UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

USO DA TOMOGRAFIA DE IMPEDÂNCIA ELÉTRICA ASSOCIADO A DADOS CLÍNICOS E VENTILATÓRIOS PARA AVALIAÇÃO DO PROCESSO DE DESMAME DA VENTILAÇÃO MECÂNICA DE PACIENTES COM SARA

IURI CHRISTMANN WAWRZENIAK

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RESUMO

Base teórica: A síndrome da angustia respiratória aguda (SARA) é caracterizada por intensa resposta inflamatória e a ventilação mecânica (VM) protetora é fundamental. A presença da ventilação espontânea tem efeitos benéficos, porém em casos mais graves pode ser deletéria. A repercussão da ventilação espontânea durante o desmame da VM dos pacientes com SARA ainda é pouco entendida e estudada.

Objetivo: Avaliar o desmame da VM em pacientes com SARA através da tomografia de impedância elétrica (TIE) associado a parâmetros clínicos e ventilatórios.

Métodos: Estudo de coorte prospectivo de pacientes com SARA que tiveram critérios de melhora e foram definidos pela equipe assistente aptos para suspender o uso de bloqueador neuromuscular (BNM) e sedativos e iniciar o desmame da VM. Os dados da TIE e da mecânica pulmonar foram coletados em quatro momentos: basal (Tpre) e após 30 minutos (T30min), 2 horas (T2h) e 24 horas (T24h) após a troca do modo ventilatório controlado (VCV ou PCV) para modo ventilatório espontâneo (PSV).

Resultados: o estudo incluiu 25 pacientes entre julho/2017 e fevereiro/2019. Os pacientes foram divididos conforme o tipo de desmame: 09 simples, 08 difícil e 08 prolongado. A duração da VM, delirium, agitação, fraqueza adquirida na UTI, traqueostomia, tempo de internação na UTI foram significantemente maiores no grupo de desmame difícil e prolongado. O volume corrente (VC) e a *driving pressure* (ΔP) aumentaram significativamente durante mudança do modo ventilatório controlado para espontâneo no grupo de desmame quando

comparado com o desmame simples (p tempo=0,0001). Os pacientes com desmame prolongado apresentaram maiores volumes pulmonares após o início da ventilação espontânea(p=0,02)*. Os pacientes com desmame prolongado tiveram uma tendência de maior de ventilação em regiões posteriores e redução da relação ventral/dorsal (V/D) visualizados pela TIE.

Conclusão: O desmame da VM de pacientes com SARA tem elevada proporção de desmame difícil e prolongado associados com piores desfechos clínicos. As alterações pulmonares visualizada através da TIE e da avaliação da mecânica pulmonar mostraram ser relevantes no grupo de desmame prolongado da VM e poderiam ser monitorizadas rotineiramente. Mais estudos poderiam ser realizados para avaliar a ventilação espontânea e o desmame da VM em pacientes com SARA para continuar a proteger os pulmões.

Palavras chave: síndrome da angustia respiratória aguda; desmame da ventilação mecânica; tomografia de impedância elétrica; mecânica pulmonar

ABSTRACT

Background: The acute respiratory distress syndrome (ARDS) is characterized by an intense inflammatory response and protective mechanical ventilation (MV) is essential. The presence of spontaneous breathing has beneficial effects, however, it can be harmful in more severe cases. The repercussion of spontaneous breathing and its repercussion during weaning from MV in patients with ARDS is still poorly understood and studied.

Objective: Evaluate weaning from MV in patients with ARDS using electrical impedance tomography (EIT) with clinical and ventilatory parameters.

Methods: Prospective cohort study of patients with ARDS who presented improvement criteria and were judged by the attending team to be able to suspend the use of neuromuscular blocker (NMB) and sedatives, and start weaning from MV. The EIT and pulmonary mechanics data were collected at baseline (Tpre) and after 30 minutes (T30min), 2 hours (T2h) and 24 hours (T24h) after changed from controlled mode (VCV or PCV) to spontaneous mode (PSV).

Results: The study included 25 patients between July,2017 and February,2019. The patients were 09 simple, 08 difficult and 08 prolonged weaning. The duration of MV, delirium, agitation, intensive care unit–acquired weakness (ICU-AW), tracheostomy, length of stay (LOS) and mortality of the ICU were higher difficult and prolonged weaning group. The tidal volume (TV) and driving pressure(ΔP) increased when changing from controlled to spontaneous mode, mainly in the prolonged weaning group when compared with simple weaning group (p time=0.0001). The patients with prolonged weaning presented larger total volumes after begin of the spontaneous ventilation (p=0.02). The prolonged

weaning group had a tendency more posterior region ventilation and reduction of the ventral/dorsal(V/D) ratio visualized by EIT.

