respiratória".

Nesse sentido, alguns estudos têm sido desenvolvidos a fim de melhorar à dificuldade respiratória das pessoas que apresentam estas doenças e entre as formas de tratamento temos o uso de um aparelho chamado de ventilador (BIPAP), o qual funciona com a colocação de uma máscara no rosto do paciente e oferece a liberação de "ar" ajudando a melhorar a dificuldade em respirar.

Assim, o paciente irá realizar a nebulização junto com o aparelho para que possamos realizar um novo estudo, o qual poderá trazer benefícios no tratamento dos indivíduos que chegam nos serviços hospitalares e apresentam uma destas doenças. Principalmente, pelo fato de não termos outros estudos realizados desta maneira e isto poderá contribuir na melhora dos pacientes com cansaço e dificuldades para respirar.

DURAÇÃO DO ESTUDO:

O estudo constará de apenas uma fase, onde os pacientes serão selecionados para realizar a inalação com um dos tipos de nebulizadores associado com o aparelho.

DESCRIÇÃO DO ESTUDO:

Esta pesquisa tem como objetivo analisar como a névoa ("fumaçinha da nebulização") consegue chegar até o interior dos pulmões através de um exame chamado de cintilografia pulmonar. Teremos 2 grupos de pacientes: Grupo 1 (vai inalar com um nebulizador de jato) e o grupo 2 (vai inalar com um outro tipo de nebulizador, semelhante ao ultrassônico). Só poderão participar desta pesquisa: pessoas a partir dos 18 anos até 65 anos e de ambos os sexos com e sem uma das duas doenças já comentadas anteriormente. Os indivíduos serão triados no Laboratório de Fisioterapia Cardiorespiratória e encaminhados com a presença do pesquisador ao setor Medicina Nuclear do Hospital das Clínicas do estado de Pernambuco e ao chegar no local do exame fará uma avaliação rápida do sopro em um aparelho (espirometria) para verificar a função dos pulmões e em seguida receberão a nebulização de acordo com a colocação em um dos dois grupos comentado acima. Depois vão realizar o exame de cintilografia pulmonar. Após o exame será visto pelo visto pelo médico e o fisioterapeuta, para verificar se estão bem, confortáveis e se precisam de alguma assistência. Após serão liberados para retornar a sua residência.

RISCOS:

O uso do aparelho com a máscara pode relatar sufocação e pode ficar mal adaptado ao uso da máscara, a qual será prontamente retirada. Além disso, para realizar o exame de cintilografia irão inalar um radioisótopo, o qual será utilizado em baixa concentração e sendo eliminado do organismo de forma rápida e sem repercussões sistêmicas.

BENEFÍCIOS:

O estudo trará benefícios aos profissionais da Área de Saúde, inclusive aos fisioterapeutas que utilizam este aparelho (BiPAP) com a máscara para aquelas pessoas que têm asma ou DPOC e são atendidos nas emergências e enfermarias dos hospitais, bem como em ambulatórios. Além disso, os pacientes também serão beneficiados do ponto de vista clínico, pois será analisado um novo de inalador e, sendo eficaz, poderá reduzir os custos em comparação a outros tipos de inaladores utilizados pelos pacientes.

CONFIDENCIALIDADE:

As informações obtidas através desse estudo serão sigilosas, não daremos informações sobre o nome ou outros dados das pessoas que participarem e os resultados do estudo serão divulgados publicamente, mas vale lembrar mais uma vez, a identidade do participante não é revelada.

PARTICIPAÇÃO VOLUNTÁRIA / RETIRADA:

A sua participação nesse estudo é voluntária. Você pode recusar-se a participar ou parar de participar a qualquer momento da pesquisa.

CONSENTIMENTO DO VOLUNTÁRIO

Li e entendi as informações procedentes descrevendo esse estudo, e todas as minhas dúvidas em relação ao estudo e a minha participação nele foram respondidas satisfatoriamente. Dou livremente meu consentimento em participar do estudo até que decida pelo contrário.

Assinando este termo de consentimento, concordo em participar desse estudo e não abro mão, na condição de participante de um estudo de pesquisa, de nenhum dos direitos legais que eu teria de outra forma.

_____	_____	_____
Nome do Voluntário	Assinatura	Data
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Pesquisador responsável	Assinatura	Data
_____	_____	_____
Testemunha 1	Assinatura	Data
_____	_____	_____
Testemunha 2	Assinatura	Data

APÊNDICE 3

PROJETO DE PESQUISA

ANÁLISE CINTILOGRÁFICA DA DEPOSIÇÃO PULMONAR DE RADIOAEROSSOL APÓS ASSOCIAÇÃO DA NEBULIZAÇÃO ATRAVÉS DOS DISPOSITIVOS *MESH* E JATO COM A VENTILAÇÃO NÃO INVASIVA EM INDIVÍDUOS NORMAIS E COM PNEUMOPATIAS OBSTRUTIVAS CRÔNICAS

FICHA DE AVALIAÇÃO

Nome: _____
Endereço:_____
Telefone para contato: _____

Amostra: ( ) Saudável ( ) Asma ( ) DPOC

Dispositivo: ( ) MESH ( ) JATO

Dados antropométricos:
Sexo: _____ Idade: _____ Altura: _____ Peso: _____ IMC: _____

DADOS DA FUNÇÃO PULMONAR

Avaliação Inicial:

Variáveis	**1ª. Medida**	**2ª. Medida**	**3ª. Medida**
FR (ipm)			
FC (bpm)			
SpO_2 (%)			
PAS (mmHg)			
PAD (mmHg)			
VEF_1			
CVF			
$FEF_{25-75\%}$			
PFE			
VEF_1 (% predito)			
CVF (% predito)			
FEF25-75% (% predito)			
PFE (% predito)			

