Tese de Doutorado

COMPARAÇÃO ENTRE TESTES DE VENTILAÇÃO ESPONTÂNEA ATRAVÉS DE PRESSÃO DE SUPORTE OU TUBO-T NA DESCONTINUAÇÃO DA VENTILAÇÃO MECÂNICA EM PACIENTES PORTADORES DE DOENÇA PULMONAR OBSTRUTIVA CRÔNICA - UM ENSAIO CLÍNICO RANDOMIZADO

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À minha amada filha Mônica, doce criatura divina que veio ao mundo para encher o coração dos pais de alegria e conferir à vida um novo sentido.

“Quantos às opiniões que até então eu aceitara, o melhor que podia fazer era suprimi-las de uma vez por todas, a fim de substituí-las, ou por outras melhores, ou então pelas mesmas, quando eu as tivesse ajustado ao nível da razão.”

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SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS DO TEXTO EM PORTUGUÊS:

DPOC — Doença Pulmonar Obstrutiva Crônica

TVE — Teste de Ventilação Espontânea

PSV — Ventilação em Pressão de Suporte (*Pressure-Support Ventilation*)

VM — Ventilação Mecânica

UTI — Unidade de Terapia Intensiva

EUA — Estados Unidos da América

PTR — Pressão Trans-Respiratória

PEEP — Pressão positiva ao final da expiração (*Positive End-Expiratory Pressure*)

IRRS — Índice de Respiração Rápida e Superficial

CPAP — Pressão positiva contínua na via aérea (*Continuous Positive Airway Pressure*)

ATC — Compensaçào automática de tubo (A*utomatic Tube Compensation*)

RR — Risco Relativo

TOT — Tubo Orotraqueal

VMNI — Ventilação Mecânica Não-Invasiva

LISTA DE ABREVIATURAS E SIGLAS DO TEXTO EM INGLÊS:

COPD — Chronic Obstructive Pulmonary Disease

SBT — Spontaneous Breathing Trial

PSV — Pressure-Support Ventilation

MV — Mechanical Ventilation

ICU — Intensive Care Unit

ETT — endotracheal tube

RCT — Randomized Controlled Trial

PEEP — Positive End-Expiratory Pressure

RSBI — Rapid Shallow Breathing Index

BiPAP — BiLevel Positive Airway Pressure

SAPS — Simplified Acute Physiology Score

1 RESUMO

Fundamentação: A melhor estratégia para descontinuação da VM em pacientes portadores de DPOC não está estabelecida. Os Testes de Ventilação Espontânea (TVEs) são parte essencial deste processo. Objetivo: Comparar os TVEs em Tubo "T" com PSV em pacientes portadores de DPOC. Métodos: Realizou-se extensa revisão da literatura, além de duas revisões sistemáticas com metanálise acerca do tema, e um ensaio clínico incluindo portadores de DPOC randomizados para TVE de 30 minutos em Tubo "T" ou PSV de 10cmH2O. Os desfechos primários do experimento foram o tempo total de VM e o tempo de VM após o TVE. Resultados: A literatura acerca do tema é vasta entretanto ainda inconsistente; os TVEs podem apresentar desempenho diferente de acordo com o perfil do paciente. Quanto ao ensaio clínico, 190 pacientes foram randomizados para TVE em Tubo-T (n = 99) ou TVE em PSV (n = 91). Houve 29,5% de falha de extubação em 48h no grupo Tubo-T e 24,2% no grupo PSV (p = 0,508). O tempo médio total de VM foi de 10,82 ± 9,1 dias para Tubo-T e 7,31 ± 4,9 para PSV (p < 0,001); entretanto, o tempo pré-TVE também diferiu entre os grupos (7,35 ± 3,9 e 5,84 ± 3,3 respectivamente [p = 0,002]). O tempo pós-TVE foi de 8,36 ± 11,04 dias para Tubo-T e 4,06 ± 4,94 dias para o grupo PSV (Razão de Médias = 2.06 [1.29 - 3.27]; p = 0,002), para os pacientes em desmame difícil. O TVE em Tubo-T foi independentemente associado com o tempo pós-TVE neste subgrupo, mesmo quando ajustado para potenciais confundidores. Conclusão: Para pacientes portadores de DPOC em desmame difícil, o TVE em Tubo-T foi independentemente associado com um maior tempo de VM após o TVE.

2 INTRODUÇÃO

A Doença Pulmonar Obstrutiva Crônica – DPOC – é uma condição clínica cuja prevalência mantém-se elevada no Brasil e no mundo, estando atualmente entre as principais causas de mortalidade. Entre os pacientes portadores da doença em seu estágio avançado, Insuficiência Respiratória Aguda é o principal motivo de transferência à Unidade de Terapia Intensiva (UTI), requerendo, em grande parte dos casos, instituição de Ventilação Mecânica (VM) invasiva.

A VM é fundamental no suporte de vida quando em vigência de falência respiratória. Existem, no entanto, eventos adversos inerentes, em especial no grupo de indivíduos portadores de DPOC. Por tratar-se de uma condição associada a obstrução das vias aéreas, a VM pode resultar em potencialização do alçaponamento aéreo, tendo como possíveis consequências barotrauma, comprometimento hemodinâmico e aumento da sobrecarga imposta à musculatura respiratória. Desta maneira, tão logo esteja resolvida a causa específica que desencadeou a instituição de VM nos pacientes com DPOC, deve-se dar início ao processo de descontinuação da VM, conhecido internacionalmente como desmame da VM.

O processo de desmame da VM consiste na retirada gradual do suporte ventilatório até que o paciente esteja apto a retomar a ventilação espontânea. A avaliação das reais condições de que dispõe o paciente para prosseguir com a retirada do suporte ventilatório passa pelos Testes de Ventilação Espontânea (TVE). Não existem indicadores específicos que determinem eque momento precisamente devem ter início os TVE. Caso iniciem-se muito precocemente, podem resultar em fadiga respiratória; caso tardem a iniciar-se, podem acarretar atrofia da musculatura respiratória, aumento da taxa de pneumonia associada à VM e aumento do tempo de internação na UTI. Estima-se que o processo de descontinuação da VM pode ser responsável por até 40% do tempo total de VM; nos indivíduos portadores de DPOC, esta parcela pode ser de até 60%.

Os TVEs podem ser realizados de diferentes formas. Pode-se utilizar o dispositivo conhecido como Tubo-T, que permite ventilação espontânea, desconectada do ventilador, ao mesmo tempo que fornece oxigenoterapia suplementar. Tal método pode ocasionar aumento do trabalho respiratório por meio de incremento da resistência de via aérea imposta pelo diâmetro interno e extensão do tubo orotraqueal. Como maneira de contrabalançar este efeito, pode-se lançar mão de implementação de Pressão de Suporte (*pressure-support ventilation*, ou PSV) em níveis entre 5 e 10cmH2O, suficientes para contrapor tal aumento do trabalho respiratório.

Esteban e colaboradores, em 1995, compararam 4 métodos de TVE em 130 pacientes (32% portadores de DPOC) alocados de forma randômica para TVE em Ventilação Mandatória Intermitente, TVE em PSV, TVE diário em Tubo “T” ou múltiplos TVEs ao dia em Tubo “T”. Os testes em Tubo “T”, diários ou repetidas vezes ao longo do dia, permitiram extubação de forma mais rápida do que em PSV ou em Ventilação Mandatória Intermitente, resultando em menor tempo de VM. Brochard e colaboradores conduziram outro ensaio clínico semelhante, em que 109 pacientes foram alocados para 3 métodos de TVE, incluindo Tubo-T e PSV. Estes autores encontraram um menor número de falhas com TVE em PSV do que em Tubo-T. Ambos estudos concordaram no achado de que a estratégia baseada em Ventilação Mandatória Intermitente resulta em desfechos menos favoráveis. Outros ensaios clínicos mais recentes sugerem que as estratégias de TVE em Tubo-T ou em PSV podem ter desfechos semelhantes.

No contexto específico de pacientes portadores de DPOC, dois estudos recentes compararam estratégias de TVE em populações bastante distintas. Matic e colaboradores, em recente ensaio clínico que incluiu 63 pacientes já com falha a um primeiro TVE, encontraram menor tempo de internação em UTI com o uso de PSV em comparação com TVE em Tubo-T. Neste estudo, no entanto, os desfechos foram avaliados em um número de pacientes que não atendeu o cálculo de tamanho amostral; ainda, não houve padronização acerca do uso de ventilação mecânica não-invasiva (tampouco registro da sua incidência), estratégia amplamente utilizada atualmente neste subgrupo de pacientes.

Sendo assim, a literatura não fornece informações suficientes a respeito de qual o melhor TVE para otimizar-se o processo de descontinuação da VM em pacientes portadores de DPOC, o que torna necessária a realização mais estudos que possam esclarecer este aspecto fundamental no cuidado destes pacientes.

3 REVISÃO DA LITERATURA

Epidemiologia

De acordo com a Organização Mundial da Saúde, a DPOC representa, desde o levantamento correspondente ao ano de 2002, a quinta causa global de mortalidade. Devido à sua tendência de incremento em termos de prevalência, caso não sejam implementadas medidas efetivas e especificamente direcionadas ao seu controle epidemiológico, a projeção atual é de que seja verificado um aumento na sua prevalência de em torno de 10% nas próximas duas décadas, tornando-se a terceira principal causa de mortalidade ao redor do mundo no ano de 2.030 (1).

Recente levantamento de base populacional conduzido nos Estados Unidos da América (EUA) por Mehta e colaboradores (2) foi obtido através de uma base de dados que abrange 44 estados americanos e reflete o comportamento de quase duas décadas de tendências do emprego de VM invasiva nos EUA, contemplando mais de 8 milhões de pacientes em VM entre os anos de 2003 e 2009. Neste estudo, a prevalência de DPOC enquanto indicação não-cirúrgica de VM tem-se mantido estável nas últimas décadas. De forma análoga, a mortalidade destes pacientes tem-se mantido praticamente inalterada a despeito de uma série de avanços obtidos do ponto de vista científico em termos de estratégias de ventilação mecânica e medidas farmacológicas. O comportamento da mortalidade de pacientes ventilados por DPOC é marcadamente diferente daqueles pacientes ventilados por pneumonia bacteriana, por exemplo, subgrupo em que se percebe clara tendência de redução de eventos no período estudado. Em consonância, Esteban e colaboradores (3), em seguimento de estudos transversais anteriormente publicados, analisaram dados de mais de 400 UTIs em 40 países (mais de 40% em território europeu) e identificaram a DPOC como terceira principal indicação de VM invasiva, representando cerca de 6% dos casos.

O contexto nacional mostra-se alinhado com estes dados. No estudo ERICC (4), a prevalência de DPOC entre os pacientes submetidos à VM em 45 UTIs brasileiras

chegou a 10%, e foi considerada o motivo da instituição de suporte ventilatório em 6% dos casos. Fialkow e colaboradores (5) recentemente publicaram os resultados de uma coorte de mais de mil pacientes submetidos à VM na UTI do Hospital de Clíinicas de Porto Alegre e reportaram que a DPOC segue sendo a responsável por 5,4% das indicações de suporte ventilatório invasivo; com relação à VM não invasiva (VMNI), esta proporção alcança 15% dos casos.

Tendo em vista que espera-se um aumento na prevalência global da DPOC ao redor do mundo e, da mesma forma, que esta entidade segue respondendo por grande proporção das indicações de VM invasiva e mesmo da mortalidade dos pacientes ventilados por etiologia não-cirúrgica, torna-se essencial que o intensivista esteja apto a lidar com este perfil de paciente e suas particularidades do ponto de vista clínico e fisiopatológico.

Fisiopatologia da DPOC

O paciente portador de DPOC é o hospedeiro de uma série de alterações na homeostase de diversos sistemas, tanto do ponto de vista de mecânica respiratória quanto de hemodinâmica, resposta inflamatória e mesmo compleição nutricional e muscular.

Centraliza-se na mecânica respiratória o ponto de partida para o entendimento destas interações. Para a adequada compreensão deste complexo cenário, cabe revisitar-se o conceito de equação do movimento do sistema respiratório (6). Através da sua análise, verifica-se que a pressão trans-respiratória (PTR), aquela responsável pela geração de fluxo de ar em direção ao sistema respiratório, equivale ao somatório da pressão elástica e da pressão resistiva da via aérea. Desmembrando-se seus componentes, verifica-se que a PTR é determinada na sua essência pelos seguintes parâmetros do sistema respiratório: elastância, volume, resistência inspiratória e fluxo aéreo.

Através da compreensão das alterações estruturais e mesmo inflamatórias características do paciente portador de DPOC, identifica-se que todos os componentes da mecânica respiratória supracitados apresentam graves alterações neste contexto. Tanto a perda de elastância decorrente da desestruturação arquitetural do parênquima, quanto o aumento da resistência ao fluxo aéreo, bem como o aumento do volume pulmonar e até mesmo do volume de secreções produzido desempenham papéis fundamentais neste intrincado mecanismo fisiopatológico.

Em termos de exalação, de forma ainda mais exuberante, tornam-se evidentes estes achados: sendo a expiração fenômeno essencialmente passivo em condições fisiológicas, a dependência de variáveis como resistência ao fluxo e elastância pulmonar é ainda mais marcada. Desta forma, a limitação ao fluxo aéreo exalatório, o alçaponamento pulmonar e a consequente hiperinsuflacão dinâmica tornam-se importantes mecanismos de deterioração da função pulmonar. Uma série de marcadores fisiopatológicos são daí resultantes, com destaque para o aumento das pressões de enchimento de câmaras cardíacas, do trabalho respiratório e a progressiva falência muscular. (7-9)

Estes aspectos são abordados de forma elucidativa em estudo publicado por Jubran e colaboradores, (10) que avaliaram 31 pacientes portadores de DPOC submetidos a TVE em Tubo-T quanto a pressão inspiratória máxima, resistência inspiratória, elastância dinâmica e desenvolvimento de pressão positiva ao final da expiração (positive end-expiratory pressure - PEEP) intrínseca. Já imediatamente após a descontinuação da VM, os pacientes que falharam ao TVE (n = 17) apresentavam níveis significativamente mais elevados de elastância dinâmica e e de PEEP intrínseca do que aqueles que obtiveram sucesso. Entre o início e o final do TVE estas alterações tornam-se ainda mais marcadas: o grupo dos pacientes que falharam desenvolveu ainda mais exuberantes elevações na elastância, na PEEP intrínseca e também na resistência inspiratória ao longo do período do teste, sugerindo progressivo comprometimento da mecânica pulmonar à medida que se prolonga o TVE. Estes achados são corroborados por Parthasarathy e colaboradores (11), que evidenciaram,

em estudo com 19 pacientes portadores de DPOC, que aqueles que apresentam falha ao TVE apresentam elevação progressiva da pressão intragástrica (parâmetro substituto da atividade muscular exalatória), a despeito de valores sobreponíveis no início do teste. Estes autores identificaram que, no grupo de pacientes que falharam ao teste, o aumento na pressão intragástrica foi responsável por aproximadamente 53% da PEEP intrínseca desenvolvida ao longo do TVE.

O contexto estressor do TVE também pode estar relacionado à resposta inflamatória. Sellarés e colaboradores (12) avaliaram TVEs realizados em 49 pacientes e mensuraram os níveis de interleucina-6, um marcador associado a esforço muscular, antes e após o encerramento de TVE com duração de 30 minutos. Naqueles pacientes portadores de DPOC que falham ao teste, evidencia-se uma elevação significativa da concentração sérica deste marcador ao longo do teste, o que não se verifica na população de pacientes que não são portadores de DPOC, tampouco naqueles com sucesso ao teste.

Desmame da VM no paciente portador de DPOC

Este cenário de múltiplas perturbações em diversos mecanismos patológicos próprios do indivíduo portador de DPOC reforçam a necessidade de identificar-se o momento mais apropriado para prosseguir-se à descontinuação da VM da forma mais segura possível, sobretudo nesta população. Ao passo que o processo de descontinuação da VM deve ser o mais ágil possível no sentido de evitar-se prolongamento desnecessário do tempo de VM e seus eventos adversos relacionados (necessidade de sedo-analgesia, risco para pneumonia associada à VM), a celeridade demasiada do processo pode ocasionar falha de extubação, evento relacionado de forma significativa a incremento de mortalidade na literatura (13, 14).

O processo de desmame apresenta-se como um dos principais desafios do cuidado atual do paciente crítico, e pode representar uma fração tão importante quanto 40% do tempo total de VM (15, 16), embora a definição do momento em que se inicia

este processo seja imprecisa. Alguns autores (17) sugerem que a primeira etapa do processo de desmame deva ser considerada aquela imediatamente após a admissão na UTI e mesmo à instituição de VM. Ainda que importante do ponto de vista conceitual, estas definições limitam a comparação entre os dados referentes a tempo de desmame disponíveis na literatura.

Insucessos no processo de desmame são frequentes, podendo representar até 60% de falha em populações específicas como é o caso dos pacientes portadores de DPOC. O desempenho do paciente quando submetido a tentativas de desmame pode representar importantes implicações. Uma classificação passível de ser adotada neste sentido foi proposta por Boles e colaboradores (17), como resultado de conferência de consenso em desmame da VM, e categoriza os pacientes em desmame simples, difícil e prolongado de acordo com o tempo de VM previamente ao desmame, bem como o número de falhas ocorridas neste processo. Pacientes em desmame prolongado requerem uma abordagem diagnóstica e terapêutica bastante diversa daqueles em desmame simples, e, da mesma forma, terão seu prognóstico afetado de forma significativa. A sistematização na abordagem destes pacientes é fundamental também do ponto de vista de protocolos de pesquisa, a fim de permitir-se a extrapolação das evidências disponíveis à população apropriada de indivíduos. Todavia, este sistema de classificação é produto de experiência clínica e consenso de especialistas, não de evidência científica consistente. Recentemente, Tonnelier e colaboradores (18), explorando em uma coorte retrospectiva a classificação proposta pela conferência, identificaram, através de modelo de regressão logística, que a variável desmame prolongado está associada significativamente com mortalidade na UTI, ainda que a *Odds Ratio* de 15,11 para este desfecho (com relação ao desmame simples) varie de 1,61 a 141,91, possivelmente devido ao pequeno tamanho amostral estudado.

Desta forma, identificar-se o momento ideal para proceder-se ao desmame é essencial. Uma série de evidências científicas tem-se acumulado no sentido de investigar-se os chamados “preditores de extubação”, índices que permitam reconhecer o paciente apto à descontinuação da VM de forma ágil. Tanios e colaboradores (19)

avaliaram em ensaio clínico randomizado a contribuição adicional do Índice de Respiração Rápida e Superficial (IRRS) (20) sobre um protocolo de descontinuação da VM. O grupo submetido ao IRRS como uma das etapas do protocolo teve duração mais longa do processo de desmame, sem quaisquer outros impactos em desfechos como falha de extubação, extubação acidental ou incidência de traqueostomia. De fato, Savi e colaboradores (21) demonstraram, em uma população heterogênea de 500 pacientes submetidos a avaliação de preditores no primeiro e no trigésimo minuto de um TVE em Tubo-T, que estes parâmetros não possuem poder discriminatório suficiente para identificar-se futuras falhas de extubação.

Diversos outros índices estão disponíveis na literatura, e avaliam parâmetros como oxigenação, complacência do sistema e pressões de via aérea. Duas revisões sistemáticas avaliaram diversos preditores (22, 23), apontando que estes parâmetros não possuem impacto diagnóstico suficiente para alterar-se a decisão clínica. Tampouco índices integrativos, que propõem uma avaliação conjunta de mecânica respiratória, troca gasosa e padrão respiratório possuíram desempenho capaz de nortear a predição daqueles pacientes aptos à extubação. Boniatti e colaboradores (24) avaliaram o desempenho do *modified integrative weaning index,* produto da complacência estática e da saturação arterial de oxigênio divididos pelo índice de respiração rápida e superficial aferidos em dois pontos: no primeiro e no trigésimo minuto do TVE. Nem no momento inicial ou no final do teste, tampouco levando-se em consideração a diferença entre os dois pontos, houve acurácia suficiente para predizer-se o desfecho dos pacientes ao TVE.

Testes de Ventilação Espontânea: TVE

Tomando-se em conjunto a necessidade de identificação precisa dos pacientes aptos à saída de VM e a evidência escassa acerca da contribuição dos preditores de extubação, o contexto posto favorece a utilização dos chamados Testes de Ventilação Espontânea (TVE), procedimentos através dos quais os pacientes considerados elegíveis à descontinuação da VM são submetidos a condições que propõe-se a

simular a retirada do suporte ventilatório e o cenário pós-extubação. Esteban e colaboradores (25) apontam que os TVE continuam sendo a abordagem mais popular para avaliar-se as condições de extubação ao longo da última década ao redor do mundo: no levantamento correspondente ao ano de 2004, até 62% das UTIs utilizavam os TVEs como ferramenta de triagem para esta finalidade; dentre estes, mais de 70% empregavam rotineiramente o teste em Tubo-T.

Com o intuito de identificar-se qual o melhor método para conduzir-se um TVE em pacientes considerados para desmame da VM, conduzimos recentemente uma revisão sistemática da literatura com meta-análise apresentada na última conferência da *American Thoracic Society* e submetida em texto completo para publicação nas últimas semanas (26). Selecionamos ensaios clínicos randomizados e quase-experimentos, abrangendo população adulta e pediátrica. Nossos objetivos primários foram avaliar o impacto das diferentes técnicas empregadas para realização de TVE com relação ao desfecho do teste (extubação efetiva ou falha), taxa de reintubação e tempo de VM. Definimos *a priori* análises de subgrupo para avaliar o impacto tanto da probabilidade pré-teste de sucesso baseada na duração esperada da VM (curta ou longa duração), bem como com relação à população de pacientes cirúrgicos (em pós-operatório) em comparação com pacientes clínicos.

Foram incluídos nesta revisão 31 estudos, totalizando 3.541 pacientes. Os estudos originais predominantemente compararam TVE em Tubo-T com Pressão de Suporte (PSV) (13 estudos), ou Tubo-T com *CPAP - Continuous Positiva Airway Pressure* - (9 estudos). Um menor número de autores avaliou a comparação de *CPAP* com *ATC - Automatic Tube Compensation* - (3 estudos) ou deste com PSV (outros 3 autores). Foram excluídos estudos que avaliaram pacientes traqueostomizados, bem como aqueles que incluíram o TVE como parte de um protocolo de desmame, que empregaram técnicas automatizadas de desmame ou que compararam a realização com a não-realização de um TVE.