Conclusion: The weaning from MV of patients with ARDS has a high proportion of difficult and prolonged weaning associated with worse clinical outcomes. The pulmonary changes seen by EIT and assessment of pulmonary mechanics showed to be relevant in the prolonged and difficult weaning group and could be monitored routinely. Further studies should be realized to evaluate the spontaneous breathing and weaning from MV in ARDS to continue to protect the lung.

Key Words: Respiratory Distress Syndrome, Adult; Ventilator Weaning; Respiratory Mechanics; Electric Impedance Tomography

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LISTA DE ABREVIATURAS E SIGLAS EM PORTUGUÊS

BNM – Bloqueador Neuromuscular

ΔP – Pressão de Distensão

FiO2 – Fração Inspirada de Oxigênio

IRp – Insuficiência Respiratória

PaO2 – Pressão Parcial Arterial de Oxigênio

PSV – Modo Ventilatório Pressão de Suporte

PCV – Modo Ventilatório Pressão Controlado

SARA – Síndrome da Angustia Respiratória Aguda

TIE – Tomografia de Impedância Elétrica

TC – Tomografia Computadorizada

TRE – Teste de Respiração Espontânea

UTI: Unidade de Tratamento Intensivo

VC – Volume Corrente

VCV – Modo Ventilatório Volume Controlado

VM – Ventilação Mecânica

LISTA DE ABREVIATURAS E SIGLAS EM INGLÊS

ARDS – "Acute Respiratory Distress Syndrome"

APRV – Modo Ventilatório "A*irway Pressure-Release Ventilation*"

BS – "B*reath Staking*"

ΔP – "Driving Pressure"

EIT – "Electrical Impedance Tomography"

ECMO – "Extracorporeal Membrane Oxygenation"

FiO_2 – "Fractional Inspired Oxygen Concentration"

ICU – "Intensive Care Unit"

ICU-AW – "Intensive Care Unit–Acquired Weakness"

LOS – "Length of Stay"

MRC – "Medical Research Council"

MV – "Mechanical Ventilation"

NAVA – "Neurally Adjusted Ventilatory Assist"

PEEP – "Positive End-Expiratory Pressure"

P-SILI – "Patient-self Inflicted Lung Injury"

NMB – "Neuromuscular Blocker"

PSV – "Pressure Support Ventilation" mode

PCV – "Pressure Controlled Ventilation" mode

RR – "Respiratory Rate"

SBT – "Spontaneous Breathing Trial"

SAPS 3 – "Simplified Acute Physiology Score 3"

STROBE – "Strengthening the Reporting of Observational Studies in Epidemiology"

SPSS – "Statistical Package for the Social Sciences"

TV – "Tidal Volume"

Tpre – "baseline collection performed in a controlled ventilatory mode (VCV or PCV)"

T30min – "30 minutes after changed to spontaneous mode PSV"

T2h – "two hours after changed to PSV"

T24h – "24 hours after changed to PSV'

VCV – "Volume Controlled Ventilation" mode

V/D Ratio – "Ventral and Dorsal Ratio"

VILI – "Ventilator-induced Lung Injury"

SUMÁRIO

1. INTRODUÇÃO

Desde a descrição inicial da síndrome da angústia respiratória aguda (SARA), em 1967, por Ashbaug et al., houve vários avanços do entendimento e manejo da SARA durante as últimas décadas[1]. Dentre as descobertas relacionadas à fisiopatologia estão os estudos de imagem pela tomografia computadorizada (TC) mostrando a heterogeneidade pulmonar e a formulação do conceito de *Baby Lung*[2-4]. Outro aspecto da fisiopatologia está relacionada a lesão inflamatória causada pelo fator desencadeante da SARA e o desenvolvimento do entendimento da lesão causada pela ventilação mecânica (VM), chamada V*entilator-Induced Lung Injury*(VILI)[5-8]. Através desse entendimento, puderam-se ventilar os pacientes com SARA através de maneiras mais racionais e protetoras dos danos relacionados à VILI[9]. Essas estratégias usam volumes correntes (VC) mais baixos que os usados para pacientes com pulmões normais e podem ser ajustados conforme os limites de pressões de platô, *driving pressure*(ΔP) e *mechanical power*[10, 11]. As estratégias ventilatórias protetoras também permitem o uso de hipercapnia permissiva e ajustes de *positive end expiratory pressure*(PEEP), associados, em casos mais graves, a posição prona, e, nos casos refratários, o uso de *extracorporeal membrane oxygenation*(ECMO)[12-19]. Porém, há evidências que a estratégia ventilatória protetora pode não ser suficientemente protetora em alguns pacientes[20].