DEPOSIÇÃO DO RADIOAEROSSOL PULMONAR

CONTAGEM DAS PARTÍCULAS

Padrão de deposição vertical

Segmento pulmonar	Pulmão direito	Pulmão esquerdo
1/3 superior		
1/3 terço médio		
1/3 terço inferior		
Total de partículas		

Padrão de deposição horizontal

Segmento pulmonar	Pulmão direito	Pulmão esquerdo
Região central		
Região intermediária		
Região periférica		
Total de partículas		

BALANÇO DA MASSA DO RADIOAEROSSOL NOS DIFERENTES

COMPARTIMENTOS

Deposição total = _____

Compartimento	Contagens de partículas	Valor percentual
Pulmões		
Vias aéreas superiores		
Estômago		
Nebulizador		
Máscara de VNI		
Circuito de VNI		
Filtro inspiratório		
Filtro expiratório		

APÊNDICE 4

CARTA DE ANUÊNCIA

Hospital das Clínicas
UFPE

SETOR DE MEDICINA NUCLEAR

CARTA DE ANUÊNCIA

Recife, 12 de Fevereiro de 2010.

Vimos através desta informar que temos ciência da tese de doutorado do Programa de Pós-graduação em Ciências da Saúde pela UFRN do doutorando Valdecir Castor Galindo Filho intitulado "ANÁLISE CINTILOGRÁFICA DA DEPOSIÇÃO PULMONAR DE RADIOAEROSSOL APÓS ASSOCIAÇÃO DA NEBULIZAÇÃO ATRAVÉS DOS DISPOSITIVOS *MESH* E JATO COM A VENTILAÇÃO NÃO INVASIVA EM INDIVÍDUOS NORMAIS E COM PNEUMOPATIAS OBSTRUTIVAS CRÔNICAS", orientado pela Profa. Dra. Armèle de Fátima Dornelas de Andrade, a ser desenvolvido neste serviço.

Dado conhecimento a respeito do método e por entendermos a que o referido projeto trará benefícios aos profissionais da área de saúde, inclusive os fisioterapeutas, somos de acordo com a sua realização neste serviço.

Chefe do Serviço

ANEXO 1

GUIDELINE - Respiratory Physiology and Neurobiology

RESPIRATORY PHYSIOLOGY & NEUROBIOLOGY

ELSEVIER

AUTHOR INFORMATION PACK

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DESCRIPTION

Respiratory Physiology & Neurobiology publishes original articles and invited reviews concerning **physiology** and **pathophysiology** of **respiration** in its broadest sense. Although a special focus is on topics in **neurobiology**, high quality papers in respiratory **molecular** and **cellular biology** are also welcome, as are high-quality papers in traditional areas, such as mechanics of breathing; gas exchange and acid-base balance; respiration at rest and exercise; respiration in unusual conditions, like high or low pressure or changes of temperature, low ambient oxygen; embryonic and adult respiration; comparative respiratory physiology. Papers on clinical aspects, articles on original methods, as well as theoretical papers are also considered as long as they foster the understanding of **respiratory physiology** and pathophysiology.

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Researchers in respiratory-, pulmonary- and circulatory physiology, and neurobiology

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ANEXO 2

GUIDELINE – Respiratory Medicine

Guide for Authors

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- Commentaries
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PRODUÇÃO CIENTÍFICA COMPLEMENTAR

Noninvasive Ventilation Coupled With Nebulization During Asthma Crises: A Randomized Controlled Trial

Valdecir C Galindo-Filho MSc, Daniella C Brandão MSc, Rita de Cássia S Ferreira MSc, Maria José C Menezes, Paulo Almeida-Filho MSc, Verônica F Parreira PhD, Tayse N Silva MSc, Maria da Glória Rodrigues-Machado PhD, Elizabeth Dean PhD, and Armèle Dornelas de Andrade PhD

BACKGROUND: Despite the clinical improvements attributed to noninvasive ventilation (NIV) during asthma crises, and the well established effects of nebulization, there are few studies on the effects of these interventions together. We hypothesized that nebulization coupled to NIV should raise radio-aerosol pulmonary deposition in asthmatics. The aims of this study were to assess the effects of coupling β-agonist nebulization and NIV during asthma exacerbations on radio-aerosol pulmonary deposition, using scintigraphy and cardiopulmonary parameters, to correlate pulmonary function with radio-aerosol deposition index, radio-aerosol penetration index, and pulmonary clearance. METHODS: In this controlled trial, 21 adults with moderate to severe asthma attack were randomized to a control group (n = 11) or experimental group (NIV + nebulizer group, n = 10). All subjects inhaled bronchodilators for 9 minutes, and after particles were counted with a gamma camera to analyze regions of interest and pulmonary clearance at 0, 15, 30, 45, and 60 min. RESULTS: Breathing frequency (P = < .001) and minute ventilation (P = .01) were reduced, and tidal volume was increased (P = .01) in the NIV + nebulizer group, compared with the control group. The NIV + nebulizer group had improvement from baseline values, compared to the control group in the following parameters: FEV_1 46.7 ± 0.5% of predicted vs 29.8 ± 8.9% of predicted, P = .02), FVC (41.2 ± 1.5% of predicted vs 23.2 ± 7.1% of predicted, P = .02), peak expiratory flow (67.3 ± 38.3% of predicted vs 26.9 ± 12.1% of predicted, P = .01), and inspiratory capacity (54.9 ± 28.8% of predicted vs 31.2 ± 9.1% of predicted, P = .01). No differences were observed between groups regarding radio-aerosol deposition index or pulmonary clearance. Negative correlations were found between FEV_1, forced expiratory flow during the middle half of the FVC maneuver ($FEF_{25-75\%}$), inspiratory capacity, and radio-aerosol penetration index. CONCLUSIONS: Coupling nebulization and NIV during asthma exacerbation did not improve radio-aerosol pulmonary deposition, but we observed clinical improvement of pulmonary function in these subjects. (ClinicalTrials.gov registration NCT01012050) *Key words: noninvasive ventilation; asthma; nebulization; pulmonary scintigraphy; radio-aerosol; pulmonary function.* [Respir Care 2013;58(2):241–249.