Com relação ao desfecho sucesso ao teste (extubação efetiva ou falha), a comparação direta de Tubo-T e PSV encontrou resultado neutro (RR = 1,00 [0,89 - 1,11]), com heterogeneidade considerada significativa (I^2 = 77%). Dentre as análises de subgrupo definidas *a priori*, a comparação entre pacientes cirúrgicos e clínicos parece explicar parte deste fenômeno: dentre os pacientes em pós-operatório, o desfecho sucesso da extubação obteve RR = 0,86 (0,61 - 1,22); em contrapartida, para pacientes clínicos (7 estudos; 1.273 pacientes), a mesma comparação resultou em RR = 1,07 (1,01 - 1,13; *p* = 0,02), favorecendo a estratégia PSV em comparação com Tubo-T - com I^2 = 0% para esta análise.

Os dois métodos encontrados com mais frequência nesta revisão sistemática (Tubo-T e PSV) parecem ser efetivamente aqueles empregados com maior frequência na prática clínica. Peñuelas e colaboradores conduziram levantamento epidemiológico em UTIs européias (27) em que apontam que estes dois métodos continuam a representar entre 30 e 50% das estratégias escolhidas, tanto para os subgrupos de pacientes em desmame simples, como difícil e prolongado.

Estas duas técnicas de TVE apresentam-se significativamente diferentes em vários aspectos: por Tubo-T entende-se a desconexão do tubo orotraqueal (TOT) do paciente do ventilador e o acoplamento de uma peça em formato da letra “T” à extremidade distal do TOT, o que lhe mantém em contato com uma fonte enriquecida de oxigênio e com a pressão atmosférica, sem qualquer suporte do ponto de vista pressórico. Cabe menção a alguns pontos importantes a respeito desta técnica; embora haja algum aumento de resistência de via aérea pela própria presença do TOT (aumentando matematicamente a extensão e reduzindo o calibre a via aérea) sem suporte adicional de pressão, o aumento consequente do trabalho respiratório não parece ser significativo dentro de condições aproximadas daquelas consideradas fisiológicas em termos de volume-minuto e diâmetro do TOT (28). Desta forma, persiste o receio de que o TVE realizado em Tubo-T possa comprometer a sensibilidade do teste, priorizando especificidade, por tratar-se de um TVE relacionado à imposição de uma série de alterações em mecânica de via aérea. Outros autores (29), no entanto,

argumentam que o TVE em Tubo-T pode resultar em incremento do trabalho respiratório, mas que estas condições refletem de forma até mais apurada o cenário enfrentado pelo paciente no período pós-extubação.

O teste realizado em PSV, em contrapartida, fornece um suporte pressórico constante e propõe-se a compensar a resistência imposta pelo aparato utilizado para VM (30): TOT, conexões, filtros e umidificadores, válvulas inspiratórias. A lógica deste teste seria minimizar o aspecto estressor do teste em si e a potencial injúria imposta ao paciente neste procedimento. Persiste o receio, contudo, de que esta abordagem possa permitir a extubação inadequada de pacientes que venham a evoluir para falha de extubação posteriormente.

Os TVEs geralmente compreendem uma duração entre 30 e 120 minutos, seguidos pela extubação, caso o paciente tolere o teste (17, 31). Dois ensaios clínicos randomizados (32, 33) compararam diretamente estas duas durações específicas e não encontraram diferenças significativas em termos de sucesso ao teste, taxa de reintubação em 48 horas, ou outros desfechos avaliados, quando os TVE foram aplicados através de Tubo-T (32) ou PSV (33), embora as altas taxas de sucesso ao desmame e a baixa incidência de falhas de extubação verificadas nestes protocolos limite a aplicabilidade destes dados para uma população de pacientes em alto risco para falha ao desmame. Alguns autores (34, 35) sugerem, inclusive, que o TVE possa ser estendido além dos 120 minutos, a fim de aumentar a sensibilidade para detecção de falhas de extubação em uma população selecionada de pacientes com alta probabilidade pré-teste de insucesso ao desmame. Estas recomendações, contudo, ainda carecem de embasamento científico consistente.

A potencial imposição de fadiga muscular e aumento do trabalho respiratório com o emprego de testes mais longos ou mais demandantes segue representando preocupação, embora alguns autores tenham demonstrado que fadiga clinicamente significativa ocorra infrequentemente durante testes monitorados que retomem o suporte ventilatório assim que os sinais de esforço se manifestem (36, 37). Quanto à

demanda energética imposta pelos testes, estudo recente realizado no nosso meio abordou esta questão de forma bastante interessante (38), comparando estas duas ferramentas quanto ao gasto energético aferido por calorimetria indireta. Os autores demonstraram que a média de calorias gastas ao dia é significativamente maior naqueles pacientes submetidos a TVE em Tubo-T do que naqueles submetidos ao TVE em PSV. Ainda que a diferença absoluta encontrada de cerca de 300Kcal/dia possa ser clinicamente pouco representativa, suas repercussões merecem investigação adicional.

A possibilidade de que o TVE em PSV represente uma estratégia menos demandante foi reforçada pelos achados do estudo de Ezingeard e colaboradores (39); os autores avaliaram 118 pacientes submetidos a um TVE em Tubo-T em duas UTIs francesas, dos quais 87 pacientes foram extubados; dos 31 que permaneceram em VM após falha ao TVE em Tubo-T, 21 foram extubados com sucesso após novo TVE, mas agora em PSV. De forma muito interessante, a taxa de reintubação daqueles indivíduos extubados após sucesso ao Tubo-T ou após PSV (13 e 19%) não diferiu de forma significativa (p = 0,39), indicando que parece ser seguro adotar tal estratégia. Ainda merece destaque o fato de que 38% dos pacientes portadores de DPOC foram efetivamente extubados após o TVE realizado em PSV, contra 13% após o TVE realizado através de Tubo-T.

Também do ponto de vista hemodinâmico, estes testes podem resultar em comportamentos distintos. Cabello e colaboradores (40) avaliaram 14 pacientes em um estudo de base fisiológica, do tipo *cross-over* - todos os pacientes foram submetidos, em ordem aleatória, a 3 formatos de TVE: Tubo-T, PSV com acréscimo de PEEP e PSV sem associação de PEEP. Foram avaliados diversos parâmetros relacionados à mecânica ventilatória, pressões de enchimento e gases arteriais. O teste realizado em Tubo-T apresentou resultados numericamente piores em todos as variáveis estudadas, notadamente IRRS, desenvolvimento de PEEP intrínseca e trabalho respiratório, indicando que o mesmo paciente pode responder de formas variadas quando submetido a modalidades diferentes de TVE. Estes mecanismos parecem de alguma forma subjacentes ao desenvolvimento de descompensação cardiovascular associado

à falha ao desmame por uma parcela significativa de pacientes: somada à hiperinsuflação e ao alçaponamento aéreo resultando em aumento de pressões de enchimento, a descompressão súbita das câmaras direitas quando da retirada abrupta da pressão positiva (em tubo-T, por exemplo), pode representar um aumento no retorno venoso que excede a capacidade - e a velocidade - de adaptação cardiovascular destes pacientes, que por fim entram em falência cardio-pulmonar.

Achado a destacar-se deste estudo é a prevalência e comportamento dos pacientes portadores de DPOC (7 dos 14 da amostra). Destes, 6 indivíduos apresentaram elevação de pressão de oclusão da artéria pulmonar durante o teste realizado em Tubo-T. De fato, achados semelhantes já haviam sido reportados por Lemaire e colaboradores (41), em estudo clássico avaliando 15 pacientes portadores de DPOC grave submetidos a um período tão breve quanto 10 minutos de TVE; neste estudo, os autores identificaram um incremento no índice cardíaco, na pressão arterial, na frequência cardíaca, e, de forma representativa, na pressão de oclusão da artéria pulmonar (de 8 ± 5 para 25 ± 13 mmHg, $p < 0,001$) e no índice de volume diastólico final do ventrículo esquerdo (de 65 ± 24 para 83 ± 32 / m^2, $p < 0,001$). Após tratamento com diuréticos e efetiva perda de peso, 9 destes 15 pacientes tiveram sucesso no desmame da VM.

Estes aspectos parecem estar vinculados a uma série de mecanismos que conectam a DPOC com doença cardiovascular. A prevalência de insuficiência cardíaca, por exemplo, é até três vezes maior na população portadora de DPOC, mesmo quando ajustada para idade e fatores de risco. Ainda, uma proporção tão elevada quanto 30% das suspeitas exacerbações de DPOC na sala de emergência são devidas a insuficiência cardíaca descompensada (42, 43). Além de fatores de risco compartilhados, talvez ainda mais relevante seja o fato de haver uma série de vias fisiopatológicas em comum entre as duas entidades: estresse oxidativo, aterosclerose, caquexia, resposta inflamatória sistêmica, ativação do tônus simpático sistema renina-angiotensina-aldosterona e avidez tubular por sódio fazem parte deste complexo contexto.

No intuito de esclarecer qual o desempenho comparativo dos dois principais TVE empregados no nosso meio e ao redor do mundo, conduzimos uma revisão sistemática com metanálise específica para estão questão de pesquisa (44). Foram selecionados apenas ensaios clínicos randomizados, abrangendo desmame simples, difícil e prolongado, que comparassem diretamente PSV e Tubo-T e reportassem algum dos desfechos preestabelecidos.

Doze estudos, incluindo 2.161 pacientes, preencheram nossos critérios de inclusão. Sete destes avaliaram o cenário de desmame simples (dois destes em pacientes cirúrgicos). Sete estudos utilizaram TVE com duração de 120 minutos; outros dois protocolos utilizaram 30 minutos de TVE. Apenas dois autores (45, 46) incluíram exclusivamente portadores de DPOC, sendo que um destes (45) incluiu apenas pacientes portadores de traqueostomia, em desmame prolongado, internados em unidades específicas de cuidados respiratórios de longo prazo. Nos demais estudos, a porcentagem de pacientes portadores de DPOC variou desde 10 a 47% da população; três autores não reportaram a prevalência desta condição.

Quanto aos desfechos de interesse, o TVE não influenciou de forma significativa a taxa de sucesso ao teste (RR = 1,23 [0,94 - 1,61]), tampouco a mortalidade na UTI (RR = 1,11 [0,80 - 1,54]) ou a taxa de reintubação (RR = 1,21 [0,90 - 1,63]). Com relação às análises de subgrupo definidas *a priori*, o TVE realizado em PSV pode ser superior ao Tubo-T em termos de sucesso ao teste naqueles pacientes em desmame simples (RR = 1,44 [1,11 - 1,86]), enquanto que para aqueles em desmame prolongado, o teste em Tubo-T foi associado a uma menor duração do desmame (diferença média ponderada = 3,08 dias [0,92 - 5,24]). De maneira geral, a evidência disponível foi considerada de baixa ou muito baixa qualidade, limitando a adequada interpretação e aplicação clínica destes resultados.

No que diz respeito ao escopo específico desta tese, a comparação direta de TVE exclusivamente no subgrupo de pacientes portadores de DPOC, excluindo-se

pacientes traqueostomizados em desmame prolongado, cabe a discussão mais detalhada acerca de dois estudos previamente publicados. Matic e colaboradores (46) randomizaram 136 pacientes portadores de DPOC em VM por período superior a 24 horas para o emprego de TVE em PSV (n = 70) ou Tubo-T (n = 66). A taxa de falha ao teste (46 e 47%, respectivamente) foi sobreponível entre os grupos.

Um aspecto que suscita discussão com relação a este estudo é o fato de que aqueles pacientes que obtiveram sucesso ao primeiro TVE foram excluídos das análises posteriores dos desfechos de interesse, contabilizando para a amostra final apenas 32 pacientes para o grupo PSV e 31 para o grupo Tubo-T. Desta forma, a interpretação dos resultados é ambivalente: se de um lado, a análise feita considerando-se toda a população inicialmente recrutada para o estudo (136) e compatível com o cálculo de tamanho amostral efetuado demonstra resultados neutros, a análise posteriormente realizada no subgrupo de pacientes com uma falha sugere superioridade em uma série de desfechos (duração do desmame, duração total da VM, tempo de internação na UTI e taxa de extubação bem-sucedida) favorecendo a estratégia em PSV.

Uma série de limitações podem ser apontadas com relação à extrapolação destes resultados, além da questão supracitada referente à estratégia de randomização: trata-se de um estudo unicêntrico, que por definição incluiu apenas pacientes em desmame difícil, e que não atingiu o tamanho amostral calculado para seus desfechos principais. Ainda, não houve padronização acerca das indicações de uso de ventilação mecânica preemptiva após a extubação, tampouco existe referência à prevalência do uso desta ferramenta na população estudada.

Molina-Saldarriaga e colaboradores (47) conduziram outro protocolo cujo objetivo era comparar dois TVEs na população de pacientes portadores de DPOC ventilados por mais de 48 horas; neste estudo, no entanto, os autores empregaram como comparador para o Tubo-T o teste em CPAP - *continuous positive airway pressure.* A titulação da CPAP foi pré-estabelecida em 85% da PEEP intrínseca aferida no início do protocolo.

Cabe destacar que neste protocolo a decisão de instalar-se VMNI pós-extubação foi considerada critério de exclusão. O cálculo de tamanho amostral realizado pelos autores previa a necessidade de que fossem incluídos 107 pacientes em cada grupo para detectar-se um incremento de 20% na taxa de sucesso ao TVE, com poder do estudo de 80% e erro alfa de 5%.

Foram incluídos, contudo, 50 pacientes considerados aptos ao desmame ao longo de 3 anos de estudo em 3 UTIs colombianas. Seriam avaliados os desfechos sucesso ao TVE, taxa de reintubação e desenvolvimento de alçaponamento aéreo através da mensuração de PEEP intrínseca. O estudo, contudo, foi interrompido precocemente por baixa taxa de recrutamento de pacientes. De qualquer forma, os autores reportam as taxas de sucesso de extubação de 76% no grupo CPAP e 60% no grupo Tubo-T (RR = 1,27 [0,86 - 1,87]). Ainda, a baixa taxa de reintubações verificada (3 eventos no grupo Tubo-T e nenhum evento no grupo CPAP) limitam de forma importante a interpretação destes resultados. Não foi identificada qualquer diferença no desenvolvimento de PEEP intrínseca (5,46 e 5,23 cmH2O, respectivamente; p = 0,763). De maneira análoga à questão das reintubações, a prevalência de pacientes com alçaponamento aéreo definido por PEEP intrínseca maior que 8cmH2O foi inferior a 14%. Os autores elencaram como principais motivos para o encerramento precoce do estudo o referenciamento de pacientes portadores de DPOC para outras unidades especializadas no cuidado desta condição, criadas durante o decorrer do protocolo, e o incremento na utilização da VMNI pós-extubação neste subgrupo de pacientes.

O papel da VMNI

De fato, ao longo das últimas duas décadas, o emprego da VMNI tem-se disseminado nas salas de emergência e UTIs ao redor do mundo, tanto no que diz respeito ao tratamento da insuficiência respiratória, para evitar-se intubação e VM invasiva, quanto como estratégia para agilizar-se o desmame da VM invasiva e prevenir-se a disfunção respiratória pós-extubação. Com relação ao tratamento da insuficiência respiratória aguda especificamente no paciente portador de DPOC, a

recomendação de mais recente diretriz canadense para o emprego de VMNI é classificada como 1A, fruto de diversos ensaios clínicos randomizados, que compilados resultam em uma estimativa de redução de risco relativo para intubação orotraqueal e mesmo mortalidade da ordem de 60 e 50%, respectivamente (48). Importante ressaltar-se que a quase totalidade dos estudos excluiu pacientes portadores de DPOC que se apresentaram com pneumonia sobreposta.

Com relação ao uso da VMNI como adjuvante para o desmame de pacientes portadores de DPOC, para aqueles indivíduos que falharam um TVE ou mesmo ainda não atingiram critérios de elegibilidade para que fossem submetidos a TVE, o mesmo documento de consenso gradua a recomendação para seu uso como 2B, devendo ser empregada em centros que tenham experiência suficiente na utilização desta ferramenta, dado o risco de postergar-se inadvertidamente uma reintubação nesta população de muito alto risco para evolução desfavorável. Trevisan e colaboradores (49) randomizaram 65 pacientes (35% deles portadores de DPOC) que haviam falhado previamente a TVE em Tubo-T para extubação seguida de VMNI ou para o tratamento convencional com VM invasiva. O grupo submetido a VMNI teve menor taxa global e complicações, mediada por menor incidência de pneumonia associada à VM, bem como necessidade de traqueostomia.

Uma questão correlata, mas sensivelmente diferente, diz respeito à instalação preemptiva de VMNI imediatamente após a extubação programada. Quatro ensaios clínicos (50-53) recentes avaliaram esta estratégia para pacientes classificados como de alto risco para disfunção respiratória pós-extubação, quais sejam: idade superior a 45 anos; falha em TVEs consecutivos, ICC, paCO2 acima de 45mmHg após extubação, estridor pós-extubação (mais de um dos anteriores); exacerbação de DPOC; hipercapnia durante o TVE. Apesar de alguns critérios diferirem entre os estudos, quando este subgrupo de pacientes foi tratado com VMNI preemptiva no período pós-extubação, os resultados agregados de riscos relativos para reintubação e mortalidade na UTI foram iguais a 0,42 (IC 95% 0,25 - 0,70) e 0,35 (IC95% 0,16 - 0,78), respectivamente (48).

Os efeitos da VMNI em termos de mortalidade de longo prazo são corroborados por ampla revisão sistemática recentemente publicada, que incluiu 78 ensaios clínicos randomizados, compreendendo mais de 7 mil pacientes (54): sobretudo no contexto de tratamento de insuficiência respiratória em pacientes portadores de DPOC, a VMNI atinge resultados expressivos (número necessário a tratar = 11), devendo ser considerada tratamento de primeira linha neste cenário.

Com relação à prevenção de disfunção respiratória pós-extubação planejada, uma segunda revisão sistemática com meta-análise (55) incluiu 9 estudos, sendo que dois deles (50, 56) incluíram exclusivamente pacientes portadores de DPOC. Avaliando-se através de análise de subgrupo unicamente os pacientes portadores de DPOC destes e de outros estudos incluídos, a taxa de reintubação dos pacientes submetidos à VMNI é de 12,3%, em comparação a 36,5% naqueles pacientes que receberam tratamento convencional (RR = 0,33 [0,16 - 0,69]). Não verificou-se heterogeneidade para este desfecho neste subgrupo (I^2 = 0%).

4 JUSTIFICATIVA

A DPOC é uma das comorbidades mais frequentemente encontradas nos pacientes portadores de Insuficiência Respiratória Aguda hospitalizados na UTI, estando associada com risco para ventilação prolongada, aumento do tempo de internação na UTI, e falhas do processo de descontinuação da VM.

Uma vez que o risco de falha após uma extubação sem TVE pode chegar a 40%, faz-se necessário uma avaliação criteriosa de quais pacientes estão aptos à ventilação espontânea, o que pode ser realizado de diferentes formas, sendo as mais comumente utilizadas a ventilação em PSV com baixos níveis de suporte pressórico ou a ventilação espontânea em Tubo-T.

Se, de um lado, o TVE em Tubo-T parece identificar com maior especificidade aqueles pacientes realmente aptos à ventilação espontânea e extubação, ele também pode precipitar fadiga em pacientes com obstrução ao fluxo aéreo, por aumento da resistência de via aérea, o que pode retardar a extubação destes indivíduos. De outra maneira, o TVE com o auxílio da PSV pode atenuar a resistência de via aérea e o trabalho respiratório, mas pode não reproduzir fielmente as condições reais da via aérea no período pós-extubação.

Pelos dados conflitantes e inconclusivos à disposição na literatura, e pela relevância da questão clínica, justifica-se a realização deste estudo.

5 OBJETIVOS

Os objetivos primários deste estudo são comparar os TVEs em Tubo-T e PSV quanto à duração total da VM e quanto ao tempo de VM após a realização do TVE em pacientes portadores de DPOC.

Os objetivos secundários são identificar fatores associados com o tempo de VM após o TVE e com a taxa de falha de extubação em 48 horas; comparar os TVEs quanto à taxa de extubação no primeiro TVE; à taxa total de reintubação a qualquer tempo; à incidência de traqueostomia e à mortalidade na UTI.

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7 ARTIGO I

Title:

Pressure-Support or T-Piece Spontaneous Breathing Trials for COPD patients - A Randomized Controlled Trial

Abstract:

Rationale*: Little is known about the best strategy regarding weaning of chronic obstructive pulmonary disease (COPD) patients. Spontaneous breathing trials (SBT) with T-piece or pressure-support ventilation (PSV) have a central role in this process.* ***Objective****: To compare T-piece and PSV SBTs according to days in mechanical ventilation (MV) in COPD patients.* ***Methods****: COPD patients with at least 48 hours up to 20 days of MV support were randomized to 30 minutes of T-piece or PSV of 10cmH2O once considered able to proceed a SBT. All patients were preemptively connected to non-invasive ventilation after extubation. Tracheostomized patients were excluded. Primary outcomes were duration of MV and time spent in ventilator after SBT performance.* ***Results:*** *Between 2012 and 2016, 190 patients fulfilled inclusion / exclusion criteria and were therefore randomized for T-piece (99) or PSV (91). Extubation at first SBT was performed in 78% of patients; 48-hour failure was verified in 29.5% of T-piece group and 24.2% in PSV (p = 0.508). Mean total MV duration was 10.82 ± 9.1 days for T-piece and 7.31 ± 4.9 for PSV group (p < 0.001); however, pre-SBT interval also differed (7.35 ± 3.9 and 5.84 ± 3.3 respectively; p = 0.002]). Post-SBT duration was 8.36 ± 11.04 days for T-piece and 4.06 ± 4.94 days for PSV (univariate mean ratio = 2.06 [1.29 - 3.27], p = 0.003), for difficult weaning patients. Study group was independently associated with post-SBT duration in this subgroup, even when adjusting for several potential confounders.* ***Conclusion****: For difficult-weaning COPD patients, T-piece SBT was independently associated with post-SBT longer MV duration.*

Introduction:

Chronic obstructive pulmonary disease (COPD) is a widely prevalent condition in intensive care units (ICUs). Recent data indicate that it represents one of the main indications for ventilatory support worldwide. Mortality trends, however, seem to be stable, despite recent advances in mechanical ventilation (MV) policies and pharmacological strategies (1-5).