A eliminação dos esforços ventilatórios espontâneos nas fases precoces da SARA tem mostrado redução da mortalidade[21]. Entretanto, há estudos mostrando que a preservação da ventilação espontânea melhora as trocas gasosas em formas menos graves da SARA [22, 23]. Papazian et al. demonstrou o benefício do emprego de bloqueador neuromuscular (BNM) na face precoce

da SARA o que poderia ser explicado pelo melhor controle da contratura da musculatura respiratória, estabilização de unidades alveolares instáveis e redução da VILI(21). Porém, o estudo ROSE trial não mostrou diferenças significativas nos desfechos para pacientes que usaram BNM comparados com os controles(24). Devido a esses resultados conflitantes, ainda há na literatura um debate sobre o real benefício do BNM na SARA através da abolição dos movimentos ventilatórios espontâneos e assincronias do pacientes com a VM(25). Brochard et al. tem preconizado em pacientes com SARA a instituição de VM para minimizar os efeito deletérios da ventilação espontânea em fases iniciais dos pacientes com SARA, o chamado *Patient-Self Inflicted Lung Injury*(P-SILI)(26). Apesar desse conhecimento nas fases iniciais da SARA, estudos em fase tardia da SARA em que geralmente está ocorrendo o processo de desmame da VM não têm sido realizados. Postulamos que durante o processo de desmame da VM pode ocorrer piora do quadro pulmonar devido à perda parcial ou completa do controle da estratégia ventilatória protetora e, consequentemente, falha do desmame da VM em alguns pacientes. Essas alterações durante o desmame da VM dos pacientes com SARA necessitam ser mais estudadas assim com o desenvolvimento de novas ferramentas poderiam ser de grande valia no entendimento desse processo e suas repercussões(27).

O uso da tomografia de impedância elétrica (TIE) tem demonstrado ser uma ferramenta auxiliar na avaliação e monitorização de pacientes com SARA(28). A avaliação não invasiva da TIE abrange a visualização em tempo real das imagens pulmonares assim como auxilia na titulação da PEEP, monitorização dos volumes e pressões pulmonares, identificação de pneumotórax, assincronias, *pendelluft*, estimativa da perfusão pulmonar e débito cardíaco(29-

32). Apesar dos poucos estudos do uso de TIE no processo desmame da VM, essa ferramenta parece ser promissora na avaliação pulmonar nos pacientes com SARA em desmame da VM(33).

Portanto, o estudo da influência da ventilação espontânea e suas repercussões no momento do desmame do suporte ventilatório dos pacientes com SARA é necessário e fundamental para evitar danos relacionados a VILI e P-SILI. O presente estudo tem por finalidade a avaliação do processo de desmame da VM em pacientes com SARA e suas repercussões através do uso da TIE e de parâmetros clínicos e ventilatórios da mecânica pulmonar.

2. REVISÃO DA LITERATURA

2.1 Estratégias para localizar e selecionar as informações

A revisão da literatura foi realizada visando os aspectos relacionados a avaliação do desmame da VM em pacientes com SARA, VILI e uso de TIE. Foi realizado busca no período de 1967 a 2020 e nas seguintes bases de dados eletrônicas: MEDLINE, LILACS, Pubmed e CAPES e sites de ciência relevantes. A busca foi limitada a artigos em língua inglesa e/ou portuguesa e usamos os vocabulários controlados quando possível. Foram usados os seguintes *Mesh terms* do MEDLINE: (1)"Respiratory Distress Syndrome, Adult"[Mesh], (2)"Ventilator Weaning"[Mesh], (3)"Respiratory Mechanics"[Mesh], (4)"Ventilator-Induced Lung Injury"[Mesh], (5)"Tomography"[Mesh], (6)"Electric Impedance"[Mesh]. Após os resultados, foram selecionados os artigos de relevância ao tema do estudo proposto conforme a figura 1.