Introduction

Asthma is highly prevalent worldwide and exacerbations can lead to acute respiratory failure.[1–3] The first line of treatment for asthma exacerbations is nebulization with β agonists in order to reverse the bronchospasm.[2,4–8]

Mr Galindo-Filho, Ms Brandão, Ms Ferreira, Ms Silva, and Dr Dornelas de Andrade are affiliated with the Department of Physiotherapy, Universidade Federal de Pernambuco, Recife, Brazil. Ms Menezes and Mr Almeida-Filho are affiliated with the Department of Nuclear Medicine, Hospital Português, Recife, Brazil. Dr Parreira is affiliated with the Universidade Federal de Minas Gerais, Minas Gerais, Brazil. Dr Rodrigues-Machado is affiliated with the Faculty of Ciências Médicas, Minas Gerais, Brazil. Dr Dean is affiliated with the University of British Columbia, Vancouver, Canada.

The benefits of noninvasive ventilation (NIV) in the treatment of asthma include reduced work of breathing, improvements in oxygenation, increased peak expiratory flow (PEF) and FEV_1,[9–16] and accelerated bronchodilation.[17] Despite the clinical improvements attributed to NIV and the well established effects of nebulization, there are few studies addressing the use of both methods together. Such studies would help to elucidate whether or not the improved deposition of β agonists with NIV enhances the effects of bronchodilators.

SEE THE RELATED EDITORIAL ON PAGE 380

We found no studies involving the scintigraphic analysis of radio-aerosol deposition coupled with NIV during asthma crises. However, a previous study published by our group found lesser deposition after coupling NIV to nebulization in healthy subjects.[18] However, we hypothesized that nebulization of bronchodilators coupled with NIV would increase pulmonary deposition in acute asthma, and thus improve clinical parameters, compared to nebulization alone.

The aims of the present study were to assess the effect of coupling nebulization with NIV during asthma crises on radio-aerosol lung deposition and cardiopulmonary parameters, and to correlate pulmonary function with the radio-aerosol deposition index, radio-aerosol penetration index, and pulmonary clearance.

Methods

This work was performed at Professor Barros Lima Hospital and Português Hospital, Recife City, Brazil.

Subjects and Study Design

A controlled randomized trial was carried out in a public emergency room. Thirty-nine males and females, ages 18–65 years, with acute asthma, were enrolled in the study.

QUICK LOOK

Current knowledge

Aerosol delivery of β agonists for reversal of bronchospasm is the mainstay of treatment for asthma exacerbations. Application of noninvasive ventilation (NIV) in asthmatic exacerbations may reduce the work of breathing and improve bronchodilator delivery, but has not been shown to alter outcomes. The use of NIV coupled with aerosolized β agonists has not been specifically evaluated in acute asthma.

What this paper contributes to our knowledge

The addition of aerosolized β agonists to NIV during asthma exacerbation did not improve radio-aerosol pulmonary deposition. NIV use was associated with more efficient ventilation, a reduction in respiratory rate, and increased tidal volume.

Subjects were diagnosed by the attending physician, and inhaled salbutamol (2.5 mg) and ipratropium bromide (0.25 mg) according to prescription. Spirometry was performed after 30 min (Vitalograph 2120, Vitalograph, Buckingham, United Kingdom).[10] A variance of 0.2 L was allowed between tests, and the average of 3 measurements was recorded.[19]

This study was approved by our human research ethics committee, and all subjects gave written informed consent after being fully informed about the protocol. The trial was registered in *ClinicalTrials.gov* according to the registration number NCT01012050.

Inclusion and Exclusion Criteria

The following were the inclusion criteria: moderate to severe asthma ($FEV_1 < 60\%$ of predicted values),[20,21] breathing frequency > 25 breaths/min, more than one year elapsed since the diagnosis of asthma, current asthma attack lasting < 7 days, and reversibility of $FEV_1 \leq 10\%$ following administration of bronchodilator. On the other hand, exclusion criteria were smoking history, cardiopulmonary diseases (COPD, pneumonia, cardiac failure, myocardial infarction, pneumothorax) hyperthermia, indication for mechanical ventilation, hemodynamic instability (heart rate > 150 beats/min and systolic blood pressure < 90 mm Hg), arrhythmia, changes in consciousness, pregnancy, and contraindications for use of NIV.[11]

Procedures

Subjects were randomly allocated, with the use of a computer program, into 2 groups. The control group consisted of subjects using nebulization alone (control), and

Dr Dornelas de Andrade presented a version of this paper at the meeting of the European Respiratory Society, held September 12–15, 2009, in Vienna, Austria.

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the experimental group consisted of subjects receiving NIV coupled to nebulization (NIV + nebulizer group). Group allocation was assigned after admission, which prohibited blind allocation. For ethical reasons, no sham group was used.