COPD patients are physiologically complex in essence. Beyond respiratory mechanics, a series of hemodynamic, metabolic and inflammatory derangements show up when these individuals are mechanically ventilated. Following flow obstruction and air trapping, available evidence shows that these patients are prone to increased work of breathing and cardiac filling pressures and consequent muscle fatigue (6-8).

While timely weaning from MV remains a fundamental goal in caring for these patients, it's undoubtedly a tough task. Evidence suggest that the weaning itself could take up to 40% of total MV duration (9), and failures in these processes are exceedingly common, reaching 50-60% in COPD population. Unfortunately, weaning predictors are not sufficiently accurate to identify which patients are suitable for a safe extubation (10), and recent work points out that the protocolized utilization of these indices tend to prolong MV duration (11).

Spontaneous breathing trials (SBTs) are commonly employed to deal with this scenario, corresponding to the current weaning policy of more than 60% of the european ICUs according to Esteban et al (12). These trials are based on the simulation of the conditions that will be imposed to the patient on the post-extubation scenario, after endotracheal tube (ETT) removal (13). This could be achieved through a variety of strategies, among them low-levels of pressure-support ventilation (PSV) and T-piece are widely reported in literature, comprising up to 30 to 50% of the methods employed for simple, difficult or even prolonged weaning (14).

Mechanical properties of each test are remarkably different; while in T-piece SBT patients are disconnected from ventilator and allowed to breathe at room air without any pressoric support, in PSV a low level (e.g., 5 to 10cmH2O) of positive pressure is set to overcome the increased airway resistance imposed by the mechanical apparatus (ETT, respiratory valves and the circuit itself) (15). These singularities can account for different outcomes even when the same patient is subjected to different tests (16).

Comparative studies addressing this subject are available. A recently published systematic review from our group (17) included twelve randomized clinical trials including 2,161 patients and concluded that although PSV can represent a better option in terms of weaning success (i.e., tolerance to the test and consequent extubation) for the subgroup of simple weaning patients, T-Piece may be related to faster weaning process for prolonged weaning patients. However, COPD patients represent only a small fraction of this population, varying from 10 to 47% of the study population. Only two studies (18, 19) enrolled exclusively COPD patients, but with remarkably heterogeneous patient profiles and results, making scientific progress in this area warranted.

Therefore, our objetive was to compare MV duration according to T-Piece or PSV in terms of (1) total MV duration and (2) post-SBT MV duration, in COPD weaning patients ventilated for more than 48 hours.

Methods:

Study Design:

We conducted a multicentric, randomized, open-label, parallel-group trial, that enrolled mechanically ventilated COPD patients admitted to 3 clinico-surgical ICUs in southern Brazil.

Patients:

Patients were consecutively included if submitted to invasive MV for at least 48 hours and no longer than 20 days before the first SBT was performed (i.e. simple weaning (20)). We decided to predeterminate this interval anticipating potential clinical heterogeneity between acutely ill and prolonged weaning patients profiles.

COPD diagnosis was made according to previous clinical history, physical examination, medical records, as well as radiological findings. No spirometric data were required to fulfill a COPD diagnosis, if clinically plausible.

We excluded tracheostomized patients (or that had been submitted to tracheostomy previously to the first SBT); patients under 18 years; individuals previously allocated in another RCT; MV for less than 48 hours; patients who have been already intubated at the index hospitalization; and those who died before the first SBT could be carried out.

This study protocol complies with the ethical principles of the Declaration of Helsinki (21) and of the National Health Council 466/12 resolution, being previously approved by institutional research ethic committees. Written informed consent was obtained from every included patient or from the next of kin.

Study Protocol and Randomization:

This research protocol was conducted in three different clinico-surgical ICUs: a universitary hospital unit (Hospital de Clínicas de Porto Alegre), a large public hospital unit (Hospital Nossa Senhora da Conceição), and a community hospital (Hospital Montenegro).

Patients were included when lasted for 48 hours in invasive MV, as soon as the informed consent was obtained. Clinical and epidemiological data were collected at baseline, preserving patient identification privacy. MV was instituted using Servo-i (Maquet SA, Ardon, France), Evita-4 (Dräeger, Lubeck, Germany) or Nellcor Puritan-Bennett 840 (Carlsbad, CA), according to the allocation center.

Randomization was accomplished by random sequence generation by a web-based software (www.randomizer.org), on a 1:1 ratio. Block randomization with a block size of 10 was performed and stratified according to SAPS III score. Allocation concealment was warranted by sequentially-numbered, opaque, sealed envelopes.

Envelopes were opened at the moment the weaning process were considered to begin – when the patient was deemed able to perform the first SBT - and determined the study allocation group, and, hence, SBT modality: T-piece or PSV.

The study protocol was approved by the institutional review board of Hospital de Clínicas de Porto Alegre and Hospital Nossa Senhora da Conceição and was registered at the database ClinicalTrials.gov (NCT01464567) prior to initiation.

Interventions:

SBTs were performed in the following fashion: PSV-group patients had their pressure-support level adjusted to 10cmH2O, maintaining previously employed PEEP and FiO2 parameters; T-piece group patients had their tracheal tube disconnected from

the ventilator and attached to a “T” connector, that permitted continuous oxygen supply for a goal of SaO2 of at least 92%, while in absence of positive pressure. Both SBTs were accomplished in 30 minutes, in a semi-seated position.

Patients were continuously monitored by multi-parametric monitors during SBTs. We registered the following parameters at 0, 15 and 30-minutes: heart rate, respiratory rate, pulse oximetry, as well as patient tolerance according to clinical evaluation. Respiratory rate, tidal volume and minute ventilation were measured at 0 and 30 minutes using a handheld Wright respirometer (Ferraris Medical, Hertford, Herts, UK). Rapid shallow breathing index (RSBI) and central venous oxygen saturation were also collected at 0 and 30 minutes.

The decision to proceed to extubation after SBT was made on clinical grounds, according to the charging team judgement, and did not follow predetermined clinico-physiological criteria.

Patients considered not being able to extubation were then returned to their previous MV settings for at least 24 hours previous to the next trial. SBT modality was maintained for further SBTs, until the maximum of three trials; patients still failing at this point could then be crossed-over to the opposite group.

All extubated patients were preemptively connected to NIV (BiPAP, Vision; Philips Respironics Inc., Murrysville, PA) immediately following tracheal tube removal, for a period of at least 4 hours, unless contraindications were present. NIV overall duration was not prespecified and was therefore determined according to clinical criteria defined by the ICU staff.

Data Collection:

Data regarding to baseline characteristics and demographical variables were collected by study personnel, using medical records and clinical appraisal.

To minimize observer bias, data collection regarding SBT itself was performed at bedside by respiratory therapists in charge of the patient weaning process, using standard collection charts. The decision to proceed extubation after the 30-minute interval was done in the same fashion, by the multidisciplinary team caring to the patient, and had not been influenced by study investigators.

All patients were followed until hospital discharge, death, or tracheostomy procedure.

Study Outcomes:

The primary outcomes were (1) Total MV days, calculated as the time interval between the intubation day and one of the following: successful extubation (for at least 48 hours without invasive ventilatory support), death while in MV, or tracheostomy procedure; and (2) post-SBT MV duration, defined as the interval between the day the first SBT was performed and the ocurrence of one of the three aforementioned limiting events. Once post-SBT duration could be measured only for individuals not successfully extubated at their first SBT, this outcome was restricted to the previously classified difficult weaning population (20).

Secondary outcomes were to identify potentially associated factors with post-SBT duration and 48-hour failure rate. Other evaluated secondary outcomes included first SBT extubation rate, overall reintubation rate, tracheostomy incidence and ICU mortality.

Statistical Analysis:

Sample size was calculated considering the mean MV duration in COPD patients admitted to the Hospital Nossa Senhora da Conceição ICU (5.8 ± 2.44 days). Hence,

the enrollment of 190 patients would provide an 80% power for detecting a reduction of 1 day of total MV duration.

Continuous variables were reported as means ± standard deviation or medians and interquartile range, according to normality criteria. Categorical variables are shown as frequencies and proportions. Baseline between-group differences were analyzed with t-test for two independent samples or Wilcoxon-Mann-Whitney *U* test according to normality criteria; Fisher exact test was applied to categorical variables.

The primary analysis were unadjusted, intention-to-treat comparisons between the two study groups regarding the two primary outcomes of total MV duration and post-SBT interval. These data were all positively skewed representing violation of one of the assumptions on which ordinary least square models are based. Therefore, we adopted generalized linear models and specified that data follow a gamma distribution and a log link function. This allowed having the proportional impact of the T-piece strategy over PSV: the effect size measure used for primary outcomes was, therefore, mean ratios.

For unadjusted 48-hour reintubation rate secondary outcome, we created Poisson linear models with robust estimation. Outputs from this analysis are then summarized as Risk Ratios.

Multivariate generalized linear models were constructed for identifying variables independently associated with post-SBT duration and 48-hour reintubation rate. For both multivariate analysis, study group was maintained as interest variable. *A priori* defined external factors were variables previously reported in literature to be associated with these outcomes or those plausibly associated: age, SAPS score, CO2 retention status, fluid balance and pre-SBT duration. Besides, we included any variable that resulted in p-value under 0,20 in univariate analysis. Regression was then constructed through backward method, excluding non-significantly associated variables at each step, until accomplishing final model.

All the analysis were made using IBM SPSS Statistics software, version 20.0 (IBM corp., Armonk, NY, USA). Statistical significance was set at 0.05.

Interim analysis in 6-month intervals were conducted by investigators for security concerns.

Results:

Between 2012 and 2016, 292 COPD patients underwent MV for more than 48 hours and were, therefore, screened for eligibility. Among them, 190 fulfilled inclusion / exclusion criteria and were randomized, as depicted in Figure 1; ninety-nine patients were submitted to T-piece SBTs and 91 to PSV SBT.

Baseline characteristics of study population are shown in Table 1. Patients enrolled in the two study groups were similar according to clinical and demographic variables, including SAPS III severity score, CO2 retention and fluid balance. Physiological and biochemical parameters at 0 and 30 minutes of SBT performance were registered and not associated with trial outcome, with the exception of 30-minute RSBI. Five patients (2,7%) had contraindications for NIV (somnolence = 1; NIV unavailable = 1; facial abnormalities = 2; physician disagreement = 1) and hence did not received such adjunctive therapy.

MV stages are demonstrated in Table 2. Owing to a baseline imbalance, patients allocated to T-piece group had a longer pre-SBT interval (a variable not affected by the intervention itself) than PSV group: 7.35 versus 5.84 days ($p = 0.002$). Total MV duration (a variable that incorporate pre-SBT interval) for T-piece and PSV groups was, thereby, also different: 10.82 and 7.31 days, respectively ($p < 0.001$). For difficult weaning subgroup ($n = 71$), mean post-SBT MV duration was 8.36 days for T-piece and 4.06 days for PSV, resulting in unadjusted mean ratio of 2.06 (95% CI 1.29 - 3.27; $p = 0.003$). The proportion of difficult weaning patients did not differ according to study group (39.4% for T-piece and 35.2% for PSV; $p = 0.553$).

Secondary outcomes are shown at Table 3. We did not identify any significant differences between study groups regarding to extubation at first SBT, 48-hour failure rate, overall reintubation rate, tracheostomy incidence or ICU mortality.

We then constructed a generalized linear model aiming to identify variables associated with Post-SBT duration, including only patients classified as difficult weaning (n = 71; Table 4). In univariate analysis, besides T-piece study group, male gender (1.71 [1.05 - 2.79]; p = 0.031) was associated with longer post-SBT duration. When controlling for other important variables (age, SAPS score, CO2 retention status, fluid balance and pre-SBT duration), only study group remained independently associated with post-SBT duration (1.96 [1.18 - 3.24]; p = 0.009). In post-hoc analysis, we excluded two outliers in T-piece group and the results remained unchanged (1.65 [1.04 - 2.63]; p = 0,034). We developed an additional model for this analysis including two important variables that could bias these results: tracheostomy incidence and ICU mortality. Even in this scenario, T-piece group maintained association with longer post-SBT duration (1.92 [1.21 - 3.03]; p = 0.005).

In a secondary analysis, we aimed to identify variables associated with 48-hour extubation failure rate through a Poisson regression model (Table 5). In univariate analysis, male gender (1.99 [1.16 - 3.39]); p = 0.012) and Pre-SBT duration (1.07 [1.02 - 1.14]; p = 0.007) were associated with the outcome. In multivariate analysis, both variables retained independent association: (1.93 [1.14 - 3.26]; p = 0.014) and (1.07 [1.01 - 1.14]; p = 0.03), respectively. Study group, however, was not associated with this outcome in any step of these analysis.

Discussion:

The main result of this multicentric, randomized, controlled trial, was that, for difficult weaning COPD patients, T-piece SBTs were associated with longer MV duration after first SBT attempt. This finding revealed itself consistent in multivariate analysis,

retaining significant association when adjusting for different models and when censoring outliers that could influence the results.

The decision to proceed with two adjustment models in our multivariate analysis was determined by our outcomes definition, considering completion of MV duration when one of the terminating events occurred: successful extubation (for at least 48 hours), death in MV, or tracheostomy procedure. Indeed, a major finding of this study is that post-SBT duration is associated with study allocation group, independently of important clinical variables included in model 1 and even of tracheostomy or ICU mortality (model 2).

This aspect, taken in conjunction with the finding that 48-hour or even overall reintubation rate are unaffected by SBT technique, indicate that T-piece should not be considered first option for these patients, thus favoring PSV strategy. This could be of relevance when choosing which is the best way to proceed extubation for this severely ill subgroup.

Total MV duration, the other primary outcome of this study, also differed according to study groups, with longer duration in T-piece patients. This aspect, however, could be completely attributed to a baseline imbalance we faced in pre-SBT MV duration. Therefore, we focused our post-hoc analysis and discussion in post-SBT duration, a variable not directly affected by this casual shortcoming.

Many physiological, experimental and even interventional studies have recognized T-piece SBT as a more demanding test, challenging patients to deal with additional ventilatory, hemodynamic and even inflammatory burden. This could be of interest regarding test specificity, but might be too hard to overcome for some patients that in fact could achieve successful extubation through other ways. This should be even more important as patient's severity increases. For difficult weaning COPD patients, T-piece choice culminate in applying the most stressful trial for the most frail population, a combination that shall determine unfavorable outcomes.

Other authors had already demonstrate that PSV could be a superior approach over T-piece for performing SBTs for heterogeneous critically ill population. Brochard et al. (22) compared 3 different strategies for gradual weaning from mechanical ventilation for difficult weaning patients. Beyond T-piece and PSV, the authors randomly assigned subjects to a third group using gradual titration of synchronized intermittent mandatory ventilation. T-piece SBTs were performed up to 8 times a day, progressing from 5 to 120 minutes in progressive steps. Subjects assigned to the PSV group, had their PSV level systematically adjusted 2 times per day to maintain a breathing frequency between 20 and 30 breaths per minute in decremental steps of 2 – 4 cmH_2O. These authors reported a lower failure rate with PSV approach, as well as a significantly lower weaning duration, compared to the other strategies evaluated.

Esteban et al. (23), however, compared, in a difficult weaning population, once-a-day T-piece SBTs with 3 other methods: intermittent mandatory ventilation, intermittent trials of spontaneous breathing (conducted two of more times a day if possible), and PSV. These authors encountered a higher rate of successful weaning for the T-piece group, making these strategy about twice as quickly as PSV in terms of weaning duration.

The above mentioned studies included SBTs as part of weaning protocols, making those results hard to incorporate in our current practice, where SBTs gained itself a central role, even as a cornerstone of the decision-making process of extubation. More recently, Matic et al. (24) randomized 260 patients for 120 minutes of PSV of 8cmH2O or T-piece (10% of whom with COPD) and reported that, for the whole study population, both tests had similar performance in terms of the rate of successful weaning; for the difficult weaning subgroup (30 patients in each study group), however, the authors identified a lower duration of MV support, and even a lower ICU length of stay favoring PSV strategy.

The same group published years later a similar study, now enrolling exclusively COPD patients (19) ventilated for more than 24 hours for PSV (n = 70) or T-Piece (n = 66). Failure to tolerate the test itself was similar between study groups (46 and 47%, respectively). Nevertheless, for patients who had at least one trial failure, superiority was identified for PSV over T-piece in terms of weaning duration, total MV duration, and ICU length of stay. Overall, these results appear in line with ours, notwithstanding it was a unicentric study whose authors did not standardize post-exubation NIV utilization and did not report its incidence, nor had their results adjusted for potential confounders, making those results difficult to translate to current clinical practice.

Our group recently published a systematic review with meta-analysis of randomized controlled trials that compared PSV to T-piece for weaning patients (17). Among our *a priori* defined analysis was COPD condition. Of the twelve included studies only two enrolled exclusively COPD patients (18, 19). However, we identified remarkable clinical heterogeneity that prevented pooling.

Pre-SBT interval was independently associated with 48-hour weaning failure rate (RR = 1.07 [1.01 - 1.14], p = 0.03), while allocation group was not. This could be attributable to a series of explanations: first, this could be simply a marker of severity parameters not taken in consideration in SAPS score (ventilatory demand, infection acquisition, refractory bronchospasm), and, thus, correlate to to worse overall prognosis; second, as pre-SBT interval increases, MV duration do so as well, resulting in muscle atrophy, sedation requirements and a series of unintended outcomes mentioned above, potentially contributing to higher extubation failure rates in these patients; third, physician influence toward excessive caution in proceeding weaning in these individuals could be counterproductive, inconsistent to a tendency of systematic and protocolized weaning daily evaluation.

Another variable that we found independently associated with 48-hour failure rate was male gender (1.932 [1.143 - 3.266]), p = 0.014. A number of previous studies pointed out gender-specific behaviors according to susceptibility for development,

severity of, and response to management (25), with a greater prevalence and mortality among men, although this trend could be currently in modification (26), potentially reflecting tobacco prevalence patterns. Genetic (27) and hormonal (28) factors may also play a role in these discrepancies. Phenotypically, men tend to behave as emphysematous, while women tend to manifest overt airway responsiveness and bronchitis. Comorbidities profile are also unequal: among men, ischemic heart disease, alcoholism and cancer are more common, while osteoporosis, reflux disease, and psychiatric disorders prevail. Previous evidence suggest that women are more prone to exacerbations (29), although there are conflicting data in this subject (30). However, Gonzales et al. (31), in a recent report of a Canadian registry comprising more than 40,000 individuals after their first COPD-related hospitalization, found that male sex was associated with a significantly increased risk of death (adjusted HR = 1.45 [1.42 to 1.49]). To the best of our knowledge, our results concerning a sex-specific prognostic profile for critically ill COPD patients are still unique.

Strengths and Limitations:

Our study has several limitations. First, casual imbalance in baseline pre-SBT duration between study groups precluded more definitive conclusions concerning total MV duration, a variable traditionally related to quality of care, even in a wider scope that goes beyond weaning itself, sometimes reflecting even unit organizational policies. However, we decided to include pre-SBT interval in every multivariate modeling, allowing us to conclude about other relevant outcomes. Second, outcomes definitions are not uniform concerning weaning and SBT studies. More than classic hard outcomes such as mortality or ICU and/or hospital stay, these trials usually assess end points like weaning success (i.e. ability to tolerate a SBT and proceed extubation), extubation success (usually defined as 48 hours without ventilatory support, although variable definitions coexist) and duration of ventilatory support according to the stage of weaning (17). We, as others (19, 22, 23), decided to focus on the expeditiousness of weaning process that could be provided by an adequately chosen SBT. Duration of MV support is a widely adopted parameter of efficiency in weaning procedure, both by preventing

ventilator-associated events (e.g., ventilator-associated pneumonia, muscle deconditioning, sedation requirements) and by cost rationalization and allocation of limited resources (32), both for medical and surgical patients (33). Finally, difficult weaning subgroup consisted of a small fraction of study population, making our results concerning SBT strategy performance not generalizable for the whole COPD ventilated population.

We also had numerous strengths providing our results confidence: this was a multicentric study, reflecting different organizational policies and patient profiles, and should be considered representative to the population of university, community and public hospitals. Also, NIV standardization as part of the study protocol assured that the results encountered are not influenced by the use of this potentially adjunctive intervention, once it was adopted to every included individual. This protocol was conducted in a pragmatic way, focused in reflecting concrete weaning practices in recruiting ICUs; according to this, the study intervention concentrated the protocol-driven actions: other important factors, as extubation decision (or even posterior reintubation), as well as NIV duration were all left at physician and therapists discretion, perhaps making our results even more consistent. Multivariate analysis were conducted with rigorous statistical methods, applying the most appropriate tools according to data behavior. Our results remained consistent even when adjusting for several important clinical factors and even different models, providing our result robustness.

Conclusion:

In this multicentric, randomized controlled trial, T-piece SBT was independently associated with longer post-SBT MV duration in difficult-weaning COPD patients, not influencing overall or 48-hour reintubation rates. PSV SBT should be therefore considered first choice for this severely ill subgroup. For the whole COPD population, SBT strategy did not influence any of the evaluated outcomes.

7.1 REFERÊNCIAS DO ARTIGO 1

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7.2 TABELAS DO ARTIGO 1

Table 1: Baseline characteristics of study population *

Characteristic	T-piece (99)	PSV (91)
Age — years	67.99 ± 11.37	67.30 ± 9.83
Male sex — n (%)	52 (52.2)	50 (54.9)
Setting from which patient was admitted to iCU — n (%)		
Emergency room	56 (57.1)	44 (49.4)
Ward	32 (32.7)	37 (41.6)
Others	10 (10.1)	8 (8.8)
ICU admittance diagnosis — n (%)		
Respiratory	53 (54.1)	50 (56.2)
Sepsis	30 (30.6)	24 (27)
Others	15 (15.1)	15 (16.5)
SAPS III score	68.04 ± 12.36	67 ± 14.28
Comorbidities — n (%)		
Stage IV Heart Faiure	11 (11.1)	6 (6.7)
Immunossupression	4 (4.0)	4 (4.5)
CO2 retention — n (%)	69 (70.4)	55 (61.8)
Tracheal intubation indication — n (%)		
Bronchospasm	40 (40.4)	36 (40.4)
Pneumonia	35 (35.4)	34 (38.2)
CNS depression	8 (8.1)	7 (7.9)
Others	16 (16.1)	12 (12.8)
24h pre-SBT fluid balance — ml	128.52 ± 1436	375. 73 ± 1428

* Plus-minus values are means ± SD. There were no significant differences between the two groups in any of the characteristics listed. PSV denotes Pressure-Support Ventilation, ICU intensive care unit, SAPS simplified acute physiology score, CNS central nervous system and SBT spontaneous breathing trial.