| MEDLINE LILACS | | PubMed | |
| SciELO | | CAPES | |

34421 /407	**1**	19105	**204 artigos**
29		48446	
7577 /180	**2**	3867	**25 artigos**
42		9.763	
21998 /244	**3**	26227	**26 artigos**
73		30280	
7709 /11	**4**	5662	**21 artigos**
10		12153	
654170 /1688	**5**	906813	**57 artigos**
3142		998195	
24412 /241	**6**	16613	**4 artigos**
35		113640	
1504 /2	**1 + 2**	196	**39 artigos**
0 (2 artigos)		1893	
1568 /0	**1 + 3 + 4**	35	
1 (14 artigos)		1568	
2815 /15	**5 + 6**	1676	**51 artigos**
4		5547	
142/4	**1 + 5 + 6**	63	**12 artigos**
0 (7 artigos)		206	
28/0	**2 + 5 + 6**	5	**4 artigos**
0		47	
1233/6	**2 + 3**	262	
1 (3 artigos)		1158	
723/0	**2 + 4**	77	**64 artigos**
0		917	
733/0	**2 + 3 + 4**	1	**21 artigos**
0		994	

Figura 1: Estratégia de Busca de Referências Bibliográficas

Em cada box central os números indicados correspondem aos descritores do fator de estudo:(1)"Respiratory Distress Syndrome, Adult",(2)"Ventilator Weaning", (3)"Respiratory Mechanics", (4)"Ventilator-Induced Lung Injury", (5)"Tomography" e (6) "Electric Impedance";
*Critérios de exclusão dos artigos: tema não relacionado aos objetivos da pesquisa; artigos não disponíveis na integra; artigos não disponíveis em inglês e/ou português

2.2 Revisão da Literatura

2.2.1 SARA: Resposta Inflamatória ao Fator Desencadeador

A SARA é uma síndrome descrita desde 1967 e se caracteriza por intensa resposta inflamatória pulmonar(1, 34, 35). Posteriormente, um consenso definiu melhor os seus critérios em 1994 e foram atualizadas suas definições pelo consenso de Berlim em 2012(36, 37). É caracterizada por infiltrado pulmonar bilateral de causa não cardiogênica associado a hipoxemia e redução da complacência pulmonar(34). A importante resposta inflamatória é desencadeada por fatores predisponentes de múltiplas etiologias. As etiologias podem ser de causas diretas pulmonares, como uma pneumonia ou aspiração pulmonar, ou de causas indiretas não pulmonares, como uma sepse não pulmonar, politrauma ou pancreatite(34). No entanto, a presença de um fator desencadeador não é suficiente para o desenvolvimento da SARA. Isso sugere que é necessário que outros fatores como genéticos, virulência de patógenos, condições coexistentes e fatores comportamentais contribuam para o desenvolvimento desse quadro pulmonar(34, 38). A histologia típica da lesão pulmonar caracteriza-se por dano alveolar difuso e é causada pela liberação de citoquinas pró-inflamatórias tais como fator de necrose tumoral, interleucinas 6 e 8(34). O aumento dessas citoquinas leva a ativação de neutrófilos e liberação de mediadores tóxicos como espécies reativas de oxigênios e proteases lesando o endotélio capilar e epitélio alveolar. O dano endotelial e epitelial associados a restos celulares e a saída de fluidos ricos em proteínas para o espaço alveolar confluem para o desenvolvimento de edema alveolar. Esse edema alveolar juntamente com a perda da surfactante pulmonar gera colapso alveolar levando a piora do *shunt*

pulmonar, hipoxemia e redução da complacência pulmonar(34). Apesar dos avanços no seu entendimento e cuidados desde a sua descrição inicial, é uma síndrome frequente de admissão na unidade de terapia intensiva (UTI) com elevada mortalidade e morbidade(39-43).

2.2.2 SARA: Lesão induzida pelo ventilador - VILI

A VM é usada para preservar a vida e manter as trocas de gases e a homeostase ácido-base. Ela é uma ferramenta de suporte ventilatório até a recuperação do paciente diante de uma disfunção respiratória aguda ou crônica secundária a um insulto pulmonar ou sistêmico(44). A VM invasiva ganhou destaque desde a epidemia de poliomielite na década de 50. Naquela epidemia os pacientes tratados com traqueostomia e pressão positiva a mortalidade reduziu de 87% para em torno 40%(45). A VM foi originalmente instituída em pacientes com pulmões normais em pacientes comatosos durante procedimentos cirúrgicos ou poliomielite. Nesses casos, a VM era realizada com baixos níveis pressões e era relativamente segura visto ser usada na maioria em pacientes com pulmões normais.