The cardiopulmonary parameters were measured before and after inhalation protocol, and we considered the average obtained after 3 maneuvers from each parameter in both groups (breathing frequency, S_{pO_2}, tidal volume [V_T], minute ventilation [$\dot{V}_E$], heart rate, systolic blood pressure, diastolic blood pressure, and inspiratory capacity), using pulse oximetry (Active, Ecafix, São Paulo, Brazil), a manual pressure manometer (DS 44–11, Welch Allyn, Beaverton, Oregon), and a ventilometer (Wright Respirometer Mark 8, Ferraris Medical, London, United Kingdom). For inspiratory capacity, the reference values reported by Stocks and Quanjer were used.[22]

An established protocol was used for the radio-aerosol inhalation of diethylene triamine penta-acetic technetium (DTPA-Tc^{99m}) with radioactivity of 25 millicuries.[23] The jet nebulizer (NS Products, São Paulo, Brazil) was positioned between the mask and exhalation orifice using a T piece, with particle size generation in the 5 μm range (according to the manufacturer's information), and oxygen flow titrated at 7 L/min (OXI, Biotecmed, São Paulo, Brazil) for 9 min (sufficient time to complete the dose). DTPA-Tc^{99m} was added to the bronchodilator, and saline solution was used to complete 4 mL. V_T and inspiratory flow were measured at the 3rd, 6th, and 9th min by a flow sensor (TRACE-5, Intermed, São Paulo, Brazil) placed in the circuit without interruption of inhalation or affecting drug delivery. Bi-level positive airway pressure (BiPAP Synchrony, Respironics, Murrysville, Pennsylvania) was applied using a face mask (ComfortFull 2, Respironics, Murrysville, Pennsylvania) attached with straps. The pressures adjusted were 12 cm H_2O of inspiratory pressure and 5 cm H_2O of expiratory pressure at the beginning of the procedure. The control group performed inhalation using the same mask and straps as the NIV + nebulizer group.

Radioactivity counts were performed using a gamma camera (Forte, Adac Laboratories, Milpitas, California) at intervals of 0, 15, 30, 45, and 60 min.[18] Regions of interest were delimited based on a previous protocol.[23] The radio-aerosol deposition index was expressed as percentage and was calculated as the ratio of the count in each region of interest to the total count in each lung. The radio-aerosol penetration index for each lung was expressed as the ratio between the count in the central region to the count in the peripheral region, considering the sum of deposition in the intermediate and peripheral regions of interest:

$$\text{Radio-aerosol penetration index} = \text{central region}/\text{peripheral region} \times 100$$

Pulmonary clearance assessed the permeability of the epithelial alveoli barrier through images obtained at intervals of 0, 15, 30, 45, and 60 min.

Statistical Analysis

The primary outcomes were radio-aerosol deposition index, radio-aerosol penetration index, and pulmonary clearance. Thus, spirometry and cardiopulmonary variables after and before one hour of inhalation protocol for both groups were considered as secondary outcomes. The sample size was based on a power of 90%, $\alpha = .05$ and $\beta = .10$, using data from a previous study,[18] and established a minimum of 7 individuals per group. The Kolmogorov-Smirnov and Levene tests were employed first. The paired Student t test was used to analyze intra-group variance. The independent Student t test was used to compare intra-group variance. Pulmonary clearance analysis was performed with multivariate analysis of variance. The Pearson correlation was used to compare the radio-aerosol deposition index, radio-aerosol penetration index, and pulmonary clearance with pulmonary function. The results are expressed as mean ± SD, considering a 95% CI ($P < .05$).

Results

Thirty-nine subjects were admitted during the study, but 6 declined to participate, 5 did not meet the eligibility criteria (age and smoking history), 2 did not adapt to the NIV mask, and 5 did not complete the experiment. Thus, 21 subjects participated and were randomly allocated to the 2 groups, as shown in Figure 1. Subject characteristics (ie, anthropometric data and pulmonary function) were similar between groups, as presented in Table 1.

Cardiopulmonary Parameters

There was a reduction in breathing frequency and $\dot{V}_E$ and an increase in V_T and inspiratory capacity in the NIV + nebulizer group, in comparison to the control group, as shown in Table 2. No statistically significant differences were detected between groups with regard to heart rate, S_{pO_2}, systolic blood pressure, and diastolic blood pressure following intervention. There were percentage gains in FEV_1, FVC, and PEF in the NIV + nebulizer group, in comparison to the control group, as presented in Table 3. No significant differences were detected between groups with regard to forced expiratory flow during the middle half of the FVC maneuver ($FEF_{25–75\%}$). V_T and inspiratory flow increased in the NIV + nebulizer group, in comparison to the control group: V_T 1.0 ± 0.39 L vs 0.6 ± 0.20 L ($P = .01$), inspiratory flow 47.4 ± 11.1 L/min vs 34.7 ± 11.1 L/min ($P = .02$).

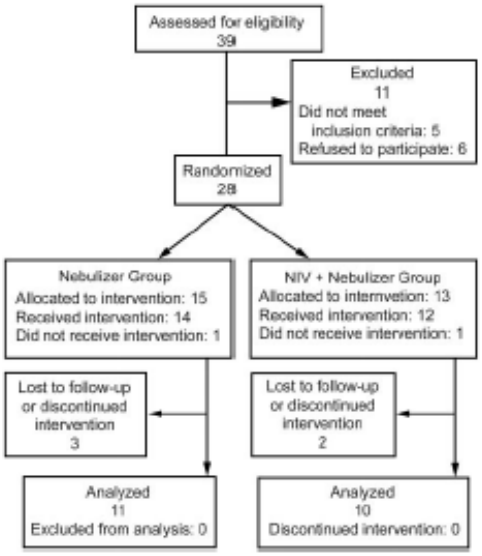

Fig. 1. Flow diagram of the study.