Table 2: Mechanical ventilation stages

Interval	T-piece (99)	PSV (91)	Unadjusted Mean Ratio	*p*
pre-SBT no. 1 — days	7.35 ± 3.9	5.84 ± 3.3	1.28 (1.10-1.49)	0.002§
Difficult Weaning — n (%)	39 (39.4)	32 (35.2)	-	0.553¶
post-SBT no.1 — days †	8.36 ± 11.04	4.06 ± 4.94	2.06 (1.29-3.27)	0.003§
total MV duration — days	10.82 ± 9.1	7.31 ± 4.9	1.48 (1.22-1.80)	< 0.001§

Data are presented as mean ± standard deviation or number (percentage). PSV denotes Pressure-Support Ventilation, SBT spontaneous breathing trials and MV mechanical ventilation.

§ Univariate Generalized Linear Model considering Study Group as a predictor for each outcome, PSV as reference. *p*-values refer to Omnibus test.

† For difficult weaning subgroup, n = 71.

¶ Fisher's exact test

Table 3: Secondary outcomes

Outcome	T-Piece (99)	PSV (91)	Risk Ratio (95% CI)	*p*
Extubation at first SBT — n (%)	78 (78.8)	71 (78.8)	1.01 (0.73-1.39)	0.953
48-hour failure rate — n (%)	28 (29.5)	22 (24.2)	1.22 (0.70-2.13)	0.485
Overall reintubation rate — n (%)	35 (36.8)	40 (44)	0.84 (0.53-1.32)	0.445
Tracheostomy — n (%)	22 (22.2)	15 (16.5)	1.35 (0.70-2.60)	0.369
ICU mortality — n (%)	26 (26.5)	25 (28.4)	0.93 (0.54-1.61)	0.807

Data are presented as number (percentage). PSV denotes Pressure-Support Ventilation, CI confidence interval, SBT spontaneous breathing trials and ICU intensive care unit. All *p*-values refer to univariate Poisson regression model.

Table 4: Gama log link models for Post-SBT MV duration outcome

Variable	Post-SBT days (mean ± SD)	unadjusted analysis ¶	*p*-value	Adjusted - Model 1 *	*p*-value	Adjusted - Model 2 **	*p*-value
Study group							
T-piece	8.36 ± 11.04	2.06 (1.29-3.27)	0.002†	1.96 (1.18 - 3.24)	0.009‡	1.92 (1.21 - 3.03)	0.005‡
PSV	4.06 ± 4.94	1.00		1.00		1.00	
Gender							
Male	7.58 ± 10.53	1.71 (1.05 - 2.79)	0.031†	1.70 (0.99 - 2.89)	0.051‡	1.42 (0.85 - 2.35)	0.176‡
Female	4.42 ± 5.18	1.00		1.00		1.00	

* Model 1 refers to adjustment for the following variables: age, simplified acute physiology score score, CO2 retention status, 24 hours fluid balance and pre-SBT duration.

** Model 2 refers to Model 1 plus Tracheostomy and ICU death.

¶ Data presented as Mean Ratios (95% CIs).

† Omnibus test.

‡ Wald test.

Table 5: Poisson models for 48-hour failure rate outcome

Variable	incidence — n (%)	unadjusted analysis ¶	*p*-value †	adjusted analysis ¶ *	*p*-value ‡
Study group					
T-piece	28 (29.5)	1.32 (0.81 - 2.17)	0.265	1.19 (0.73 - 1.94)	0.478
PSV	22 (24.2)	1.00			
Gender					
Male	35 (35.0)	1.99 (1.16 - 3.39)	0.012	1.93 (1.14 - 3.26)	0.014
Female	15 (17.4)	1.00			
Pre-SBT duration	-	1.07 (1.02 - 1.14)	0.007	1.07 (1.01 - 1.14)	0.003

* Model adjusted for the following variables: age, simplified acute physiology score score, CO2 retention status and 24 hours fluid balance.
¶ Data presented as Risk Ratios (95% CIs).
† Omnibus test.
‡ Wald test.

7.3 FIGURAS DO ARTIGO 1

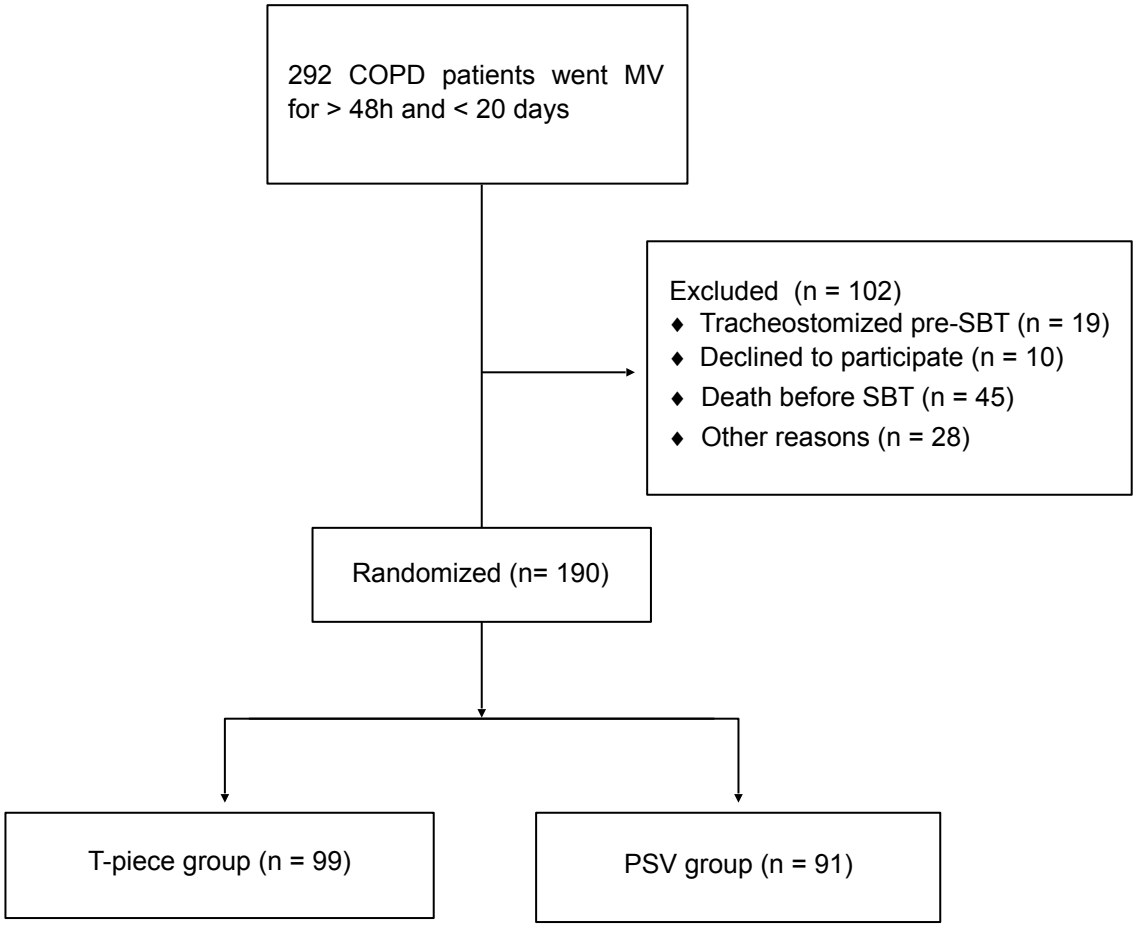

Figure 1: Patients enrollment and randomization.

8 ARTIGO II

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Spontaneous Breathing Trials with T-piece or Pressure Support Ventilation

Running Head: T-Piece or PSV: a Systematic Review of RCTs

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Competing Interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Contributions of authors

Drs. Pellegrini and Teixeira had full access to all data and take responsibility for the integrity of data and the accuracy of final data analysis. Drs. Pellegrini and Moraes independently extracted the data and consulted Dr. Teixeira when in disagreement. Dr. Ribeiro was responsible for epidemiologic consultation and data interpretation. Drs. Oliveira, Maccari, Savi and Burns contributed substantially to the study design, data analysis and interpretation and the writing of the manuscript.

Abstract

Spontaneous Breathing Trials (SBTs) are among the most commonly employed techniques to proceed weaning from mechanical ventilation (MV). The preferred SBT technique, however, is still unclear. To clarify the preferable SBT [T-piece or pressure support ventilation (PSV)], we conducted this systematic review.

We then searched MEDLINE, EMBASE, SciELO, Google Scholar, CINAHL, ClinicalTrials.gov, and Cochrane CENTRAL databases through June 2015, without language restrictions. We included randomized controlled trials involving adult patients being weaned from MV comparing T-piece with PSV and reporting (a) weaning failure, (b) reintubation rate, (c) intensive care unit (ICU) mortality or (d) weaning duration. Anticipating clinical heterogeneity among the included studies, we compared pre-specified subgroups: (a) simple, difficult or prolonged weaning; and (b) chronic obstructive pulmonary disease (COPD) patients. We summarized quality of evidence for intervention effects using the GRADE methodology.

We identified 3674 potentially relevant studies and reviewed 23 papers in full. Twelve studies (2161 patients), met our inclusion criteria. Overall, the evidence was of very low to low-quality. SBT technique did not influence weaning success [risk ratio (RR) 1.23 (0.94 – 1.61)], ICU mortality [RR 1.11 (0.80 – 1.54)] or reintubation rate [RR 1.21 (0.90 – 1.63)]. Pre-specified subgroup analysis suggested that PSV might be superior to T-piece with regard to weaning success for simple weaning patients [RR 1.44 (1.11 – 1.86)]. For prolonged weaning subgroup, however, T-piece were associated with a shorter weaning duration [WMD – 3.08 days (- 5.24, - 0.92)]. In conclusion, low-quality evidence is available concerning this subject. PSV may be associated with lower weaning failure rates in simple weaning subgroup. In contrast, in prolonged weaning patients, T-piece may be related with a shorter weaning duration, although this is at high risk of bias. Additional study of the difficult weaning and COPD subgroups is required.

Keywords: weaning; mechanical ventilation; critical care

Introduction

Successful weaning of patients from mechanical ventilation (MV) constitutes one of the most challenging tasks for intensive care unit (ICU) practitioners. Timely identification of patients who are capable of spontaneous breathing (SB) can shorten the MV duration and potentially reduce MV-related complications.[1-5]

Once a patient is deemed ready to breathe spontaneously, a screening test, called a spontaneous breathing trial (SBT), is usually performed, although the literature remains conflicting on this subject.[6-10] A SBT is typically performed by disconnecting the patient from the ventilator and attaching a T-piece to the endotracheal tube.[11] Some clinicians, however, prefer to use low levels of pressure support ventilation (PSV), or automatic tube compensation (ATC).[8]

Switching from continuous mandatory ventilation to SB can decrease left ventricular performance and unmask latent left ventricular heart failure (LVHF). Concerns exist regarding the potential for SBT failure rates to be higher with T-piece SBTs than with low levels of PSV, possibly because of the increased expenditure of respiratory muscle energy[12] and cardiogenic pulmonary edema secondary to the Muller maneuver.[13] While PSV may be a less demanding SBT with regard to respiratory muscle effort and hydrostatic homeostasis, especially with the addition of PEEP to prevent the development of LVHF, it may also dull the clinical picture of intolerance compared with that of unassisted T-piece SBTs.[13]

Many trials have previously assessed this question, although heterogeneous methodological aspects and conflicting results limits adequate evidence appraisal. Previous metanalyses have been conducted in this field, but did not directly compared SBTs or demand for updated information.[14]

Objectives

To clarify the preferred SBT technique [T-piece or low levels of PSV] for critically ill patients weaning from MV according to ICU mortality, reintubation rates, weaning failure and weaning duration.

Methods

We conducted a systematic review based on standard methods and reported our findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15]

Data sources and searches

We aimed to identify all randomized controlled trials (RCTs) assessing the efficacy and outcomes of T-piece compared with PSV trials in adult patients weaning from invasive MV.

We conducted electronic searches of MEDLINE, EMBASE, Cochrane CENTRAL, CINAHL, SciELO, Google Scholar, and the ClinicalTrials.gov database for studies actively recruiting patients. All databases were searched from their inception to June 2015. Our MEDLINE search included the following terms and keywords: ("weaning" OR "Ventilator Weaning"[Mesh]) AND ("Mechanical Ventilation" OR "Respiration, Artificial"[Mesh]) AND (“spontaneous breathing trial” OR "T piece" OR "t tube"), using the Robinson and Dickersin RCT filter for PubMed.[16] The electronic search strategy applied standard filters for the identification of RCTs from each database. We screened the reference lists of retrieved publications for potentially eligible trials. We did not apply language restrictions.

Study selection

We restricted our analysis to RCTs aiming to limit potential sources of bias. We excluded crossover trials and quasi-randomized trials. Regardless of specific weaning protocols, included trials had to compare between T-piece and PSV for conducting SBTs. We considered T-piece SBT to be the procedure of temporarily disconnecting a patient from the ventilator while maintaining an external oxygen supply, commonly by using a T-piece connected to the endotracheal tube. PSV was considered to be an SBT when employed in a systematic fashion, following a predefined protocol specifically designed to identify patients for extubation or, in the case of tracheostomized patients, for definitive removal from MV.

Outcome measures

The outcomes assessed included the following: (a) ICU mortality; (b) the rate of reintubation within 48 h following extubation; (c) weaning failure (WF) precluding extubation; and (d) the weaning duration. We used authors' definitions for the post-randomization weaning duration.

Data extraction and quality assessment

Two independent reviewers (JP and RM) screened the titles and abstracts of retrieved citations and the full texts of potentially eligible studies to identify trials that met our inclusion criteria. Data from each potentially relevant trial were independently extracted by the reviewers using a predefined data extraction form.

According to Cochrane risk of bias tool, we appraised the adequacy of random sequence generation, the reporting of allocation concealment, the blinding of participants and outcome assessments, the descriptions of losses to follow-up and exclusions; we still assessed adherence to the intention-to-treat principle. We solved disagreements by consulting a third reviewer (CT) when needed.

Data synthesis and analysis

Qualitative analysis

We used a narrative summary approach to qualitatively describe the study characteristics and variations in quality indicators and to consider how these factors affected our understanding of the outcomes of the included RCTs.

Quantitative analysis

We used the Cochrane Collaboration guidelines to conduct our meta-analysis.[17] All statistical analyses were performed with Review Manager, version 5.3 (*The Nordic Cochrane Center, Copenhagen, Denmark*), the Cochrane Collaboration's software for preparing and updating Cochrane systematic reviews. We expressed the pooled effects estimates for binary and continuous variables using risk ratios (RRs) and weighted mean differences (WMDs) with 95% confidence intervals (CIs).

We tested for heterogeneity between studies using the *Cochran Q* and I^2 tests. We predefined statistical heterogeneity as being low, intermediate or high, correlated to I^2 statistics less than 25%, from 25% to 50%, or greater than 50%, respectively.[17] Meta-analyses with random-effects models were employed for all outcomes, owing to anticipated clinical heterogeneity in terms of patient populations. We attempted to identify clinical factors as potential sources of heterogeneity assessing for pre-specified subgroups, including (a) weaning difficulty (simple, difficult or prolonged weaning), and (b) COPD (vs. non-COPD patients).

To assess the potential publication bias from small study effects, we constructed funnel plots displaying the *log* RR on the horizontal axis and the standard error of the *log* RR on the vertical axis. We employed Egger's test to evaluate the risk for publication bias. We summarized the quality of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines[18] and reported them using the GRADE pro web-based tool.

Results

Study selection

Our initial electronic search identified 3674 abstracts. Of these, we excluded 3651 because they did not describe RCTs, did not evaluate weaning techniques, were duplicate references, or were not relevant. We retrieved 23 studies for a more detailed, full-text analysis, and we excluded 11 of these studies[19-29] (Figure 1). We then identified 12 suitable studies comprising 2161 patients. Both reviewers completely agreed on the final selection of included studies. We also identified two ongoing RCTs, including one from our group, from the ClinicalTrials.gov database (Pellegrini, https://clinicaltrials.gov/ct2/show/study/NCT01464567; Agarwal, https://clinicaltrials.gov/ct2/show/NCT00911378?term=spontaneous+breathing+trial+and+weaning&rank=3).

Study description

The included studies were published between 1994 and 2015 and were from 10 countries. Eight of the 12 included studies were single center studies.[30-37] One study was published only in abstract form,[37] and full details of the study were not available to the authors of this review.

Table 1 summarizes the components of the risk of bias assessment. Due to the nature of the intervention being studied, all studies were unblinded with regard to the patients enrolled and the outcomes assessed. Only three studies specified adequate random sequence generation, and seven studies did not report adherence to the intention-to-treat principle. Our qualitative analysis of key study characteristics is summarized in Table 2.

Outcomes assessed

All but two trials[31] included in the study reported WF outcome, which was defined as failure to extubate the patient immediately following the SBT. All but one[36] study, apart from those assessing only tracheostomized patients, reported 48-hour reintubation rates. Eight studies reported ICU mortality.[32-40]

Study protocols

Brochard et al.[38] compared three different strategies for gradual weaning from MV. Beyond T-Piece and PSV, the authors randomly assigned patients to a third group using gradual titration of synchronized intermittent mandatory ventilation (SIMV). T-Piece SBTs were performed up to eight times a day, progressing from 5 to 120 minutes in progressive steps. In patients assigned to the PSV group, the PSV level was systematically adjusted two times per day to maintain a respiratory rate between 20 and 30 breaths per minute in decremental steps of 2 to 4 cmH_2O. Esteban et al.[41] compared once-a-day T-piece SBTs with three other methods, including intermittent mandatory ventilation (IMV) and SIMV in addition to PSV.

The study by Vitacca et al.[40] differed from the other included studies by enrolling only chronic obstructive pulmonary disease (COPD), difficult weaning, and tracheostomized patients who required MV for at least 15 days. This trial was conducted in three long-term weaning units, with patients transferred from 24 ICUs after a range of 15 to 39 days on MV. The authors also compared their results with historical controls, or an “uncontrolled clinical practice”. Jubran et al.[34] assessed a similar population. Patients who required MV for more than 21 days in a long-term weaning unit were randomly assigned to unassisted breathing through a tracheostomy collar or to progressive reductions in PSV based on their respiratory rates.

Six studies included simple weaning patients, according to previously published definitions.[2, 30-32, 35, 36, 39] Three studies assessed difficult weaning patients, [33, 38, 41] and two studies included prolonged weaning and tracheostomized patients.[34, 40] Two additional studies evaluated post-operative patients.[35, 37]

In the studies that predefined the SBT duration, a 120-minute trial was most commonly employed (7 studies). Three authors reported progressively increasing duration of SBTs based on patient tolerance.[34, 38, 40]

Although included in various trials, COPD patients represented only a small fraction of the study population. Only two of the included studies specifically assessed COPD patients;[33, 40] one of these also specifically enrolled prolonged weaning patients.[40]

Evidence synthesis

T-piece SBTs were associated with an RR (95% CI) of 1.11 (0.80 – 1.54) for ICU mortality and 1.21 (0.90 – 1.63) for the 48h-reintubation rate and (Figures 2 and 3). The evidence from trials addressing these outcomes was considered very low to low-quality based on the GRADE approach (Table 3). Study limitations, inconsistency and imprecision contributed to downgrading the overall quality of evidence in the pooled RCTs.

For WF, we found an RR of 1.23 (0.94 – 1.61) (Figure 4), with moderate to high heterogeneity (I^2 = 48%). When evaluating potential sources of clinical heterogeneity, we excluded prolonged weaning studies from our analysis (8 studies remaining; 1237 patients) and noted an RR of 1.47 (1.17 – 1.84) favoring PSV with regard to weaning success. The I^2 statistic for this analysis was 0%, suggesting that prolonged weaning studies represent an important source of clinical heterogeneity.

Subgroup analyses

Weaning difficulty

Seven studies (1600 patients), focused on simple weaning, which was defined as success on the first SBT in the absence of previous WF. PSV in this population was associated with better outcomes related to weaning success (RR = 1.44, 1.11-1.86; I^2 = 0%) but not with lower reintubation or ICU mortality rates.

Three studies (197 patients) specifically assessed difficult weaning patients. In this subgroup, significant differences in clinical outcomes were not found between the alternative SBT techniques.

Only two studies, comprising 364 patients, focused on prolonged weaning patients. While the SBT technique had no effect on WF rate or ICU mortality, T-piece was associated with a shorter weaning duration [WMD = - 3.08 (- 5.24; - 0.92) days of weaning] than that associated with PSV (Figure 5). These aforementioned outcomes had an $I^2 = 0\%$ in this subgroup.

COPD patients

In the 12 included studies, we identified 338 patients with COPD, although 3 studies did not specifically report this condition.

Between the two studies enrolling exclusively COPD patients, we identified remarkable clinical heterogeneity preventing pooling. While the Matic study[33] included difficult weaning COPD patients (defined as one failed weaning attempt), the Vitacca study[40] included tracheostomized patients ventilated for at least 15 days. The RRs in the Matic and Vitacca studies for WF with T-piece SBTs were 1.61 (0.82 – 3.16) and 0.86 (0.33 – 2.21), respectively, and for ICU mortality were 2.06 (0.41 – 10.47) and 0.67 (0.12 – 3.67), respectively.

We performed funnel-plot analysis for each outcome and did not identify publication bias. The funnel plot for weaning failure is shown in Figure 6. Egger's test did not suggest publication bias (P = 0.367).

Discussion

Summary of evidence

T-piece and PSV are two of the most commonly used techniques when conducting SBTs in clinical practice today. Nevertheless, existing evidence directly comparing these two approaches is sparse, heterogeneous, and of poor overall quality. Small study populations with low event rates, variability among the applied SBT techniques, and remarkably different populations limit the pooling and adequate interpretation of evidence.