No entanto, a VM pode não ser tão benéfica e segura em todos os aspectos de pacientes graves com lesão pulmonar. Pode haver melhora das trocas de gases e do equilíbrio ácido-básico, porém em casos com dano pulmonar grave há a necessidade de parâmetros ventilatórios elevados para essa correção. Os respiradores podem gerar grandes pressões pulmonares aumentando o risco de lesão secundária, denominada barotrauma(45). Webb e Tierney avaliaram, na década de 70, através de experimentos em ratos que o uso de elevadas pressões de distensão pulmonar levava a edema pulmonar e lesões pulmonares

semelhantes a SARA(46). Dreyfuss et al. mostraram que a presença de volumes pulmonares elevados também podem causar lesão pulmonar através de hiperdistensão alveolar, o chamado volutrauma(8, 47). No final da década de 90, demonstrou-se que a lesão pulmonar associado a VM deletéria gerava liberação de mediadores inflamatórios do pulmão para outros órgãos ocasionado ou perpetuando a disfunção de múltiplos órgãos e sistemas, o chamado biotrauma(6, 7, 48, 49). Essa lesão poderia ser por hiperdistensão alveolar ou por outro mecanismo deletério ocasionado pela abertura e fechamento cíclico alveolar, o atelectrauma(8).

Além da inflamação relacionado ao fator desencadeador da SARA, a VM *per se* também pode ser um causador e perpetuador da lesão pulmonar inflamatória. Por isso, os mecanismos clássicos descritos acima de barotrauma, volutrauma, atelectrauma e biotrauma, levam ao que chamamos de lesão induzida pela VM – VILI(8). Ranieri et al. também sugeriu que a VILI poderia desenvolver e propagar a inflamação em pacientes com SARA(50). Muitos fatores podem estar relacionados ao seu desenvolvimento e estratégias protetoras de VM baseadas em redução do VC e das pressões nas vias aéreas foram formuladas baseadas no conceito do "*Baby Lung*" e comprovadas na redução dos efeitos deletérios da VM(2, 8, 13, 14, 51). Além disso, as alterações hemodinâmicas relacionadas a relação entre coração/pulmão de pacientes com VM podem ocasionar alterações no fluxo sanguíneo pulmonar e disfunção do ventrículo direito e também estar correlacionados na formação do edema e lesão pulmonar(52, 53). Portanto, o entendimento das forças aplicadas nos pulmões – *stress* – e a deformação resultante – *strain* – aliados aos conceitos de VILI são essenciais para proteção pulmonar dos efeitos nocivos da VM(54).

2.2.3 SARA: Lesão Pulmonar Induzida pelo Paciente – P-SILI

A escolha da melhor maneira de ajustar a VM tem avançado através de estratégias ventilatórias protetoras principalmente em pacientes com lesão pulmonar(55). O objeto da VM não se restringe somente em adequar as trocas gasosas, mas em ajustar a VM baseados em parâmetros para prevenção de VILI(56). Diante disso, o VC e os níveis da PEEP podem estar implicados na melhor estratégia de VM para cada paciente. No entanto, a gravidade da lesão pulmonar associado a fatores do paciente como nível de sedação, presença de ventilação espontânea e uso de BNM vão influenciar na avaliação e, consequentemente, na melhora ou piora da resposta inflamatória pulmonar e sistêmica. Recentemente, Brochard et al. tem mostrado que um novo fator relacionado ao esforço ventilatório do paciente pode causar lesão inflamatória, a denominada P-SILI(57). Em pacientes com insuficiência respiratória (IRp), a presença de intensos esforços ventilatórios do próprio paciente causa lesão pulmonar e piora o quadro respiratório. Esses intensos esforços ventilatórios geram elevados VCs e movimentos estruturais multidirecionais - *swings* - pulmonares e são relacionados ao aumento do estímulo central do sistema nervoso central – *drive* - respiratório de forma inapropriada(26, 58).

Papazian et al. avaliou em pacientes com SARA precoce o uso de BNM – Acurasys trial – e mostrou redução da mortalidade e efeitos adversos relacionados a VM(21). Essa intervenção tem mostrado que a presença de grandes esforços ventilatórios espontâneos pode ser deletéria em pacientes mais graves e que o uso do BNM ajuda na abolição desses esforços ventilatórios. Entretanto, Moss et al. – ROSE trial - não conseguiu os mesmos resultados com o uso do BNM em pacientes com SARA(24). Em editorial de Slutsky e Villar, a

falta de desfechos similares dos dois estudos com o uso de BNM em SARA estava relacionado a exclusão de pacientes com uso prévio de BNM, ao uso de critérios diferentes para definição de SARA, a falta de avaliação das assincronias dos pacientes com o respirador e do esforço ventilatório espontâneo(25). Chang et al. realizou meta-análise do uso BNM em SARA e mostra redução da incidência de barotrauma e mortalidade em pacientes que usaram BNM(59). Além de ensaios clínicos, há dados na literatura mostrando que persistentes e intensos esforços inspiratórios aumentam o *stress* tecidual e a pressão transvascular, fluxo vascular, edema alveolar e, consequentemente, a lesão pulmonar(26, 60-62). Por isso, os mecanismos da lesão inflamatória causada pelo fator desencadeador, pelo respirador e esforço do paciente devam ser contemplados, entendidos e controlados desde o início da VM até o desmame do suporte ventilatório para o melhor manejo dos pacientes com SARA(27).