Table 1. Anthropometric and Cardiopulmonary Characteristics

	Nebulizer Control Group (n = 11)	NIV + Nebulizer Group (n = 10)	P
Age, y	44.2 ± 10.3	49.5 ± 8.93	.58
Male/female, no.	4/7	2/7	
BMI, kg/m^2	26.4 ± 3.46	27.9 ± 4.76	.57
Breathing frequency, breaths/min	29.2 ± 1.40	30.2 ± 2.04	.22
S_{pO_2}, %	95.4 ± 1.74	95.6 ± 1.50	.69
V_T, L	0.37 ± 0.09	0.35 ± 0.07	.67
V_E, L	10.6 ± 2.45	10.7 ± 2.23	.90
Heart rate, beats/min	83.4 ± 11.4	79.2 ± 12.79	.59
Systolic blood pressure, mm Hg	126.4 ± 16.4	125.8 ± 13.89	.50
Diastolic blood pressure, mm Hg	84.5 ± 10.3	81.0 ± 10.22	.57
FEV_1, % predicted	44.2 ± 18.7	51.3 ± 11.5	.44
FEV_1, L	1.18 ± 0.45	1.28 ± 0.23	.53
FVC, % predicted	43.1 ± 18.7	50.2 ± 11.3	.74
FVC, L	1.49 ± 0.52	1.59 ± 0.50	.73
PEF, % predicted	41.6 ± 10.3	40.4 ± 9.7	.70
PEF, L/min	158.7 ± 45.55	140.19 ± 47.64	.49
$FEF_{25-75\%}$, % predicted	31.8 ± 11.9	38.5 ± 7.2	.12
$FEF_{25-75\%}$, L	1.03 ± 0.56	1.20 ± 0.44	.45
Inspiratory capacity, % predicted	55.4 ± 15.5	59.9 ± 15.8	.79
Inspiratory capacity, L	1.16 ± 0.37	1.26 ± 0.52	.38

Except for male/female, the values are mean ± SD.
NIV = noninvasive ventilation
BMI = body mass index
V_T = tidal volume
V_E = minute ventilation
PEF = peak expiratory flow
$FEF_{25-75\%}$ = forced expiratory flow during the middle half of the FVC maneuver

Radio-aerosol Pulmonary Deposition

There were no significant differences in radio-aerosol lung deposition between groups. The total amount of radio-aerosol particles deposited in the right lung was 216,058 ± 56,462 counts and 193,235 ± 115,501 counts in the control and NIV + nebulizer groups, respectively. Regarding the left lung, the total amount of deposition reached was 173,626 ± 69,835 counts and 161,143 ± 96,912 counts in the control and NIV + nebulizer groups, respectively.

Table 4 presents the results of the intra-group analysis of radio-aerosol deposition index with respect to the vertical and horizontal differences for each region of interest. There were intra-group differences, except when the upper and lower thirds of the left lung were compared in the NIV + nebulizer group. There was no difference in radio-aerosol penetration index between groups, but there was a negative correlation between radio-aerosol penetration index and FEV_1, $FEF_{25-75\%}$, and inspiratory capacity obtained upon admission of the subjects in the control group, and $FEF_{25-75\%}$ in the left lung in the NIV + nebulizer group, as shown in Table 5. The analysis of qualitative radio-aerosol deposition revealed greater particle deposition in the central region in the right and left lungs in both groups, characterized by the presence of "hot spots," as shown in Figure 2. For the pulmonary clearance analysis, zero time was considered the first image obtained at the end of inhalation. After intervals of 15, 30, 45, and 60 min, new images were taken in order to perform a temporal analysis. There was an intra-group count reduction in pulmonary clearance over time (P = .82), but no difference was detected between groups.

To compare radio-aerosol deposition across time intervals, linear regression models were adjusted for each group and logarithmic equations were obtained:

$$\text{Log } T_{clearance} = 12.57 - 0.0147 \times \text{time}$$

(NIV + nebulizer group)

in which log $T_{clearance}$ is a logarithm transformation in relation to the time of pulmonary clearance, and

$$\text{Log } T_{clearance} = 12.78 - 0.0154 \times \text{time (control group)}$$

Based on these equations, mean radio-aerosol half-life was approximately 34 min in the NIV + nebulizer group and 39 min in the control group, as shown in Figure 3. Thus, Figure 4 illustrates the qualitative pulmonary clearance in subjects with different degrees of obstruction.

Table 2. Ventilatory Data

	Nebulizer Control Group (n = 11)	NIV + Nebulizer Group (n = 10)	P
f, breaths/min			
Before	29.2 ± 1.40	30.2 ± 2.04	.22
After	21.1 ± 2.21	14.3 ± 2.54	< .001
V_T, L			
Before	0.37 ± 0.09	0.35 ± 0.07	.67
After	0.46 ± 0.08	0.55 ± 0.07	.01
$\dot{V}_E$, L			
Before	10.6 ± 2.45	10.7 ± 2.23	.90
After	9.65 ± 1,63	7.77 ± 0.84	.006

Values are mean ± SD. Level of significance $P < .05$ via Student t test for independent samples.
NIV = noninvasive ventilation
f = breathing frequency
V_T = tidal volume
$\dot{V}_E$ = minute ventilation