T-piece and PSV techniques have theoretical singularities that may influence bedside judgement when choosing one SBT technique over another. When using T-piece SBTs, one might be looking for specificity and thus might proceed with extubation only for those patients able to tolerate the hemodynamic perturbations of this disturbing test.[13, 42] Also, previous studies have shown that the post-extubation work of breathing could be more closely paralleled by unassisted breathing (as in T-piece trial) than by low-PS trial.[43]

By contrast, Ezingeard et al. demonstrated that more patients could be successfully extubated after a PSV SBT, including some patients who previously failed a T-piece SBT.[44] These findings are supported by moderate-quality evidence with regard to simple weaning patients, for whom PSV might be associated with reduced weaning failure rates, not adversely influencing reintubation rates.

In contrast, low-quality evidence suggests that prolonged weaning patients[31, 37] appear to benefit from T-piece SBTs in terms of weaning duration. In these patients, progressive steps toward predetermined reductions in PSV according to patient's tolerance may prolong the duration of MV, potentially increasing the risk for MV-related complications. However, we observed that the few studies including patients who experienced such events found that SBT technique has no influence on mortality in this subgroup.

COPD patients represent a growing population worldwide, remaining as one of the most important reasons for MV.[45-47] These individuals represent some of the most challenging groups to wean from MV;[48] paradoxically, this population is underrepresented in RCTs. Two authors evaluated COPD patients exclusively, but their studies included markedly different profiles. One author[33] enrolled difficult weaning COPD patients, and the other[40] focused on tracheostomized, prolonged weaning patients in long-term weaning units. Recognizing that clinical heterogeneity would hinder the interpretation of findings, we decided not to pool these results.

A relevant aspect that should be kept in mind concerns to the consideration of SBTs as an intervention rather than a diagnostic test trying to identify patients who are potential candidates for extubation, predicting tolerance of unassisted breathing.

In the latter approach, questions focuses on diagnostic accuracy, and then weaning failure or reintubation rates are important endpoints for describing weaning trials sensitivity or specificity.

Nevertheless, the assessment of diagnostic properties of SBTs for predicting successful extubation is not straightforward. Extubation failure rates are widely reported as being around 15 to 20%, which makes specificity of the trial for predicting successful extubation only 80 to 85%. On the opposite side, test sensitivity (the proportion of patients able to tolerate extubation despite failing the weaning test) is difficult to evaluate because patients who fail a weaning test are usually not extubated. Furthermore, criteria for termination of a weaning trial and even definitions of test failure are essentially subjective and clinician-dependent, potentially biasing outcomes beyond test itself.

Accordingly, we decided to stay in line with previous studies and assess the clinical impact of SBTs as an intervention in important outcomes, beyond its diagnostic role in predicting patient tolerance to MV discontinuation.

Overall, our results are consistent with those of a recent Cochrane review[14] and are suitable to the general weaning population encountered by clinicians in clinical practice. Our review, however, adds important additional information from four recently published RCTs, increasing the size of the included population (2161 patients here versus 1208 patients previously analyzed). In addition, we defined an *a priori* subgroup analysis aimed at identifying different effects of the alternative SBT techniques based on weaning difficulty and the presence of COPD. Very low to low overall quality of evidence strongly limits definitive findings in this field.

Strengths and limitations

We conducted a systematic search of several databases without language restrictions to identify all RCTs comparing T-piece and PSV SBT techniques in weaning patients. We employed standardized techniques to assess risk of bias and overall quality of evidence.

Our review has several limitations that reduce the strength of inferences that can be made. First, quality assessment permits classifying the evidence as very low to low-quality. While some aspects of bias assessment are not relevant in this area (e.g., blinding of patients and investigators in necessarily unblinded trials), others such as sequence generation and allocation concealment reveal methodological issues that may impact study findings. Imprecision of available data was an important source of downgrading of evidence for many outcomes. Second, we identified important clinical heterogeneity among studies that hinders the pooling of estimates and limited the generalizability of our findings. Some aspects related to MV settings (different PS levels and protocols, adjunctive use of PEEP) certainly contribute to conflicting results. This could be considered one of the most important issues in this review. Third, subgroup analysis should be interpreted with caution, accordingly to study populations and outcomes reported. Finally, the difficult weaning patient and COPD patient subgroups remain scarcely studied, limiting conclusions in these areas.

Conclusions

Quality of available evidence precludes definitive conclusions about assessed outcomes. Low-quality evidence suggests that PSV SBTs may result in lower WF rates in simple weaning patients but do not affect reintubation rates or other important outcomes. Conversely, in prolonged weaning patients, a T-piece may reduce the weaning duration compared with PSV SBTs. Future trials should compare SBT techniques in difficult weaning and COPD patients.

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8.2 TABELAS DO ARTIGO II

Table 1. Risk of bias assessment

Study	Adequate Sequence Generation	Allocation Concealment	Blinding of Participants and Investigators	Blinding of Outcome Assessment	Description of Losses and Exclusions	Intention to Treat Analysis
Brochard et al[38]	Not clear	SNOSE	No	No	Yes	Yes
Esteban et al[39]	Yes	SNOSE	No	No	Yes	Not clear
Esteban et al[40]	Yes	SNOSE	No	No	Yes	Not clear
Vitacca et al[41]	Not clear	Not clear	No	No	Yes	Not clear
Haberthür et al[30]	Not clear	SNOSE	No	No	Yes	Yes
Koksal et al[31]	Not clear	Not clear	No	No	Yes	Yes
Matić et al[32]	Not clear	SNOSE	No	No	Yes	Yes
Matić et al[33]	Not clear	SNOSE	No	No	Yes	Not clear
Jubran et al[34]	Not clear	SNOSE	No	No	Yes	Yes
Lourenço et al[35]	Yes	No	No	No	Yes	Not clear
Zhang et al[36]	Not clear	Not clear	No	No	No	Not clear
Chittawatanarat et al[37]	Not clear	Not clear	No	No	Not clear	Not clear

SNOSE = sequentially numbered, opaque, sealed envelopes

Table 2. Qualitative analysis of key study characteristics

Study	Multi-Center	Mode of Weaning	SBT Duration (min)	COPD Subjects (%)	Days on Mechanical Ventilation Pre-SBT (Mean ± SD)	Weaning Failure	Re-Intubation Within 48 h	Mortality
Brochard et al[38] ($N = 66$)	Yes	Difficult	120	24	T-piece: 17 ± 31; PSV: 14 ± 17	Yes	Yes	Yes
Esteban et al[39] ($N = 68$)	Yes	Difficult	Up to 120	47	T-piece: 8.4 ± 5.3; PSV: 10.8 ± 8.6	Yes	Yes	No
Esteban et al[40] ($N = 484$)	Yes	Simple	120	20	T-piece: 6 (IQR 4–9); PSV: 6 (IQR 4–12)	Yes	Yes	Yes
Vitacca et al[41] ($N = 52$)	Yes	Prolonged, Tracheostomized	Not prespecified	100	≥15 (range 15–39)	Yes	NA	Yes
Haberthür et al[30] ($N = 60$)	No	Simple	120	10	T-piece: 5.75 ± 3.95; PSV: 6.33 ± 5.91	Yes	Yes	No
Koksal et al[31] ($N = 40$)	No	Simple	120	NR	NR	No	Yes	No
Matić et al[32] ($N = 260$)	No	Simple	120	10	NR	Yes	Yes	Yes
Matić et al[33] ($N = 63$)	No	Difficult	120	100	T-piece: 5.2 (IQR 4.4–6.3); PSV: 5 (IQR 3.7–5.8)	Yes	Yes	Yes
Jubran et al[34] ($N = 312$)	No	Prolonged, Tracheostomized	Not prespecified	13	Trach collar: 34 (IQR 27–45); PSV: 34 (IQR 25–47)	Yes	NA	Yes
Lourenço et al[35] ($N = 28$)	No	Simple, post-surgical	30	10	Post-surgical	Yes	Yes	Yes
Zhang et al[36] ($N = 208$)	No	Simple	30	NR	T-piece: 4.46 ± 3.18; PSV: 4.84 ± 4.11	Yes	No	No
Chittawatanarat[37] ($N = 520$)	No	Simple, post-surgical	NR	NR	NR	No	Yes	Yes

IQR = interquartile range
SBT = spontaneous breathing trial
NR = not reported
NA = not applicable

Table 3. GRADE evidence profile

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects on Study Population	
No. of Participants (Studies) Follow-up	Risk of Bias*	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With PSV	With T-Piece	Relative effect (95% CI)†	Risk With PSV	Risk Difference With T-Piece
ICU mortality											
1,785 (8 RCTs)	Serious	Serious	Not serious	Serious	None	Very low	62/903 (6.9)	71/882 (8.0)	RR 1.11 (0.80 to 1.54)	69/1,000	8 more/1,000 (14 fewer to 37 more)
ICU mortality: simple weaning											
1,292 (4 RCTs)	Serious	Not serious	Not serious	Serious	None	Low	31/662 (4.7)	41/630 (6.5)	RR 1.32 (0.84 to 2.07)	47/1,000	15 more/1,000 (7 fewer to 50 more)
ICU mortality: difficult weaning											
129 (2 RCTs)	Serious	Not serious	Not serious	Serious	None	Low	6/63 (9.5)	12/66 (18.2)	RR 1.86 (0.75 to 4.62)	95/1,000	82 more/1,000 (24 fewer to 345 more)
ICU mortality: prolonged weaning											
364 (2 RCTs)	Serious	Not serious	Not serious	Serious	None	Low	25/178 (14.0)	18/186 (9.7)	RR 0.69 (0.39 to 1.22)	140/1,000	44 fewer/1,000 (86 fewer to 31 more)
ICU mortality: COPD exclusive											
115 (2 RCTs)	Very serious	Serious	Not serious	Serious	None	Very low	5/58 (8.6)	6/57 (10.5)	RR 1.21 (0.37 to 3.91)	86/1,000	18 more/1,000 (54 fewer to 251 more)
Re-intubation rate											
1,589 (9 RCTs)	Serious	Not serious	Not serious	Serious	None	Low	91/812 (11.2)	110/777 (14.2)	RR 1.21 (0.90 to 1.63)	112/1,000	24 more/1,000 (11 fewer to 71 more)
Re-intubation rate: simple weaning											
1,392 (6 RCTs)	Serious	Not serious	Not serious	Serious	None	Low	75/712 (10.5)	92/680 (13.5)	RR 1.29 (0.79 to 2.10)	105/1,000	31/per 1,000 (22 fewer to 116 more)
Re-intubation rate: difficult weaning											
197 (3 RCTs)	Serious	Not serious	Not serious	Serious	None	Low	16/100 (16.0)	18/97 (18.6)	RR 1.21 (0.66 to 2.22)	160/1,000	34 more/1,000 (54 fewer to 195 more)
Weaning failure											
1601 (10 RCTs)	Serious	Serious	Not serious	Serious	None	Very low	194/803 (24.2)	226/798 (28.3)	RR 1.23 (0.94 to 1.61)	242/1,000	56 more/1,000 (14 fewer to 147 more)
Weaning failure: simple weaning											
1,040 (5 RCTs)	Serious	Not serious	Not serious	Not serious	None	Moderate	83/525 (15.8)	115/515 (22.3)	RR 1.44 (1.11 to 1.86)	158/1,000	70 more/1,000 (17 more to 136 more)
Weaning failure: difficult weaning											
197 (3 RCTs)	Serious	Not serious	Not serious	Serious	None	Low	20/100 (20.0)	30/97 (30.9)	RR 1.52 (0.83 to 2.78)	200/1,000	104 more/1,000 (34 fewer to 356 more)
Weaning failure: prolonged weaning											
364 (2 RCTs)	Very serious	Not serious	Not serious	Serious	None	Very low	91/178 (51.1%)	81/186 (43.5)	RR 0.85 (0.69 to 1.05)	511/1,000	77 fewer/1,000 (158 fewer to 26 more)
Weaning failure: COPD exclusive											
115 (2 RCTs)	Very serious	Serious	Not serious	Very serious	None	Very low	16/58 (27.6%)	20/57 (35.1)	RR 1.28 (0.71 to 2.32)	276/1,000	77 more/1,000 (80 fewer to 364 more)
Duration of weaning											
364 (2 RCTs)	Serious	Not serious	Not serious	Serious	None	Low	178	186			MD 3.08 fewer (5.24 fewer to 0.92 fewer)

* Unclear sequence generation in 9 studies as well as allocation concealment in 5 studies; patients or outcome assessors were not blinded in any study; intention to treat analysis in only 5 studies.
† Relative effects (95% CI) are based on random-effect models.
RCT = randomized controlled trial
RR = relative risk
MD = mean difference

8.3 FIGURAS DO ARTIGO II

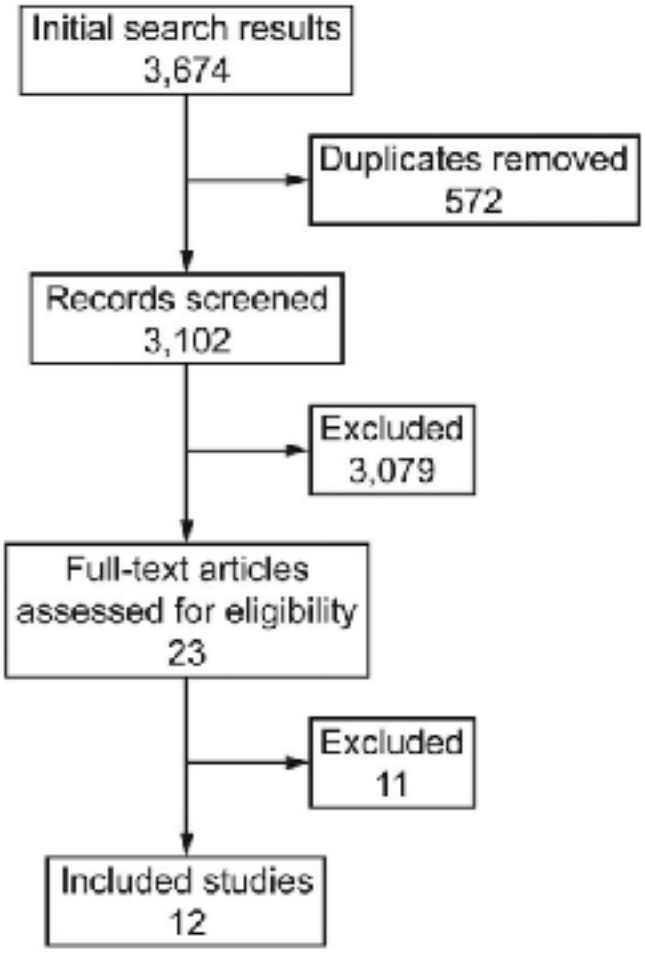

Figure 1. PRISMA flow diagram.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15]

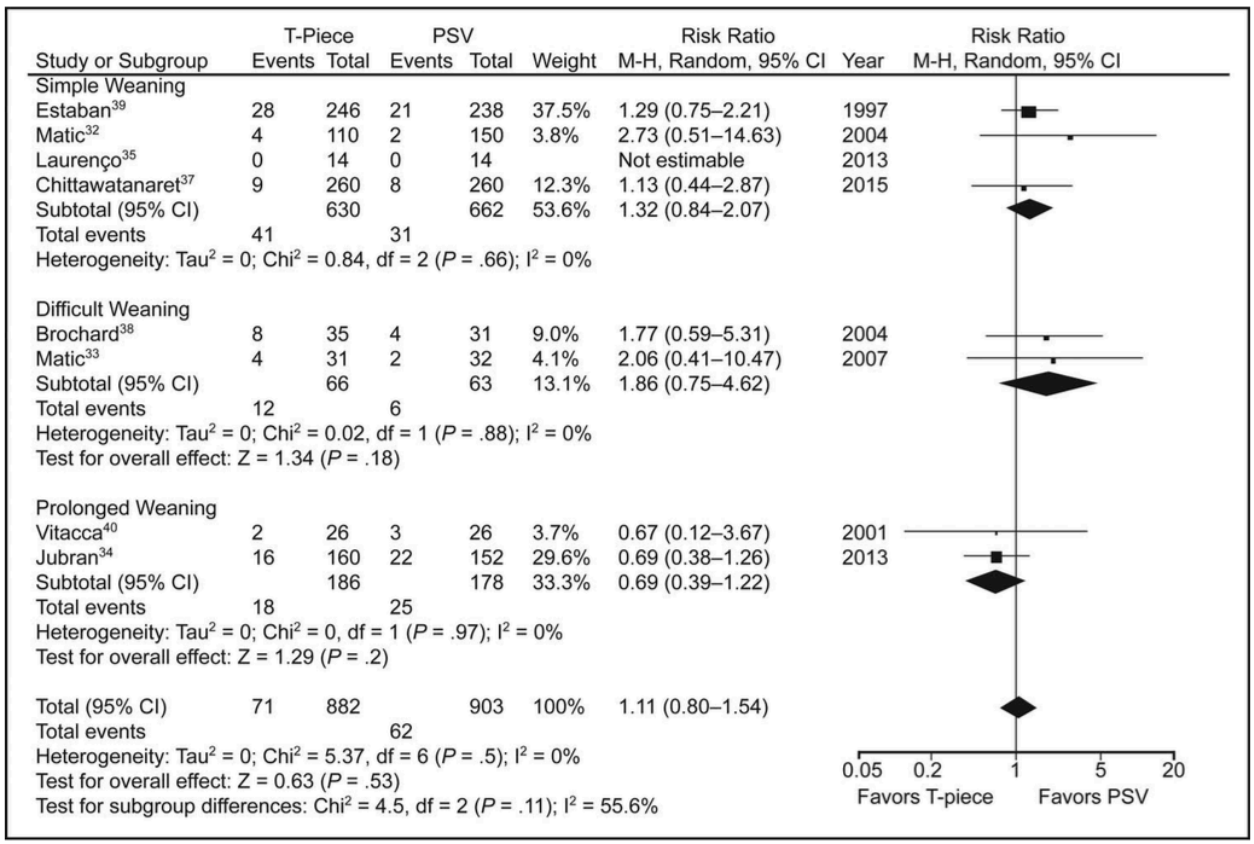

Figure 2. Intensive Care Unit Mortality.

M-H, Maentel-Haentzel; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; PSV, Pressure support ventilation.

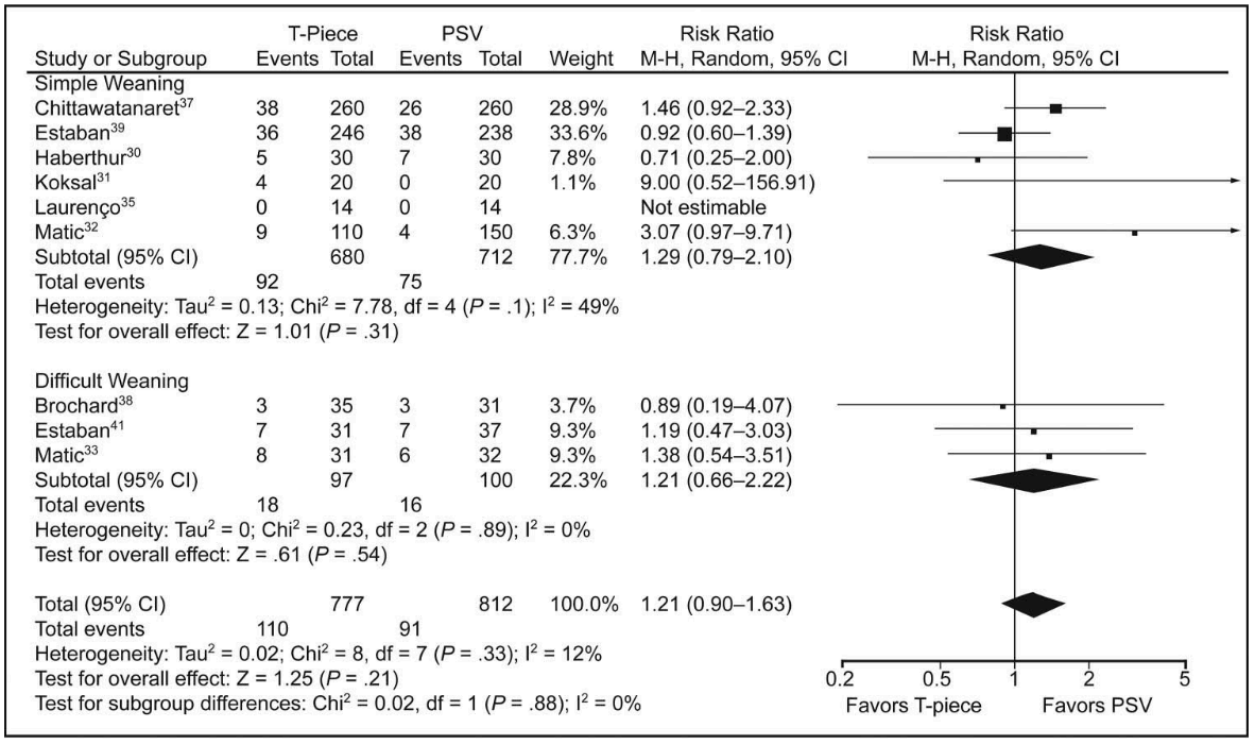

Figure 3. 48-h Reintubation rate.

M-H, Maentel-Haentzel; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; Pressure support ventilation.