2.2.4 Ventilação Controlada x Espontânea na SARA

Diante da presença de potenciais efeitos adversos da VM e o possível efeito benéfico do BNM em alguns pacientes, tem se discutido na literatura o real impacto da ventilação espontânea, principalmente, em pacientes com SARA. O objetivo da respiração é permitir que o ar chegue aos alvéolos e haja troca gasosa. Do ponto de vista fisiológico, nosso sistema respiratório está evoluído após milhões de anos para ventilação espontânea em comparação a curta evolução a partir da metade do século 20 da VM controlada e com pressão positiva(23, 45).

A ventilação se faz pelas diferenças de pressão criadas no sistema respiratório para que a chegada do VC da atmosfera chegue até os alvéolos. Em ventilações espontâneas não assistidas esse gradiente pressórico é criado somente pelo trabalho da musculatura respiratória. Na VM, o respirador é um gerador do gradiente de pressão associados a musculatura respiratória. Na VM controlada a pressão positiva direciona o VC para os alvéolos pois a musculatura está em posição passiva(63). Portanto, fisiologicamente a insuflação pulmonar ocorre na presença da pressão nas superfícies pulmonares com pressão negativa na ventilação espontânea e positiva em VM. Em pacientes com VM, a presença da ventilação espontânea gera pressões negativas que acopladas a pressão positiva do respirador, potencializam a pressão transpulmonar (Palv = pressão via aérea – pressão pleural). Por isso, a avaliação da mecânica ventilatória através da avaliação das pressões e volumes do sistema respiratório é de grande valia para entendimento do estado pulmonar e sua capacidade de tolerar a ventilação espontânea especialmente nos pacientes com SARA(63, 64). Dependendo da condição do paciente e o modo ventilatório, as pressões determinadas pelo respirador mecânico são determinadas pela equação: $Pav(t) + Pmus(t) = PEEP + (Esr \times VC(t)) + (Rrs \times Flow(t))$, onde a Pav = pressão de abertura via aérea, Pmus = pressão gerada pela musculatura respiratória, PEEP = pressão no final da expiração da Pav, Ers= elastância do sistema respiratório, VC = volume corrente, Rsr = resistência do sistema respiratório, Fluxo = fluxo via aérea. Na equação, $(Esr \times VC(t)) + (Rrs \times Flow(t))$ representa os componentes elásticos e resistivos das pressões gerada através do sistema respiratório pelo volume inspirado e expirado do ciclo respiratório. Durante a ventilação espontânea não assistida por VM, a Pav máxima é igual a PEEP (se presente)

ou a pressão atmosférica, e, portanto, PEEP (ou zero) + Pmus é a pressão total do sistema respiratório. Na inspiração, a Pmus reduz a pressão pleural (Ppl), e a Pmus é a diferença da pressão da caixa torácica relaxada e a mudança da Ppl para o volume de gás. As medidas da pressão esofágica (Pesof) ajudam a avaliar a Ppl e consequentemente da elastância da parede torácica (Ew) na avaliação a beira leito(63). Essas avaliações podem ser relevantes para avaliação e estimativa da pressão gerada pela musculatura inspiratória e o trabalho respiratório principalmente em pacientes que tenham alterações pulmonares(65). Além disso, em pacientes que tenham aumento do trabalho respiratório e intensos esforços inspiratórios podem gerar amplos *swings* negativos de pressões. Esses *swings* negativos transmitem pressões das regiões pleurais para regiões pulmonares e podem causar edema pulmonar por pressões negativas(66-68).