Table 3. Pulmonary Function Test Data

	Nebulizer Control Group	NIV + Nebulizer Group	P
FEV_1, % predicted			
Before	44.2 ± 18.7	51.3 ± 11.5	.44
After	57.4 ± 15.3	75.3 ± 15.7	< .001
Percent gain	29.8 ± 8.9	46.7 ± 0.5	.02
FVC, % predicted			
Before	43.1 ± 18.7	50.2 ± 11.3	.74
After	53.1 ± 12.8	70.9 ± 15.1	.006
Percent gain	23.2 ± 7.1	41.2 ± 1.5	.02
PEF, % predicted			
Before	41.6 ± 10.3	40.4 ± 9.7	.70
After	52.8 ± 9.9	67.6 ± 19.1	.04
Percent gain	26.9 ± 12.1	67.3 ± 38.3	.01
Inspiratory capacity, % predicted			
Before	55.4 ± 15.5	59.9 ± 15.8	.79
After	72.7 ± 16.9	92,8 ± 21.6	.02
Percent gain	31.2 ± 9.1	54.9 ± 28.8	.01

Values are mean ± SD. Level of significance $P < .05$ via Student t test for independent samples.
NIV = noninvasive ventilation
PEF = peak expiratory flow

Discussion

This controlled randomized trial demonstrated that coupling nebulization with NIV during asthma exacerbations leads to an improvement of pulmonary function, specifically FEV_1, FVC, PEF, V_T, $\dot{V}_E$, and inspiratory capacity. However, no difference in radio-aerosol pulmonary deposition was observed in either group.

During asthma attacks, patients experience an increase in work of breathing, reflected in a rise in breathing frequency, $\dot{V}_E$, and excessive recruitment of accessory muscles.[9,14] In the present study, breathing frequency and $\dot{V}_E$ decreased in the group using nebulized β agonists coupled with NIV. These findings corroborate previous studies reporting a reduction in breathing frequency and respiratory muscle recruitment, as well as improved gas exchange in patients with asthma treated with NIV in emergency rooms or hospitals.[9,10,12,13,16,24–26]

There was also an increase in V_T in the NIV + nebulizer group, when compared to the control group. This may be due to the benefits of inspiratory pressure, which diminishes muscle fatigue and dyspnea and improves V_T due to the increase in ventilatory comfort.[24]

Regarding the spirometric data, FVC, FEV_1, and PEF increased in the NIV + nebulizer group. Similar results were reported by Pollack et al,[12] who found an increase in PEF in patients with asthma after delivering β agonists through bi-level positive airway pressure, when compared to the group that received only nebulization. However, the methodology employed by the authors did not elucidate whether the increase in PEF was due to mechanical bronchodilation or greater drug deposition. In a recent study published by our group, Brandão et al[26] reported a reduction in bronchial obstruction and symptoms secondary to augmented PEF after coupling nebulization with NIV in individuals with asthma.

Soroksky et al[10] administered NIV alone using bi-level positive airway pressure on patients with asthma, and observed improvements in the spirometric data, as well as the relief of respiratory discomfort and a reduction in the intubation rate. These results could be explained by the alleviation of the load imposed on the inspiratory muscles and the direct bronchodilator effect of NIV, thereby diminishing intrinsic PEEP and favoring the recruitment of collapsed alveolar units. Soma et al[15] administered bi-level positive airway pressure for 40 min to patients with mild to moderate asthma and found improved pulmonary function and the relief of respiratory discomfort when using lower pressure levels. The fact that these studies did not administer NIV coupled to nebulization limits comparisons to our findings. Thus, to our knowledge, our study is the first controlled randomized trial using simultaneous NIV and nebulization.

There was a greater increase in inspiratory capacity in the group that received NIV + nebulizer. A number of studies have demonstrated inspiratory capacity gains in patients with COPD (ie, reduced dynamic hyperinflation) after treatment with drugs or pulmonary rehabilitation.[27,28] The higher percentage gain in inspiratory capacity was likely due to a decrease in inspiratory muscle load as a

Table 4. Radio-Aerosol Deposition Index Differences

Group		Vertical Differences		Horizontal Differences	
		Lung Region	*P*	Lung Region	*P*
Right lung	Nebulizer	Upper third < middle third	< .001	Central third > intermediate third	.02
		Upper third < lower third	< .001	Central third > peripheral third	< .001
		Middle third > lower third	.02	Intermediate third > peripheral third	< .001
	NIV + nebulizer	Upper third < middle third	< .001	Central third > intermediate third	.01
		Upper third < lower third	.007	Central third > peripheral third	< .001
		Middle third > lower third	.007	Intermediate third > peripheral third	< .001
Left lung	Nebulizer	Upper third < middle third	.002	Central third > intermediate third	.004
		Upper third = lower third	.52	Central third > peripheral third	< .001
		Middle third > lower third	.001	Intermediate third > peripheral third	< .001
	NIV + nebulizer	Upper third < middle third	< .001	Central third > intermediate third	< .001
		Upper third < lower third	.01	Central third > peripheral third	< .001
		Middle third > lower third	.02	Intermediate third > peripheral third	< .001

Values are given as mean ± SD. Level of significance $P < .05$ via Student *t* test for independent samples.
NIV = noninvasive ventilation

Table 5. Correlation of Radio-Aerosol Penetration Index, Pulmonary Function, and Inspiratory Capacity

Group	Variables	Pearson Correlation Coefficient (*r*)*		*P*	
		Right Lung	Left Lung	Right Lung	Left Lung
Nebulizer	FEV_1	−0.784	−0.656	.004	.03
	$FEF_{25-57\%}$	−0.709	−0.623	.02	.04
	Inspiratory capacity	−0.914	−0.788	< .001	.004
NIV + nebulizer	$FEF_{25-57\%}$		−0.742		.01

* Pearson correlation test was used appropriately for comparisons in each group.
$FEF_{25-75\%}$ = forced expiratory flow during the middle half of the FVC maneuver
NIV = noninvasive ventilation

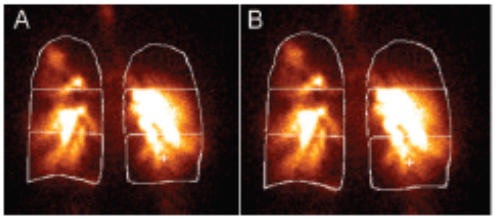

Fig. 2. Heterogeneous deposition pattern in scintigraphic images of subjects with asthma, with a predominance of radio-aerosol deposition in the central region in a subject in the control group (A) and another in the noninvasive ventilation + nebulizer group (B).

consequence of the expiratory pressure applied to reduce air trapping, with a decrease in intrinsic PEEP and an increase in inspiratory capacity.