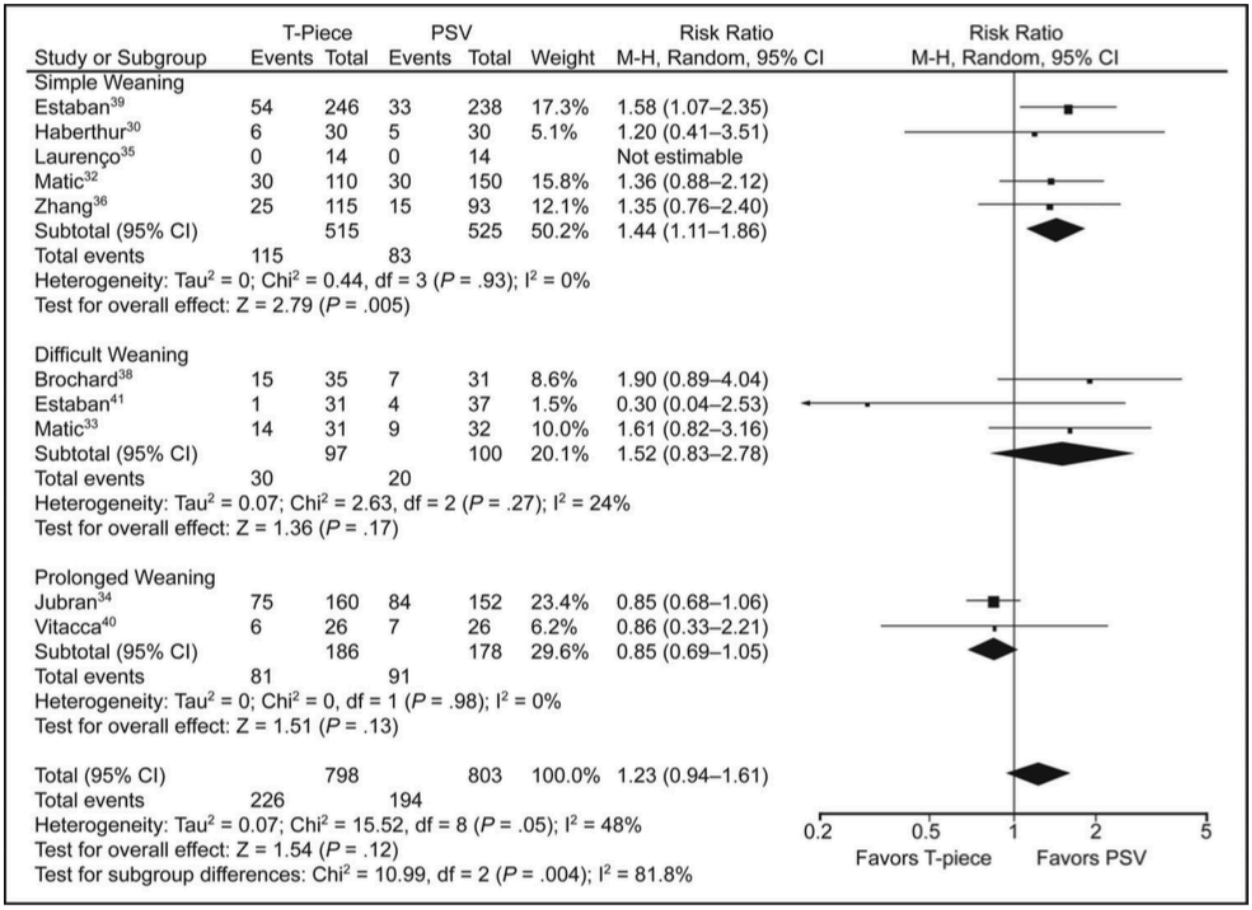

Figure 4. Weaning Failure.

M-H, Maentel-Haentzel; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; PSV, Pressure support ventilation.

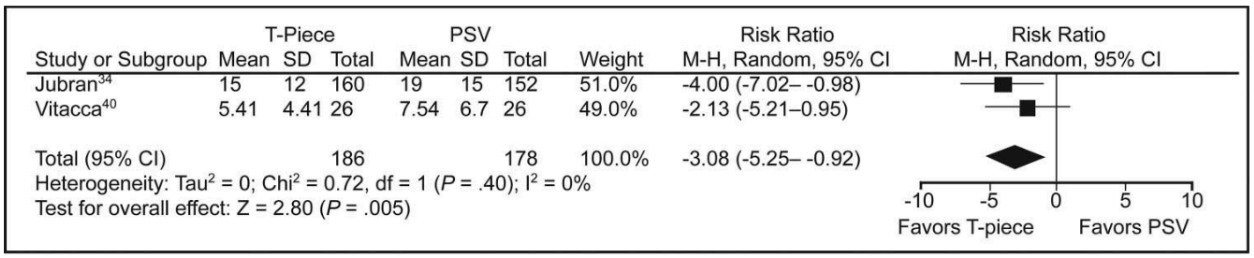

Figure 5. Forest plot of comparison: T-piece versus PSV, weaning duration.

SD, Standard Deviation; IV, Inverse Variance; CI, Confidence Interval; PSV, Pressure Support Ventilation.

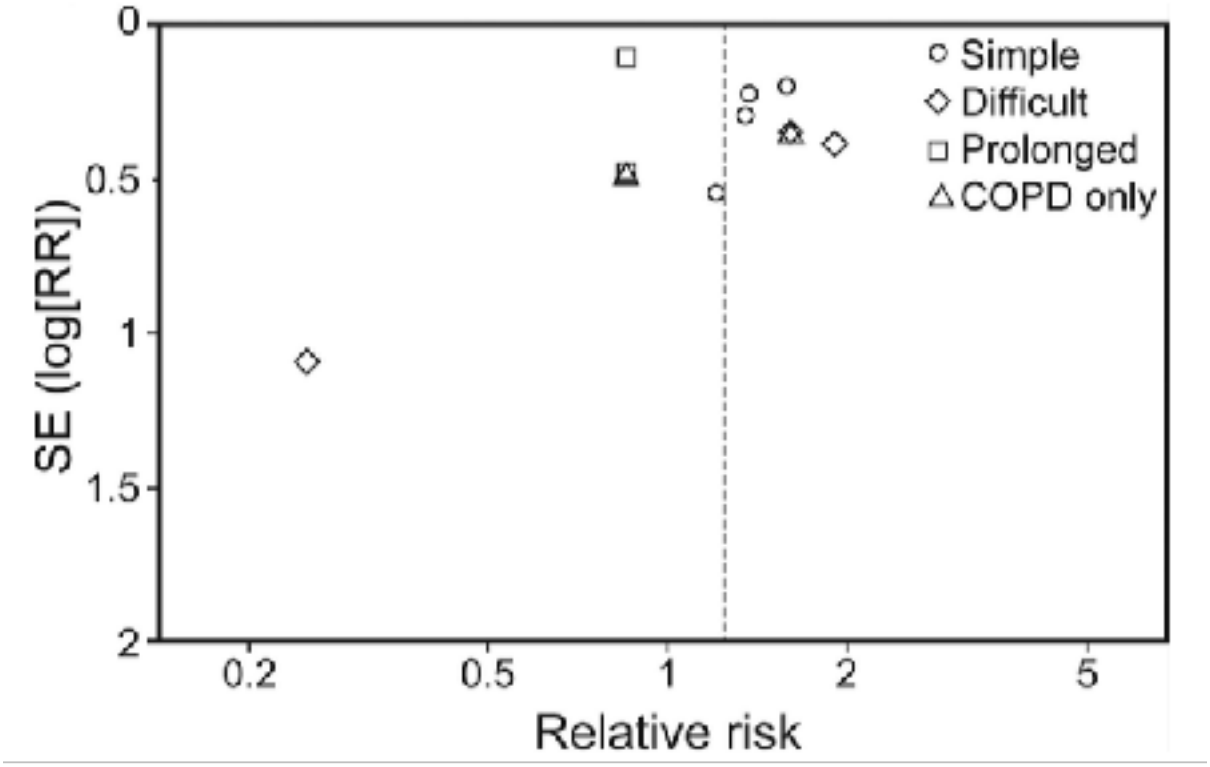

Figure 6. Funnel plot for weaning failure outcome.

SE, Standard error; RR, Risk ratio; COPD, Chronic obstructive pulmonary disease.

9 ARTIGO III

Trials Directly Comparing Alternative Spontaneous Breathing Trial Techniques: A Systematic Review and Meta-analysis

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Abstract

Objective: To summarize the effect of trials directly comparing alternative SBT techniques on clinically important outcomes in critically ill adults and children.

Data Sources: We searched MEDLINE, EMBASE, CENTRAL, CINAHL, Evidence-Based Medicine Reviews, Ovid Health Star, proceedings of 5 conferences (1990-2015), and reference lists.

Study Selection: Randomized trials comparing SBT techniques in intubated adults or children. Primary outcomes were initial SBT success, extubation success, or reintubation.

Data Extraction: Two reviewers independently screened citations, assessed trial quality, and abstracted data.

Data Synthesis: We identified 31 trials (n=3,541). Moderate quality evidence showed that patients undergoing pressure support (PS) vs. T-piece SBTs (9 trials, n=1,901) were as likely to pass an *initial* SBT [Risk Ratio (RR) 1.00, 95% confidence interval (CI) 0.89-1.11; I^2 = 77%] but more likely to be ultimately successfully extubated [RR 1.06, 95% CI 1.02-1.10; 11 trials, n=1,904; I^2=0%]. Exclusion of one trial with inconsistent results for SBT and extubation outcomes suggested that PS (vs. T-piece) SBTs improved *initial* SBT success [RR 1.06, 95% CI 1.01-1.12; I^2 = 0%]. Limited data suggests that automatic tube compensation plus continuous positive airway pressure (CPAP) vs. CPAP alone or PS increase SBT but not extubation success.

Conclusions: Patients undergoing PS (vs. T-piece) SBTs appear to be 6% (NNT =19.7) more likely to be successfully extubated and possibly 6% more likely to pass an SBT when the results of an outlier trial were excluded. Future trials should investigate patients for whom SBT and extubation outcomes are uncertain and compare techniques that maximize differences in support.

Key Words: weaning, spontaneous breathing trial, extubation, systematic review, extubation outcome

Objective

Weaning accounts for approximately 40% of the time spent on mechanical ventilation [1,2]. Compared to non-protocolized care, randomized controlled trials (RCTs) and a systematic review support that weaning protocols reduce the duration of mechanical ventilation, weaning time, and intensive care unit (ICU) length of stay [3,4]. After identification, patients may undergo a spontaneous breathing trial (SBT) to determine their ability to breathe spontaneously with either minimal or no support during inspiration or expiration.

Clinicians conduct SBTs to facilitate decision-making regarding timely extubation and minimize patient's exposure to invasive ventilation. In making extubation decisions, clinicians 'trade-off' the risks associated with delayed extubation and those associated with a premature failed attempt at extubation**.** Several techniques can be used to conduct SBTs, including pressure support (PS) with or without positive end-expiratory pressure (PEEP), continuous positive airway pressure (CPAP), Automatic Tube Compensation (ATC), T-piece, and intermittent mandatory ventilation (IMV). Whereas some SBT techniques deliver pressure during inspiration to overcome the resistance of the endotracheal tube (e.g., PS, ATC), other techniques aim to improve respiratory mechanics or cardiac function (e.g., CPAP) and may overestimate patient's ability to breathe autonomously after extubation [5]. Conversely, T-piece provides no support and is often perceived by clinicians to increase work of breathing (WOB) and underestimate a patient's ability to breathe spontaneously after extubation, although no data directly supports this assertion [5]. An international consensus conference endorsed by 5 respiratory and critical care societies supports that an SBT is *the major diagnostic test* to determine if patients can be extubated and recommends that initial SBTs be conducted with either T-piece or PS (5 to 8 cm H_2O in adults; 10 cm H_2O in children) with or without 5 cm H_2O PEEP [6].

A Cochrane review of 9 trials compared PS and T-piece 'weaning' in critically ill adults and found nonsignificant differences between techniques on weaning success, pneumonia, reintubation, ICU mortality and length of stay. In a subgroup analysis (4 trials, n = 940) the authors noted that patients were significantly more likely to pass a PS vs. a T-piece SBT [risk ratio (RR) 1.09, 95% confidence interval (CI) 1.02 to 1.17] [7]. This systematic review did not directly compare alternative SBT techniques and was limited to full publications of adult patients comparing two techniques. At present, no SBT technique has been shown to be superior to another.

We sought to summarize the RCT evidence directly comparing all alternative SBT techniques [e.g., PS vs. other techniques, CPAP vs. other techniques etc.] involving critically ill adults and children on initial SBT success, extubation success, reintubation rate (primary outcomes) and other important outcomes.

Methods

Data Sources

We searched MEDLINE (1966 to January 2016); EMBASE (1980 to January 2016); the Cochrane Central Register of Controlled Trials (CENTRAL, January 2016); CINAHL (1982 to January 2016), Evidence Based Medicine Reviews and Ovid Health Star (1999 to January 2016) to identify potentially eligible trials using database-specific search strategies without language restrictions. We used the optimally sensitive search strategies of The Cochrane Collaboration to identify RCTs in MEDLINE and EMBASE [8-10]. Two authors (KB, JF) independently screened citation titles and abstracts. The same two authors (KB, JF) retrieved and evaluated the full text versions of potentially relevant trials. Five authors hand searched annual conference proceedings from 5 scientific meetings from 1990 to 2015 (European Society of Intensive Care Medicine, American College of Chest Physicians (except 1999-2002 which were unavailable), American Thoracic Society, International Symposium of Intensive Care and Emergency Medicine, and Society of Critical Care Medicine). Ethics approval was not required.

Study Selection

We included randomized or quasi-randomized (e.g., assignment based on even/odd days or medical record number) trials comparing two or more SBT techniques (as defined by study authors) evaluating predominantly critically ill adults or children receiving invasive ventilation and reporting at least one of: initial SBT or extubation outcome (success or failure), reintubation, time to extubation or successful extubation, time to first successful SBT, mortality, ventilator-associated pneumonia (VAP), total duration of ventilation, ICU or hospital length of stay, post extubation use of noninvasive ventilation (NIV), or adverse events. We excluded trials that evaluated (i) neonatal or tracheostomized patients, (ii) SBTs as part of a weaning strategy, (iii) automated SBTs (e.g., SmartCare™, Intellivent®), (iii) NIV vs. continued invasive ventilation and (iv) SBT conduct vs. no SBT. Two authors (KB, JF) independently selected trials meeting inclusion criteria and another author (LB) adjudicated differences where required.

Data Extraction and Quality Assessment

Two unblended authors (KB, JF) abstracted data regarding study risk of bias (randomization, allocation concealment, blinded outcomes assessment, completeness of follow up, selective outcomes reporting, trial stopped early for benefit) and recorded outcomes, using authors' definitions for reported outcomes, on a standardized form [11]. We assigned a judgment related to the 'risk of bias' for each domain (Yes, Unclear, No). Disagreements were resolved by consensus and arbitration with a third author (LB) where necessary.

Data Synthesis

We pooled data across studies using random effects models. We derived summary estimates of RR and mean difference (MD) with 95% CI for binary and continuous outcomes, respectively, using Review Manager 5.3 (Cochrane Collaboration, Oxford) [12]. We pooled 'initial SBT success' in trials that conducted more than one SBT. We evaluated the impact of statistical heterogeneity among pooled studies for each outcome using the I^2 measure with threshold values of 0-40%, 30-60%, 50-90%, and $\geq$75% representing heterogeneity that might not be important or represent moderate, substantial, or considerable heterogeneity, respectively [13,14]. We summarized trials based on the SBT techniques compared (e.g., T-piece vs. other technique).

We planned subgroup analyses to compare the effects of different SBT techniques on the primary outcomes in trials (i) of perioperative vs. non-perioperative patients, (ii) based on duration of ventilation at randomization (non-perioperative studies), (iii) based on the support provided during SBTs and (iv) based on the type of lung disease and to assess for differences using the Chi-square test [15]. In sensitivity analyses, we planned to assess the impact of methodologic quality (low or moderate vs. high risk of bias) on the primary outcomes.

We used the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the body of evidence associated with the primary outcomes (SBT outcome, extubation outcome, reintubation rate) and secondary outcomes that achieved statistical significance and constructed 'Summary of Findings' tables [16]. To assess for publication bias, we examined funnel plots of the size of the treatment effect for the primary outcomes against trial precision (1/standard error) for asymmetry when at least 10 trials were identified [17].

Results

Trial Identification

We identified 3,834 unique citations in our search. From these, we assessed 183 articles for eligibility and excluded 152 studies that did not meet inclusion criteria (reference list available from authors) (Supplemental Table 1). Thirty-one trials [18-48] reporting on 3,541 patients met our inclusion criteria including 5 trials comparing 3 SBT techniques [23,24,29,30,48]. Two trials [38,46] appeared to be published, at least in part, in duplicate [49,50]. Trials predominantly compared T-piece to PS (13 trials) and T-piece to CPAP (9 trials). A smaller number of trials compared CPAP to ATC/CPAP (3 trials) and ATC to PS (3 trials). Four trials [21,34,38,40] were published only in languages other than English. Six trials [25,27,33,36,45,47] were published in abstract form; of which 2 authors [36,47] provided partial or full text manuscripts. Nine trials [19-21,23-25,44,45,47] evaluated perioperative populations including 6 cardiac surgery [19-21,24,25,44] and 3 surgical ICU [23,45,47] trials. Four trials evaluated patients with chronic obstructive pulmonary disease (COPD) [35,36,40,45] and 3 trials [28,43,46] evaluated pediatric patients.

Quality Assessment

Overall the quality of the included trials was moderate (Supplemental Figure 1). We judged randomization and allocation concealment to be at low risk of bias in 16 (52%) trials and 17 (55%) trials, respectively. One quasi-randomized trial allocated patients based on even or odd days [34]. No trial evaluated outcomes in a blinded manner. We judged 15 (48%) trials to have complete outcomes reporting. Eighteen (58%) trials conducted an intention-to-treat analysis and 26 (84%) trials did not stop early for benefit.

Primary Outcomes:

Initial SBT Success

Seventeen T-piece, 12 CPAP, 8 ATC, 13 PS trials directly compared one SBT technique to another and reported initial SBT success. Compared to T-piece SBTs, moderate quality evidence supports that patients undergoing PS SBTs were not more likely to pass an SBT [RR 1.00, 95% CI (0.89 to 1.11); p=1.0; 9 trials, n=1,901] with considerable heterogeneity (I^2=77%) (Table 1, Figure 2, Supplemental Figure 2).

Low quality evidence from 3 trials (n=247) suggests that patients were significantly more likely to pass an SBT with ATC+CPAP compared to CPAP alone [RR 1.12, 95% CI (1.04 to 1.22); p=0.005, I^2=0%]. Similarly, low quality evidence from 3 trials (n=276) showed that patients were significantly more likely to pass an SBT with ATC+CPAP compared to PS [RR 1.10, 95% CI (1.01 to 1.20); p=0.02, I^2=0%] (Table 2).

Extubation Success

Seventeen T-piece, 8 CPAP, 8 ATC and 14 PS trials compared one SBT technique to another and reported extubation success. Moderate quality evidence supports that patients undergoing PS compared to T-piece SBTs were significantly more likely to be successfully extubated [RR 1.06, 95% CI (1.02 to 1.10); p=0.007; 11 trials, n=1,904; I^2=0%] (Table 1, Figure 3, Supplemental Figure 3).

Reintubation Rate

Fourteen T-piece, 9 CPAP , 7 ATC, and 13 PS trials comparing one SBT technique to another reported reintubation rate and found no statistically significant differences between techniques (Supplemental Figure 4).

Secondary Outcomes

There was no effect of one SBT technique vs. another on ICU mortality (7 T-piece, 3 CPAP and 5 PS SBT trials), hospital mortality (4 T-piece and 4 PS SBT trials) or at the most protracted mortality measure (10 T-piece, 4 CPAP, and 7 PS SBT trials).

No trial reported time to extubation or time to successful extubation. Meta-analysis of 3 trials comparing ATC+CPAP to CPAP alone found no difference in NIV use after extubation (RR 0.53, 95% CI (0.27 to 1.06; p=0.07, I^2=0%).

Sensitivity, subgroup and post hoc analyses

Exclusion of a single quasi-randomized trial comparing PS vs. T-piece SBTs [34] did not change the significant increase in extubation success favoring PS SBTs [RR 1.05, 95% CI (1.01 to 1.10), p=0.02, I^2 =0%].

Meta-analyses of PS vs. T-piece SBTs showed benefit in 7 non-perioperative trials (n=1,273) [RR 1.07, 95% CI (1.01 to 1.13); p=0.02, I^2=94%] (high quality evidence) compared to 2 perioperative trials (n=548) [RR 0.86, 95% CI (0.61 to 1.22); p=0.41, I^2=0%] (low quality evidence); however, an interaction test showed no difference between these summary estimates (p=0.23) (Supplemental Table 2, Supplemental Figure 5). Subgroup analyses based on duration of ventilation among non-perioperative trials was not feasible given similar reported durations of ventilation. Subgroup analyses comparing more vs. less inspiratory support and presence or absence of COPD were not significant for commonly reported comparisons of alternative techniques. A risk of bias assessment was not possible due to the lack of blinded outcomes assessment across trials. Inspection of a funnel plot for 11 trials comparing PS to T-piece SBTs on extubation success did not suggest publication bias.

We conducted a post hoc analysis that excluded a single, surgical trial [47] that enrolled surgical patients, was published in abstract form only, and had internally inconsistent results (i.e., lower initial SBT success rate but higher extubation success rate for PS vs. T-piece SBTs). When this trial was excluded, meta-analyses showed that more patients passed an initial PS (vs. T-piece) SBT [RR 1.06, 95% CI (1.01 to 1.12); p=0.03] *without heterogeneity* (I^2=0%) and were similarly extubated successfully [RR 1.06, 95% CI (1.01 to 1.12); p=0.03, I^2=0%].

Discussion

We identified 31 trials of overall moderate quality reporting on 3,541 patients. Moderate quality evidence supported that SBT success rates were similar with PS and T-piece, with substantial heterogeneity. However, post hoc exclusion of an unpublished trial [47] with inconsistent results eliminated the heterogeneity and showed that SBT success was 6% more likely with PS SBTs. Meta-analysis also showed a 6% higher probability of successful extubation following PS (vs. T-piece) SBTs, with no heterogeneity, irrespective of this trial's inclusion [47]. Low quality evidence from 3 trials supported that patients were 12% more likely to pass an SBT with ATC+CPAP/PEEP compared to CPAP and 10% more likely to pass an SBT with ATC+CPAP/PEEP compared to PS, although extubation success rates were similar. We found no differences between alternative SBT techniques on reintubation rate. Subgroup analysis suggested beneficial effects of PS vs. T-piece SBTs on SBT success in 7 non-perioperative trials (high quality evidence) compared to 2 perioperative trials (low quality evidence), but the risk ratios were not statistically dissimilar.