Quando há a ventilação espontânea adicionada a pressão positiva da VM, a Pav aumenta ocasionando aumento da pressão total do sistema respiratório com elevados fluxos e elevados VCs. Essas alterações podem determinar em pacientes que foram trocados da ventilação controlada para espontânea a ocorrência de barotrauma e volutrauma. Outro aspecto que pode haver está relacionado ao risco de colapso e exsudato alveolar que é gerado do aumento da pressão transpulmonar e amplificado pela presença de elevadas Pmus do intenso esforço ventilatório. Em pacientes com intensos esforços espontâneos durante o modo ventilatório pressão de suporte ventilatório (PSV), a pressão transpulmonar pode ficar abaixo da PEEP ajustada e levar a perda de recrutamento alveolar(69). Essas alterações podem levar a ciclos ventilatórios com *swings* de Pmus e assincronia do paciente com o respirador. A avaliação

da Pmus à beira leito através da medida do uso de cateter esofágico ou da pressão gerada pela oclusão breve da via aérea são medidas úteis para estimar do esforço ventilatório do paciente e pode guiar a ajustar ventilação e evitar subassistência ou superassistência(70, 71). Outra ferramenta interessante para avaliação do esforço ventilatório é a pressão gerada durante os primeiros 100ms contra a via aérea ocluída, a "P0.1"(72). Essa medida pode ser utilizada para avaliação do *drive* respiratório aumentado em pacientes com SARA(58, 73). Amato et al. tem mostrado através de uma análise de 3562 pacientes com SARA a relevância da medida da pressão de distensão – *driving pressure* - ΔP (Pav = VC / Csr = Pressão de Platô – PEEP) nos desfechos de SARA(10). A ΔP pode ser uma forma de monitorização do *strain* aplicado no pulmão pelo VC ajustado. No entanto, a sua avaliação na presença de ventilação espontânea é mais difícil pois o paciente pode gerar esforço inspiratório, fluxo aéreo e pressão no sistema durante a avaliação(74). No entanto, Bellani et al. avaliou e demonstrou ser possível medir a ΔP em alguns pacientes em PSV o que é interessante visto a necessidade da monitorização das alterações da mecânica pulmonar de pacientes com SARA não somente durante o uso da ventilação controlada(75).

Em pacientes com SARA, outra alteração vista principalmente na retirada do BNM e liberação da ventilação espontânea do paciente são as assincronias do paciente com o respirador. Esse achado deriva da interação do esforço do paciente e o quanto o respirador consegue suprir as elevadas necessidades respiratórias desses pacientes. A relação da assincronia em pacientes com SARA pode não estar relacionado somente a aspectos do ajuste do respirador mas a fatores relacionados ao paciente como o aumento do *drive* respiratório(73, 76). A presença de assincronias de duplo disparo e disparo reverso podem

causar consecutivos disparos inspiratórios com acúmulo de VCs sobrepostos gerando uma terceira forma de assincronia que é o empilhamento - *breath-stacking(BS)*. Esse volume pulmonar gerado pelo empilhamento ou acúmulo de VCs ocasiona VC mais elevados do que o ajustado e pode estar acima dos VCs preconizados para um estratégia ventilatória protetora de pacientes com SARA (77-80). As assincronias também causam dispneia, aumento do desconforto e trabalho respiratório do paciente e podem causar piora da troca gasosa e gerar auto-PEEP. Nos casos de pacientes que apresentam elevada quantidade de assincronias e que sua correção é difícil pode haver a necessidade de sedação profunda e uso de BNM. E está relacionada a desmame da VM prolongado, aumento do tempo de VM, e mortalidade nos casos mais graves(81, 82). Um dos motivos que causa assincronia em pacientes com SARA é a redução da complacência pulmonar associados a aumento do *drive* respiratório(73). A assincronia é mais frequentemente percebida quando há retirada do BNM e redução da sedação para desmame da VM. A mudança do modo ventilatório controlado para modo ventilatório PSV é uma das medidas para tentar reduzir as assincronias nesse período inicial de desmame da VM quando a ventilação espontânea é mais presente. Devido as propriedades do sistema respiratório, a pressão negativa gerada pela contração da musculatura inspiratória pode dificultar a mudanças do fluxo e do disparo – *trigger* - do respirador. Nesses pacientes pode haver um retardo do disparo relacionado a redução da complacência pulmonar. Essa redução da complacência pulmonar acarreta uma redução rápida do fluxo inspiratório após atingir o pico inspiratório. Essa rápida redução do fluxo inspiratório pode gerar os efeitos indesejados da assincronia. No entanto, mesmo em modo PSV pode ocorrer a perpetuação da presença de

assincronias, taquipneia, esforço ventilatório excessivo e perda da estratégia ventilatória protetora. Mauri et al. avaliou a assincronia entre modo ventilatório PSV e *Neurally Adjusted Ventilatory Assist* (NAVA) em pacientes com SARA com reduzida complacência pulmonar e mostrou uma redução das assincronias de ciclagem prematura, disparo inefetivo, auto disparo e duplo disparo quando utilizado o modo NAVA comparado a PSV(83). O uso do modo NAVA tem demonstrado redução de assincronias com melhora da interação do paciente com o respirador(84-87). A promoção de ventilações espontâneas assistida pelo respirador é essencial a otimização da interação do paciente com o respirador(88). Entretanto, a avaliação da ventilação espontânea e assincronias é difícil de estimar a sua magnitude pelo profissional a beira leito e novas ferramentas de monitorização e quantificação deveriam ser empregados(89).