No reports were found in the literature on the distribution of ventilation assessed by scintigraphy on patients with asthma involving NIV and nebulization simultaneously. However, a decrease in peripheral aerosol deposition, with greater particle impaction in the upper airways, has been reported in patients with stable chronic bronchitis using intermittent positive-pressure breathing, in comparison to nebulization during spontaneous breathing.[29] On the other hand, a 30% increase in radio-aerosol deposition without impaction in the proximal airways during application of NIV has been observed in children with cystic fibrosis.[30]

In the present study, no difference was found in radio-aerosol deposition between groups. Comparisons to the studies described above are limited due to the pathological conditions of the present sample. A previous study conducted by our group on healthy subjects found greater radio-aerosol deposition in the group that nebulized only, when compared to the group that received nebulization through bi-level positive airway pressure. Thus, the study also reports a correlation between particle counts and V_T,

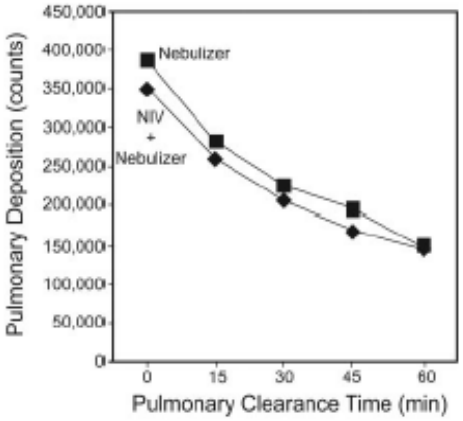

Fig. 3. Radio-aerosol lung deposition (counts) based on lung clearance time in both groups of subjects with asthma treated in the emergency room. Analysis of variance was performed to compare both groups with repeated measurements, and no difference was found between them.

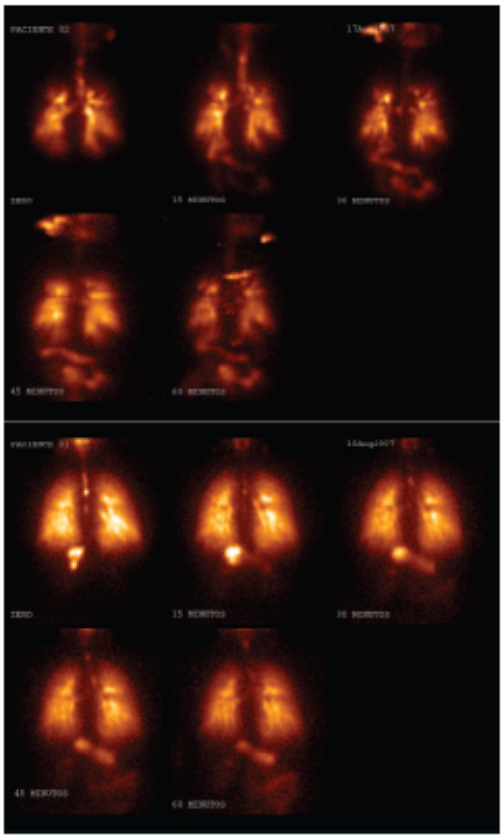

Fig. 4. Images taken during pulmonary clearance of subjects with asthma whose crisis classification was severe (A) and moderate (B).

with a lower inspiratory flow (25 L/min), which may have increased the ventilation distribution.[18]

Several factors can influence aerosol deposition, and inspiratory flow is an important determinant of particle transport and deposition. Higher flows could lead to greater aerosol impaction in the upper and central airways, as turbulent flows produce strong inertial forces that impact aerosols in the proximal airways.[31–33] Inspiratory flow and V_T were monitored during inhalation, and an increase in these variables was observed in the NIV + nebulizer group, when compared to the control group. Both groups had an inspiratory flow above 30 L/min, favoring greater penetration of radio-aerosol in the central airways. Previous studies described similar results, with flow values of around 40 L/min contributing to less peripheral deposition.[18,33]

The analysis of deposition in the vertical differences revealed greater deposition in the middle third in comparison to the upper and lower thirds, and in the lower third, in comparison to the upper third, in both lungs. However, no difference in radio-aerosol counts was detected between the upper and lower thirds of the left lung in the control group. This regional difference could be attributed to the vertical difference between the base and apex of the lung, which are in different positions on the pressure-volume curve.[34] This should be explained by the scintigraphic images obtained from asthmatics that showed a different deposition pattern, which suggests that obstruction level can affect pulmonary segments differently.

Irregular deposition pattern observed in the images suggests that obstruction may affect pulmonary segments in a variable manner. Another consideration that explains the highest deposition is that central airways are located in the middle third, and aerosol was deposited more centrally.