Most trials directly compared T-piece to PS SBTs (13 trials) and T-piece to CPAP SBTs (9 trials). Few trials assessed alternative SBT techniques in children. Most trials (n=22) were conducted in patients who were non-perioperative and for whom extubation decisions are considered more challenging. In pooling outcomes, we noted that 5 of 6 cardiac surgery trials reported a 100% SBT success rate in both arms and 3 surgical trials reported a 100% extubation success rate in both arms. These findings suggest that the most important question in postoperative patients with a high pre-test probability of SBT and extubation success may be *whether* an SBT is necessary and that questions regarding the best SBT technique to use may be most relevant to patients at indeterminate or low pre-test probability of success.

Our systematic review differs from 2 previous reviews by directly comparing SBT techniques and excluding trials evaluating SBT techniques as one component of a weaning strategy [7,51]. Moreover, we hand searched conference proceedings spanning 25 years, where feasible, and included pediatric trials. Compared to the Cochrane review of 9 trials [7], we included 9 additional trials (including 1 pediatric trial [28], 4 adult trials [34,38,42,44], 2 abstracts [27,47] and 2 three-arm trials [30,48]) comparing T-piece and PS SBTs and excluded 4 weaning trials [52-55]. Contrary to their findings, we found that patients were *only* more likely to pass a PS (vs. T-piece) SBT after exclusion of a single outlier trial [47] but were significantly more likely to be successfully extubated. This finding remained significant after exclusion of a single pediatric trial [28]. Compared to a recent meta-analysis of 12 trials [51], we included 5 additional trials (1 pediatric trial [28], 3 adult trials [34,42,48] including a three-arm trial [48], and an abstract [27]) and excluded 4 trials involving weaning or tracheostomized patients [52,53,55,56]. Similar to their review, we found that SBT technique did not influence rates of weaning success, mortality, or reintubation.

Considerable debate exists regarding the SBT technique that best simulates patient's WOB after extubation. An SBT approximates patient's ability to breathe spontaneously, but is an imperfect test as it cannot take into consideration factors (e.g., upper airway resistance, respiratory muscle fatigue, cardiac decompensation) that may occur after extubation. There are several reasons why PS SBTs may lead to more successful initial SBTs and extubations. By overcoming a portion of the pressure gradient across the endotracheal tube, low levels of PS or CPAP provide minimal but potentially important support during an SBT. A systematic review comparing the effect of different physiologic indices on SBT outcome found that metrics of patient effort (WOB and pressure time product) were significantly higher during T-piece vs. PS SBTs [57]. Most patients, especially those with high pre-test probability of success, who represent the majority of patients submitted to SBTs [6,58], can be easily separated from the

ventilator after an initial SBT [58]. Notwithstanding, T-piece SBTs may be appropriate in selected patients (e.g. severe left ventricular dysfunction, neuromuscular weakness, difficult airway) when clinicians are uncertain regarding their ability to breathe on their own and when they prioritize a low false positive rate for passing an SBT and being successfully extubated due to the risks associated with extubation failure [59]. Conversely, when T-piece (vs. PS) SBTs are used in patients with a high likelihood of extubation success, they may induce a high false negative rate. Compared to T-piece, our review suggests that PS SBTs may facilitate extubation decision-making. Even if PS SBTs underestimate post-extubation WOB, their successful completion may offset clinician reluctance to extubate, resulting in more timely and successful extubation without increased reintubation [60,61]. Although passing an initial SBT is an important outcome, patients may undergo serial SBTs before extubation and stakeholders prioritize being successfully extubated [62].

Several additional findings warrant further commentary. First, few trials reported use of daily screening, or the criteria used to identify SBT candidates and assess extubation readiness. Second, we noted wide variation in initial SBT success rates across trials comparing PS (range, 54.3% to 100.0%) and T-piece SBTs (53.0% to 100.0%) and ATC+CPAP (64.7% to 96.7%) to PS SBTs (52.6% to 86.0%) and, similarly, broad variation in extubation success rates comparing PS (60.0 to 100.0%) and T-piece SBTs (50.0% to 100.0%). Conversely, we noted higher SBT success rates in 3 trials comparing ATC with CPAP (93.3% to 96.6%) to CPAP alone (80.0% to 86.7%). While SBT and extubation summary estimates differed quantitatively across comparisons, qualitatively the direction of effect favored SBTs conducted with inspiratory support. Third, only 8 trials [25,28-30,34,37,38,43] specified addition of CPAP (or PEEP) to PS during SBTs. Finally, trials were predominantly of moderate quality.

Our review is the first to directly compare alternative SBT techniques and was strengthened by an extensive search, duplicate citation screening and data abstraction, use of random effects models to pool data, and conduct of prespecified subgroup analyses. Our review also has limitations. Summary estimates were limited by variable outcomes reporting and unclear prospective follow-up. Statistical noise could be minimized if SBT techniques were applied serially until extubation and extubation was restricted to patients who passed an SBT. Only 5 trials, comparing PS to T-piece SBTs, reported conducting SBTs daily [31,35], daily up to 3 days [29,48], and for an undisclosed time [38]. Despite subgroup analyses, we cannot fully elucidate the impact of pre-test probability of success on post-test results as patients at intermediate or high likelihood of SBT and extubation success were well-represented. The implications of our findings for patients with low pre-test probability remain uncertain.

Conclusion

Patients undergoing PS vs. T-piece SBTs appear to be 6% (NNT=19.7) more likely to be successfully extubated, and possibly 6% more likely to pass an SBT if the results of an outlier trial are excluded. Future trials should investigate patients for whom outcomes are uncertain and compare techniques that maximize differences in support.

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Competing Interest Declaration

All authors declare: (1) no support from any organization for the submitted work; (2) no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; (3) no other relationship or activities that could appear to have influence the submitted work.
LB's laboratory received equipment and/or research grants from Maquet (research on NAVA), Covidien (PAV), Philips (sleep), Fisher Paykel (high flow), Air Liquide (CPR), General Electric (lung volume) and he received lecture fees from Covidien and Maquet.

Compliance with Ethical Standards
All applicable international, national, and/or institutional guidelines for the conduct of the research were followed. No human participants were involved in this study.

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At the time of conducting this systematic review, KB and JF held Clinician Scientist - Phase 2 Awards from the Canadian Institutes of Health Research and KB also held an Ontario Ministry of Research and Innovation Early Researcher Award. Dr. Brochard holds the Keenan Chair in Critical Care and Acute Respiratory Failure (St. Michael's Hospital, Toronto, Canada)

Details of Contributions
KB and JF conducted the literature searches, selected studies meeting inclusion criteria, extracted data and assessed study quality, conducted risk of bias assessments.
KB, JF, IS, JP, LC, NR, MS screened abstracts.
JP reviewed selected studies published in foreign languages, extracted data and assessed study quality and assisted with adjudicating whether studies met inclusion criteria. JF also reviewed selected foreign language publications.
IS, AZ, NA, JW, CG searched conference proceedings and IS, KB adjudicated abstracts for inclusion.
LB adjudicated disagreements between reviewers (study selection and quality).
KB, JF, NA, JP, LB prepared initial and subsequent drafts of the manuscript, and integrated comments in to revised versions of the manuscript.

JF double checked data entry.
All authors revised and approved the final version of the manuscript.

Guarantor: KB and JF had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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9.2 TABELAS DO ARTIGO III

Table 1: Summary of Findings - PS vs. T-piece SBTs on SBT and Extubation Success

Pressure Support Compared to T-piece SBTs on SBT Success

Outcomes	Illustrative comparative risks* (95% CI)		Risk Ratio (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)
	Assumed risk **T-piece**	Corresponding risk **Pressure Support**			
PS vs. T-piece SBTs on SBT Success	**Study population**		**RR 1.00** (0.89 to 1.11)	1901 (9 trials)	⊕⊕⊕⊖ **moderate**[1]
	766 per 1000	**766 per 1000** (681 to 850)			

[1] Chittawatanarat trial [47] skews data, increases heterogeneity and changes summary estimate of effect. It also changes our interpretation of the findings.

Pressure Support Compared to T-piece SBTs on Extubation Success

Outcomes	Illustrative comparative risks* (95% CI)		Risk Ratio (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)
	Assumed risk **T-piece**	Corresponding risk **Pressure Support**			
PS vs. T-piece SBTs on Extubation Success	**Study population**		**RR 1.06** (1.02 to 1.1)	1904 (11 trials)	⊕⊕⊕⊖ **moderate**[2]
	749 per 1000	**794 per 1000** (764 to 824)			

[2] Methodologic concerns with Colombo trial (quasi-randomized) [34] and this trial carries 10% weight in the pooled extubation outcome analysis

*The **assumed risk** is based on the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

PS = Pressure Support, RR = risk ratio, CI = confidence interval, SBT = spontaneous breathing trial.

Table 2: Summary Estimates of Effect for Comparisons of ATC vs. Other Techniques on SBT Success

Comparison	Trials [n]	Risk Ratio (95% CI)	p-value	I^2
ATC/CPAP vs. CPAP	3 trials [247]	1.12 (1.04, 1.22)	0.005	0%
ATC/CPAP vs. PS	3 trials [276]	1.10 (1.01, 1.20)	0.02	0%
ATC vs. T-piece	2 trials [157]	1.03 (0.76, 1.42)	0.83	81%
ATC/PS vs. PS	1 trial [100]	1.04 (0.94, 1.15)	0.40	NA

ATC = automatic tube compensation; CPAP = continuous positive airway pressure; PS = pressure support; CI = confidence interval; I^2 = test of heterogeneity.

Supplemental Table 1: Characteristics of Included Trials

Author Year [n]	Interventions	Country	Publication Type	Population	Duration of Ventilation at Inclusion
Feeley 1975 [18] [25]	T-piece/PEEP 5 cm H_2O vs. T-piece	USA	Full	Adult	Not reported
Hastings 1980 [19] [18]	IMV/CPAP 5 cm H_2O vs. T-piece/CPAP 5 cm H_2O	USA	Full	Adult	Perioperative
Prakash 1982 [20] [28]	IMV vs. SVT (on ventilator)	Netherlands	Full	Adult	Perioperative
Koller 1983 [21] [45]	CPAP 10 cm H_2O vs. T-piece/ZEEP	Austria	Full	Adult	Perioperative
Jones 1991 [22] [106]	CPAP 5 cm H_2O vs. T-piece/ZEEP	USA	Full	Adult	Not reported
Abalos 1992 [23] [62]	SIMV vs. CPAP 4 cm H_2O vs. T-piece	USA	Full	Adult	Perioperative
Bailey 1995 [24] [82]	T-piece* vs. CPAP 5 cm H_2O vs. CPAP 10 cm H_2O	England	Full	Adult	Perioperative
Schinco 1995 [25] [30]	PS 5 cm H_2O/CPAP 5 cm H_2O vs. CPAP 5 cm H_2O	USA	Abstract	Adult	Perioperative
Esteban 1997 [26] [484]	T-piece vs. PS 7 cm H_2O	Spain & South America	Full	Adult	>48 h
Holanda 2000 [27] [35]	T-piece vs. PS	Brazil	Abstract	Adult	>48 h
Farias 2001 [28] [257]	T-piece vs. PS 10 cm H_2O ± PEEP 5 cm H_2O	Argentina	Full	Pediatric	>48 h
Haberthur 2002 [29] [90]	PS 5 cm H_2O/PEEP 5 cm H_2O vs. ATC/PEEP 5 cm H_2O vs. T-piece	Switzerland	Full	Adult	>24 h
Koksal 2004 [30] [60]	PS ≤ 10 cm H_2O/PEEP ≤ 5 cm H_2O vs. CPAP ≤ 5 cm H_2O vs. T-piece	Turkey	Full	Adult	>48 h
Matic 2004 [31] [260]	T-piece vs. PS 8 cm H_2O	Croatia	Full	Adult	>48 h
Cohen 2006 [32] [99]	ATC† /CPAP 5 cm H_2O vs. CPAP 5 cm H_2O	Israel	Full	Adult	>24 h
Liang 2006 [33] [97]	ATC vs. T-piece	Taiwan	Abstract	Adult	>4 days
Colombo 2007 [34] [120]	T-piece vs. PS 7 cm H_2O/PEEP 5 cm H_2O	Brazil	Full	Adult	>48 h
Matic 2007 [35] [136]	T-piece vs. PS (not specified)	Croatia	Full	Adult	>24 h
Fayed 2008 [36] [30]	ATC† /CPAP 5 cm H_2O vs. CPAP 5 cm H_2O	Egypt	Abstract	Adult	>24 h
Cohen 2009 [37] [180]	ATC† /CPAP 5 cm H_2O vs. PS 7 cm H_2O /CPAP 5 cm H_2O	Israel	Full	Adult	>24 h
Zhang 2009 [38] [208]	T-piece vs. PS 5 cm H_2O/PEEP 5 cm H_2O	China	Full	Adult	Not reported
Figueroa Casas 2010 [39] [122]	ATC† /PEEP 5 cm H_2O vs. CPAP 5 cm H_2O	USA	Full	Adult	>24 h
Molina-Saldarriaga 2010 [40] [50]	CPAP‡ vs. T-piece	Colombia	Full	Adult	>48 h
Cekman 2011 [41] [40]	CPAP ≤ 5 cm H_2O vs. T-piece	Turkey	Full	Adult	>48 h
Vats 2012 [42] [40]	T-piece vs. PS 7 cm H_2O	India	Full	Adult	Not reported
El-beleidy 2013 [43] [36]	ATC† /CPAP 5 cm H_2O vs. PS 6-10 cm H_2O /CPAP 5 cm H_2O	Egypt	Full	Pediatric	>24 h
Lourenco 2013 [44] [30]	T-piece vs. PS (not specified)	Brazil	Full	Adult	Perioperative
Sherif 2013 [45] [100]	PS (not specified) vs. PS/ATC	Egypt	Abstract	Adult	Not reported
Bilan 2015 [46] [51]	CPAP vs. T-piece	Iran	Full	Pediatric	Not reported
Chittawatanarat 2015 [47] [520]	T-piece vs. PS 7 cm H_2O/PEEP ≤ 5 cm H_2O	Thailand	Abstract	Adult	>12 h
Teixeira 2015 [48] [160]	PS 7 cm H_2O/PEEP 5 -8 cm H_2O vs. PAV+/PEEP 5 -8 cm H_2O vs. T-piece	Brazil	Full	Adult	>24 h

PEEP = positive end-expiratory pressure; IMV = intermittent mandatory ventilation; CPAP = continuous positive airway pressure; SVT = spontaneous ventilation trial, SIMV = synchronized intermittent mandatory ventilation; PS = pressure support; ATC = automatic tube compensation; PAV+ = proportional assist ventilation with load adjustable gain factors; USA = United States of America; MV = mechanical ventilation.

Supplemental Table 2: Summary of Findings - PS vs. T-piece SBTs on SBT Success Based on Pretest Probability

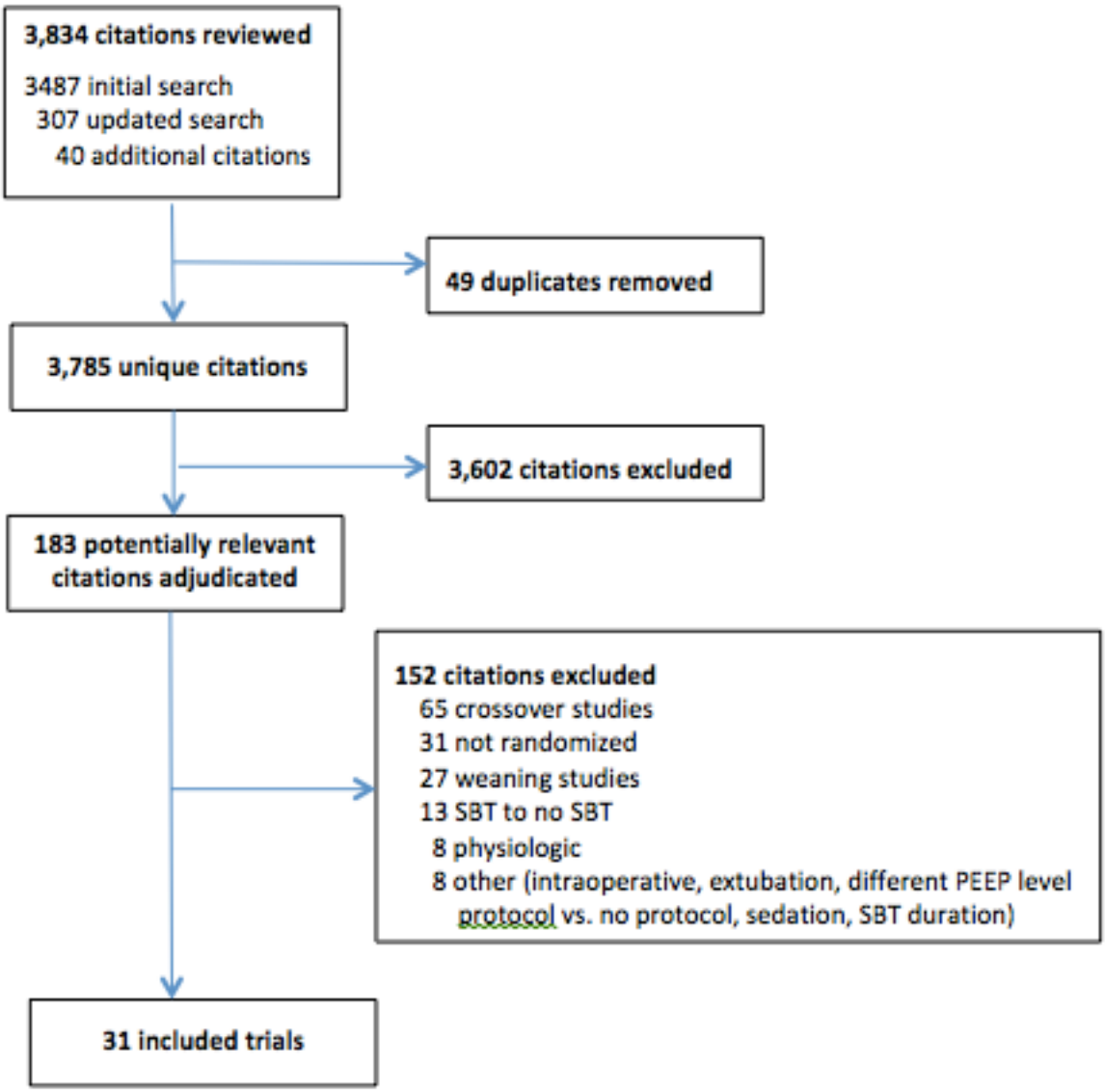
Quality assessment					No of patients		Effect		Quality
No of trials [n]	Risk of bias	Inconsistency	Indirectness	Imprecision	Pressure Support	T-piece	Relative (95% CI)	Risk Difference	
Perioperative trials									
2 trials [548]	no serious risk of bias	serious[1]	not serious	serious[2]	173/274 (63.1%)	226/274 (82.5%)	RR 0.86 (0.61 to 1.22)	115 fewer per 1000 (from 322 fewer to 181 more)	⊕⊕OO LOW
Non-perioperative trials									
7 trials [1353]	no serious risk of bias	not serious	not serious	not serious	536/680 (78.8%)	499/673 (74.1%)	RR 1.07 (1.01 to 1.13)	52 more per 1000 (from 7 more to 96 more)	⊕⊕⊕⊕ HIGH

[1] The trial by Chittawatanarat [47] skews data, increases heterogeneity and changes effect estimate. Also inclusion of this trial changes our interpretation of the summary estimate of effect. [2] No effect and the relative risk increases greater than 25% [47]

PS = Pressure Support, SBT = spontaneous breathing trial, RR = risk ratio, CI = confidence interval.