Regarding deposition in the horizontal differences, greater deposition occurred in the central region, when compared to the intermediate and peripheral regions. In regions with mild to severe obstruction, increased velocity and turbulent flows seem to promote deposition through the impaction mechanism, resulting in a concentration of radio-aerosol in "hot spots" near the obstructed areas.[33]

The radio-aerosol penetration index was higher in the central regions of the lungs in both groups, thereby reducing the percentage that reached the intermediate and peripheral regions. Fauroux et al[33] found a higher radio-aerosol penetration index in the NIV + nebulizer group, but the comparison of those data to our results is limited, as the patients assessed in the Fauroux et al study had cystic fibrosis, and the obstruction measured by the spirometry differed from those patients with asthma.

The analysis of radio-aerosol penetration index in relation to spirometric parameters and inspiratory capacity revealed a negative correlation to FEV_1, $FEF_{25-75\%}$, and inspiratory capacity in the control group and only to $FEF_{25-57\%}$ in the NIV + nebulizer group. The NIV + nebulizer group probably presented less correlation between radio-aerosol penetration index and lung function because NIV itself improved lung function substantially, which obscured the response from regional deposition aerosol.

According to pulmonary clearance, radio-aerosol particles can be eliminated through the respiratory epithelium, mucociliary clearance, and coughing, which are related to the particle deposition site.[35] DTPA-Tc^{99m} was used in the present study, which is cleared through the alveolar-capillary membrane, with a mean biologic half-life of approximately 60 min. Mean radio-aerosol half-life did not achieve statistical significance and the data were similar in both groups, possibly due to the bronchial obstruction in patients with asthma, leading to a reduction in radio-aerosol deposition in the peripheral airways. Thus, when bronchodilators are administered during an asthma crisis, pulmonary clearance time should be considered, given that it may influence the response.

Some limitations should be considered when interpreting the results of this study. First, no validated protocols were found in the literature consulted concerning the application of bi-level inspiratory and expiratory pressures in patients with asthma. For this reason, the decision was made to use the values reported in a previous study published by our group. Second, there was no determination of the extent to which this response improves other clinical outcomes, such as stay in the emergency room and hospitalization rates.

Conclusions

Finally, to our knowledge this is the first study to couple nebulization and NIV through scintigraphy in the treatment of asthma exacerbations, and we conclude that:

- NIV did not increase aerosol deposition or improve penetration index.
- It is technically feasible to deliver aerosol effectively during NIV in asthmatics.
- NIV has additive benefits to the treatment of acute asthma, as measured by the acute changes in respiratory variables.

Further studies are necessary to see if NIV reduces hospitalization rates from the emergency room, or reduces length of hospital stay.

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10. ABSTRACT

Inhalation has been commonly used to deposit bronchodilators drug directly into the respiratory tract, mainly because of the immediate responses effects and minimize systemic side effects observed by the oral route in patients with chronic respiratory disease (asthma and chronic obstructive pulmonary disease - COPD, among others). During the exacerbation of these diseases, noninvasive ventilation (NIV) has been used in clinical practice in patients with persistent respiratory distress, and its clinical benefits have been well established in the literature. The percentage of lung deposition of radiotagged aersosol using the jet nebulizer (NJ) reaches values around 1-3%, but a new generation devices to nebulize, designated vibrating mesh nebulizer (VMN), has shown promising results according to studies involving animal models and *in vitro*. Those studies reported two fold more deposition using VMN compared to JN. However, we research some databases and did not evidence *in vivo* studies involving the association between NIV with VMN in normal subjects and stable asthmatics and COPD. Thus, the objectives of this study were: 1) to quantify the amount of radioaerosol deposited in different regions of interest (ROI) in both lungs (vertical gradient - upper, middle and lower; horizontal gradient - the central, intermediate and peripheral) and 2) to analyze the deposition radioaerosol in different compartments (pulmonary and extrapulmonary) in healthy individuals, asthmatics and COPD patients after coupling nebulization with VMN and JN to NIV. Thus, three papers were produced, whose study design was a crossover clinical trial involving the samples described above. The method used was similarly for all samples and we used randomization for the election of which device to use initially. This study was divided into two phases: Phase 1 (NIV + NJ) and Phase 2 (NIV + NM). To inhalation was used 99mTc-DTPA technetium with a radioactivity of 25 mCi and bronchodilators added to saline solution (0.9% of concentration) until completing a volume of 3 ml to fill the nebulizer. NIV was used with two levels of pressure (inspiratory and expiratory pressures of 12 cmH_2O and 5 cmH_2O, respectively). After inhalation, the scintigraphic images were obtained by gamma camera and regions of interest (ROI) were delimited with all

compartments. As a result, we found a higher radioaerosol deposition using NIV coupled to VMN in comparison to JN (972013±214459 contagens *versus* 386025±130363 counts, p=0.005; 1198479±434174 conunts *versus* 426803±151758 counts, p=0.005; 1867044±456120 counts *versus* 579729±312261 contagens, p=0.005) in normal subjects, asthmatics and COPD, respectively. VMN demonstrated a highest inhaled mass percentage of radioaerosol deposited when compared to JN (23.7% versus. 13.6%, p = 0.005; 22.75% versus 27.7%, p = 0.005; 19.90% versus 7.3%, p = 0.008) in normal individuals (2.5 fold more), asthmatics (2.8 fold more) and patients (3 fold more), respectively. Thus, another interesting finding was the lower residual volume after nebulization observed in VMN in percentage terms, there was a higher deposition in the lung and lower residual in comparison to JN. In conclusion, the three papers should be considered the first crossover clinical trials involving NIV in association to VMN, showning a higher radiaerosol pumonary deposition in comparison JN in healthy individuals, and asthmatic and COPD patients. These results can direct professionals who use inhaled therapy to choose the best inhaler device able to optimize lung deposition of aerosols to treat respiratory chronic diseases.

Keywords: Pulmonary scinthigraphy, nebulizer, radioaersol, residual volume, chronic pulmoanry disease.