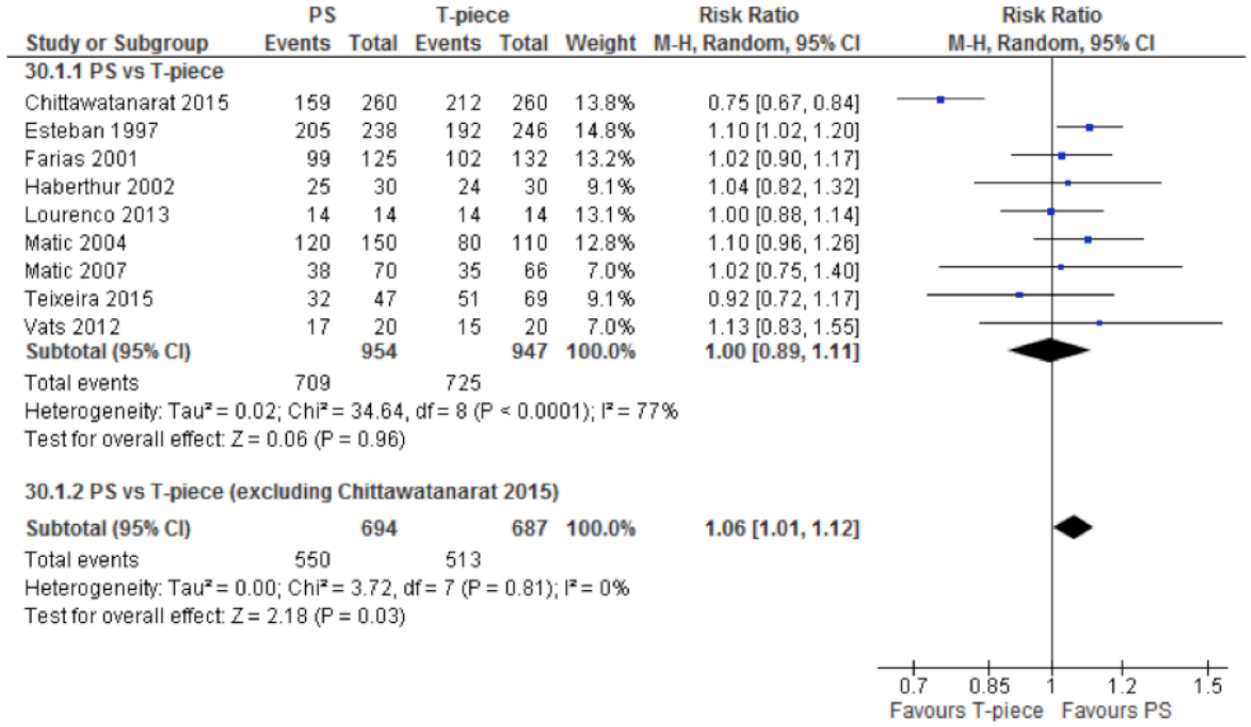
9.3 FIGURAS DO ARTIGO III

Figure 1: Identification of Trials included in the Meta-Analysis



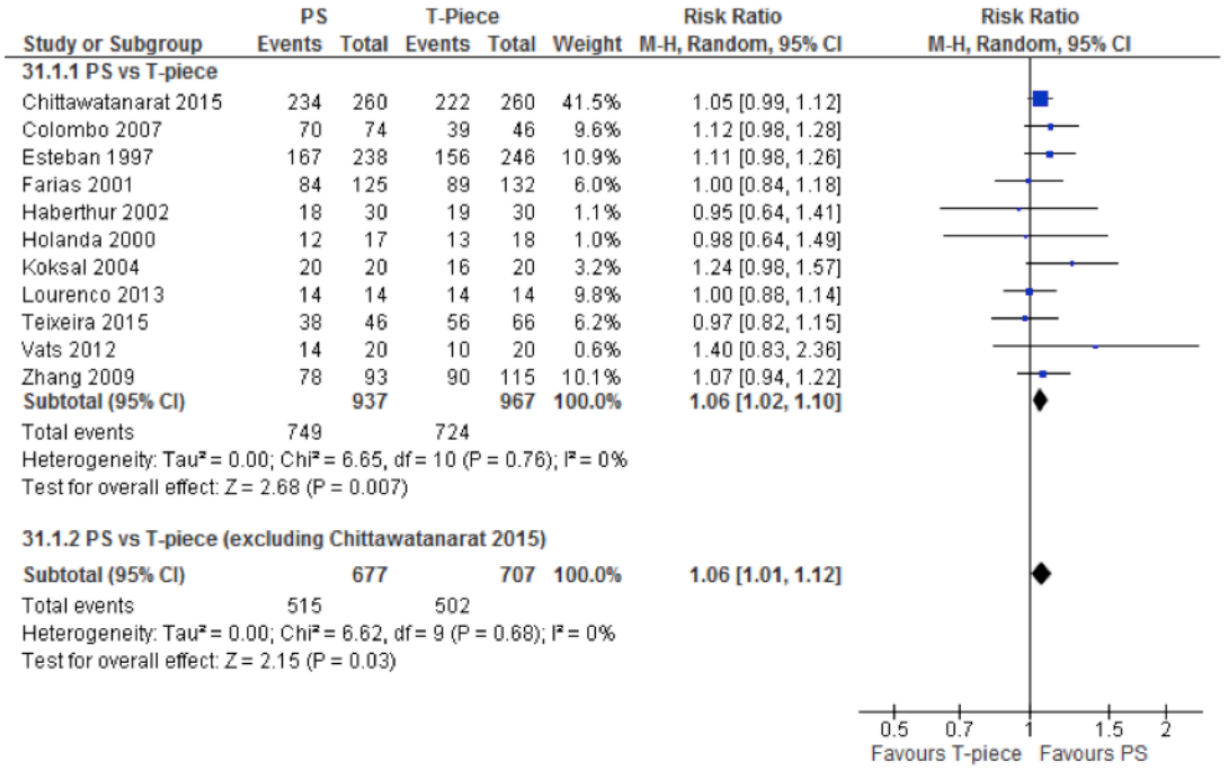
SBT = spontaneous breathing trial, PEEP = positive end-expiratory pressure

Figure 2: Forest Plot Comparing PS vs. T-piece SBTs on SBT Success



Effect of spontaneous breathing trial technique (PS vs. T-piece) on spontaneous breathing trial success. The pooled risk ratio with 95% confidence interval (CI) was calculated using a random effects model. Weight refers to the contribution of each study to the overall estimate of treatment effect. RR = risk ratio, CI = confidence interval, PS = Pressure Support

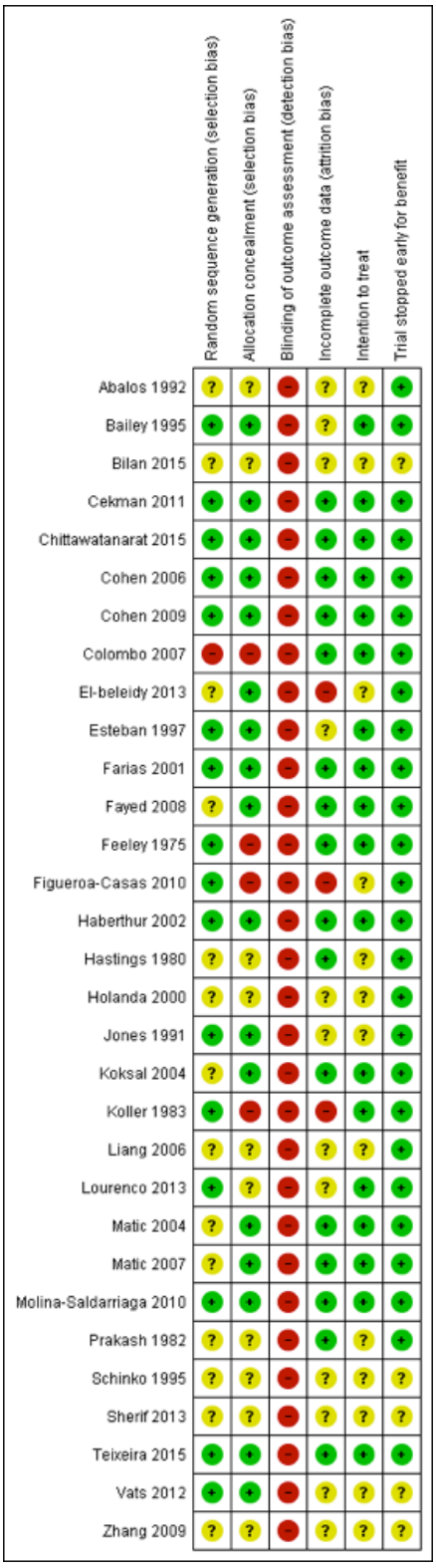
Figure 3: Forest Plot Comparing PS vs. T-piece SBTs on Extubation Success



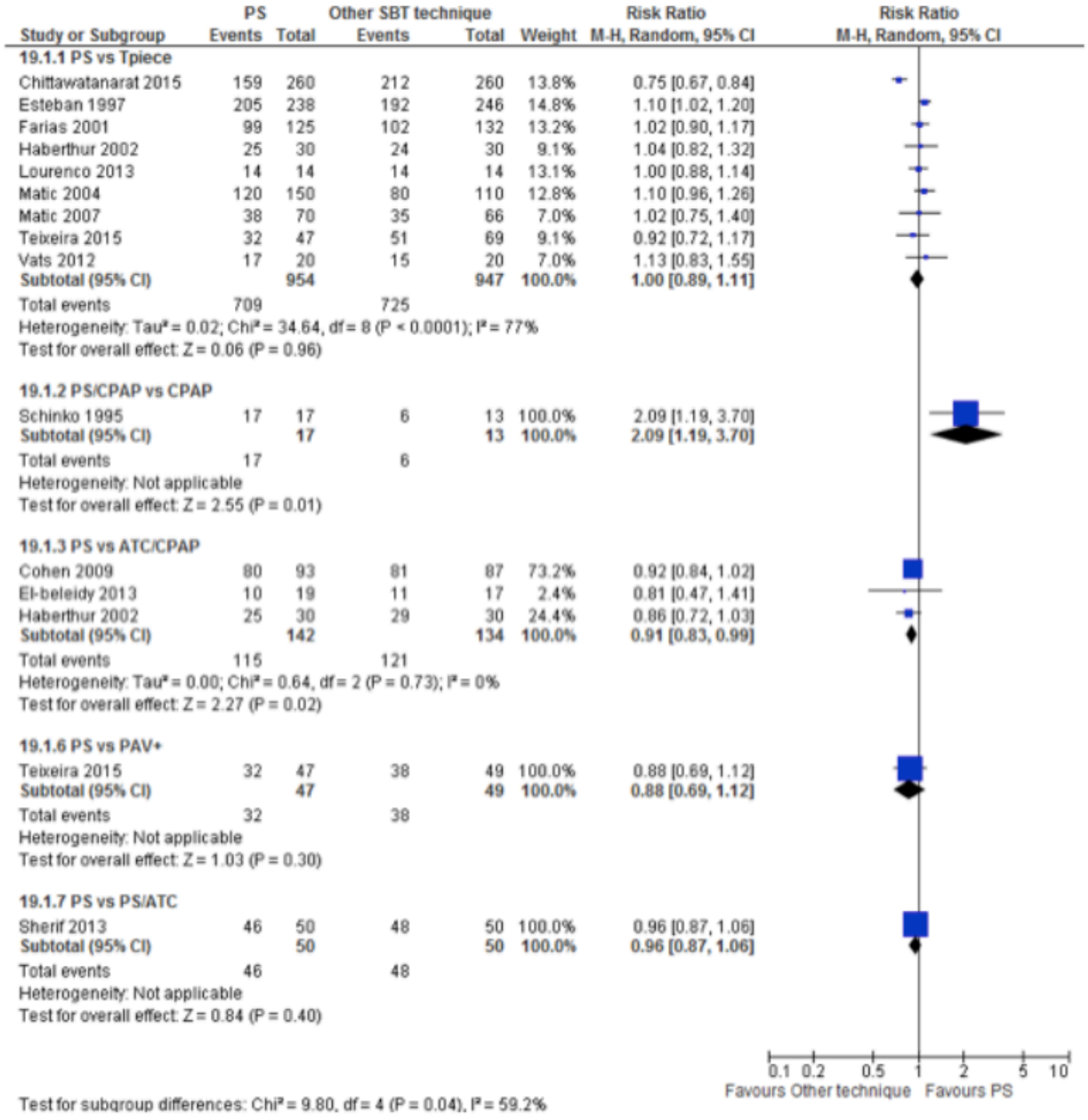
Effect of SBT technique (PS vs. T-piece) on extubation success. The pooled risk ratio with 95% confidence interval (CI) was calculated using a random effects model. Weight refers to the contribution of each study to the overall estimate of treatment effect.

RR = risk ratio, CI = confidence interval, PS = Pressure Support

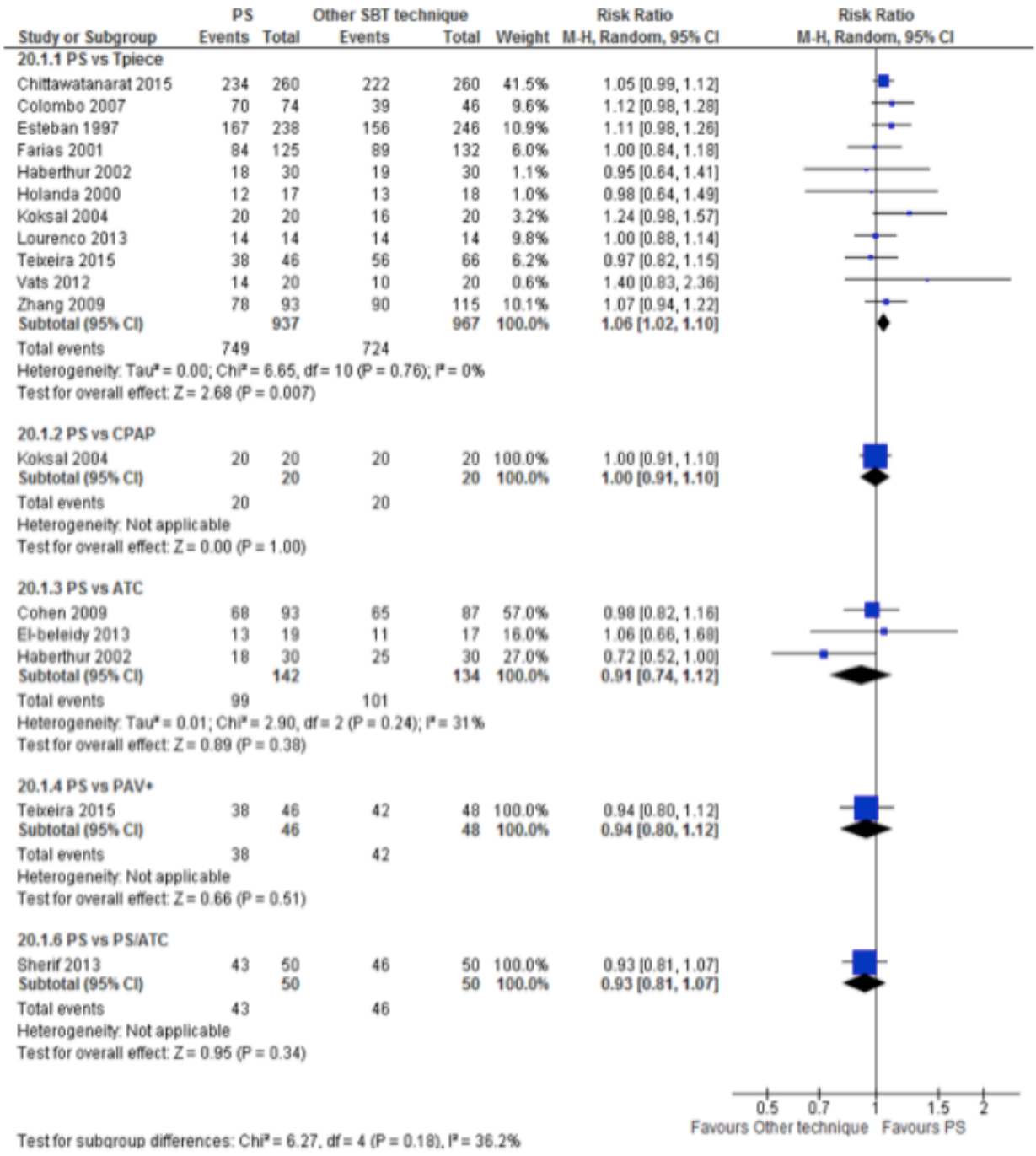
Electronic Figure 1: Risk of Bias of the Included Trials



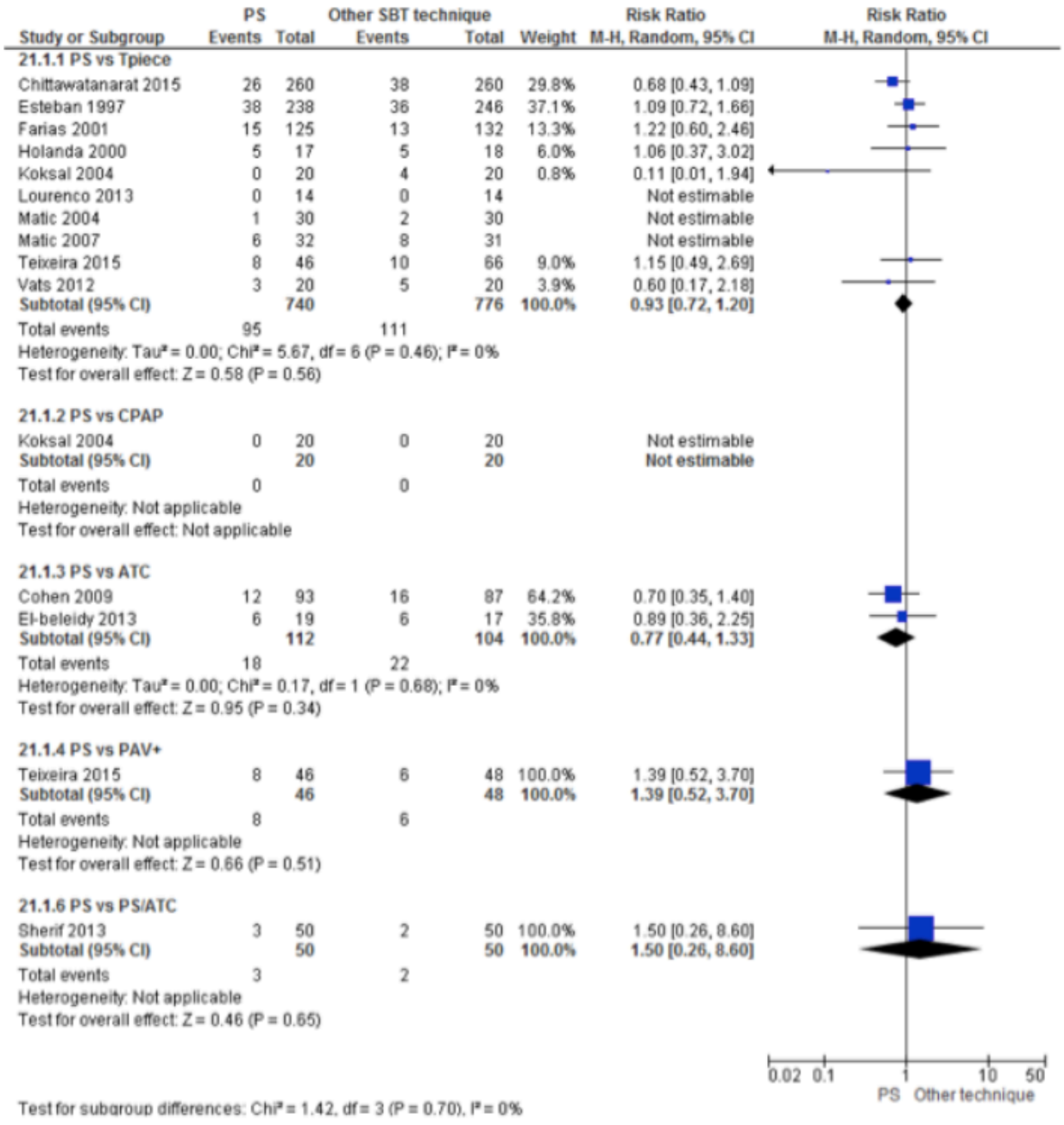
Electronic Figure 2: Forest Plot Comparing PS vs. Other Techniques on SBT Success



Electronic Figure 3: Forest Plot Comparing PS vs. Other Techniques on Extubation Success



Electronic Figure 4: Forest Plot Comparing PS vs. Other techniques on Reintubation

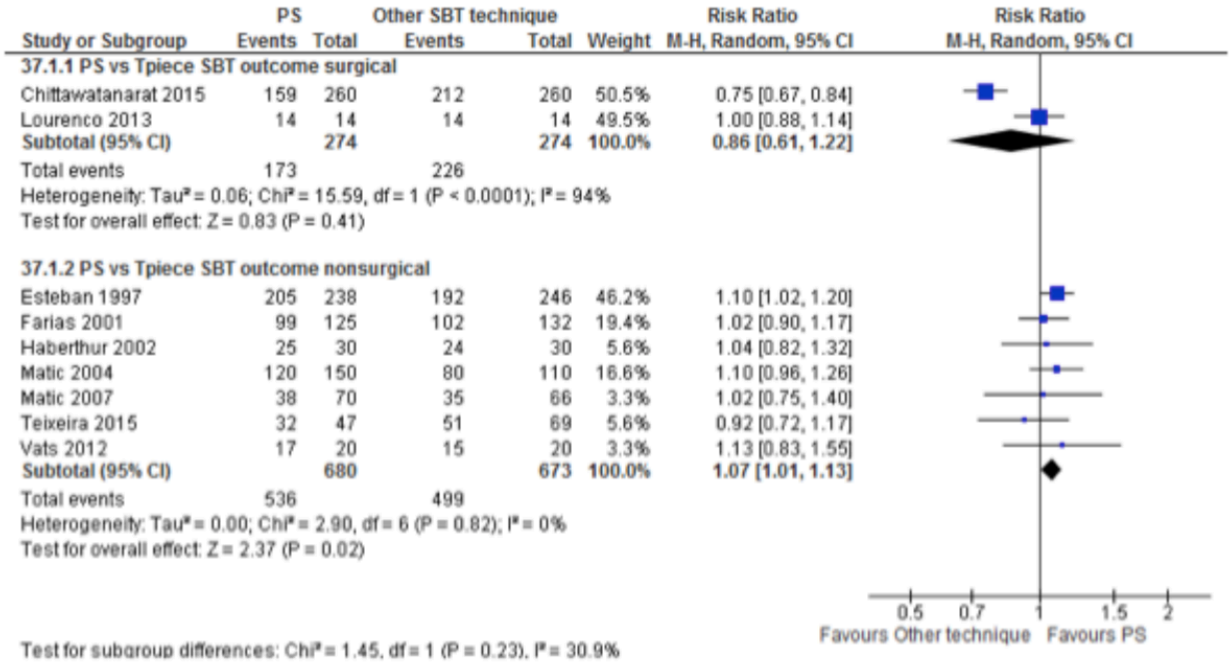


Effect of spontaneous breathing trial technique (PS vs. Other Technique) on reintubation. The pooled risk ratio with 95% confidence interval (CI) was calculated using a random effects model. Weight refers to the contribution of each study to the overall estimate of treatment effect.

Legend

RR = risk ratio, CI = confidence interval, PS = Pressure Support

Electronic Figure 5: Subgroup Analysis: Forest Plot Comparing PS vs. T-piece on SBT Success Based on Pretest Probability



RR = risk ratio, CI = confidence interval, PS = Pressure Support

10 CONCLUSÕES E CONSIDERAÇÕES FINAIS:

A descontinuação da VM em pacientes portadores de DPOC é ainda uma área do conhecimento médico em que persistem incertezas significativas, em dissonância com a relevância deste tópico levando-se em consideração a prevalência da entidade e os impactos de eventuais eventos adversos transcorridos ao longo do processo de desmame.

No que diz respeito especificamente aos TVEs, é possível concluir-se que cada teste terá um desempenho próprio de acordo com o perfil de paciente avaliado: desmame simples, complicado, prolongado, portador ou não de DPOC ou doença cardiovascular. Não é possível tecer-se recomendações genéricas para uma população heterogênea de pacientes em desmame acerca de qual o teste mais adequado para todo e qualquer contexto clínico.

O ensaio clínico realizado supre uma importante lacuna através da realização de um experimento multicêntrico e randomizado que verificou associação independente entre o teste em Tubo-T com a maior duração da VM após o teste em pacientes portadores de DPOC em desmame difícil, não havendo influência sobre a taxa de reintubação em 48 horas ou a qualquer tempo. Estes achados permitem que se recomende o teste em PSV como estratégia superior em relação ao Tubo-T para este subgrupo de pacientes. Entretanto, estes achados não podem ser generalizados para toda a população de pacientes criticamente enfermos portadores de DPOC.