Durante a VM, a presença da ventilação espontânea pode ocasionar intensos e descontrolados esforços ventilatórios levando a grandes VCs e diferenças regionais de ventilação podendo ser deletérios aos pulmões(90). Em alguns pacientes pode haver perda do controle do VC ajustado e preconizado para pacientes com SARA e, consequentemente, os riscos de VILI e P-SILI, principalmente, nas formas mais graves de SARA(91, 92). Yoshida et al. avaliou em animais a influência da presença da ventilação espontânea em lesão pulmonar leve e grave(93). Nos animais com lesão pulmonar leve a ventilação espontânea melhorou a oxigenação, a aeração pulmonar e a redistribuição de VC em regiões dependentes. No entanto, a presença de esforços ventilatórios espontâneos nos animais com lesão pulmonar grave ocasionou aumento da pressão transpulmonar e ΔP com aumento das atelectasias e do colapso cíclico(93). Yoshida et al. avaliou a ventilação espontânea com VC baixos versus

moderados. O grupo com baixos VC teve melhor oxigenação, complacência pulmonar e aeração e, no grupo VC moderado, houve a presença de mais atelectasias pulmonares(94). Yoshida et al. mostraram em animais e um paciente com SARA que somente a limitação de VC não é suficiente para eliminar os efeitos deletérios a menos que os esforços espontâneos e o estresse local pulmonar sejam reduzidos(95). Forel et al. randomizaram 36 pacientes com SARA para usar BNM. Nos pacientes que usaram BNM houve redução de citoquinas e melhora da hipoxemia(96). Além disso, os esforços espontâneos causaram uma grande insuflação e recrutamento de regiões dorsais apesar do VC e pressão transpulmonar iguais dos animais paralisados. O efeito do *stress* local em regiões dorsais dependentes é diretamente relacionado ao comportamento sólido - *solid-like* - gerado pela Ppl durante o esforço ventilatório(65). Esse comportamento está relacionado a dano pulmonar onde o parênquima é heterogêneo com regiões não aeradas como uma consolidação pulmonar. Essa Ppl negativa gerada pela intensa contração diafragmática resulta em amplificação da pressão transpulmonar distribuídas de forma não homogênea no pulmão de comportamento *solid-like*. Nesse comportamento de lesão pulmonar, as pressões geradas principalmente em regiões dorsais são maximizadas pela ventilação espontânea causada pela intensa contração diafragmática e, consequentemente, risco de P-SILI. A mesma pressão gerada em pulmões normais, comportamento líquido - *fluid-like*, é distribuída de forma mais homogênea no sistema respiratório não gerando maiores danos como no comportamento *solid-like*(65).

Outro aspecto adicional relacionado ao esforço ventilatório espontâneo descontrolado com possível dano pulmonar pode estar relacionado ao fenômeno

de movimento aéreo pendular - *pendelluft*. Esse fenômeno é o movimento pendular de ar entre as diferentes regiões pulmonares. O *pendelluft* pode ser causado por um esforço excessivo induzindo redistribuição de gás intrapulmonar antes de iniciar uma nova insuflação pulmonar. Essa redistribuição de gás pode gerar pressões diferentes em regiões pulmonares não aeradas com risco de lesão pulmonar(77). Nesse fenômeno há uma insuflação das regiões dorsais (mais negativa) durante a ação diafragmática com concomitante desinsuflação da região ventral (menos pressão negativa) gerando um gradiente e o movimento do gás pendular(77). Em pacientes com pulmão normal e comportamento *fluid-like*, a contração diafragmática e o *pendelluft* não gera tantas oscilações pressóricas negativas quanto nos pulmões com lesão e comportamento *solid-like*(97). O fenômeno de *pendelluft* pode levar a hiperinsuflação dorsal com risco de piora da lesão pulmonar e consequentemente perda da capacidade de troca gasosa com retenção de CO_2, aumento do esforço ventilatório do paciente e falha do desmame da VM. Coppadoro et al. avaliaram 20 pacientes com teste de respiração espontânea (TRE) em modo ventilatório PSV a presença de *pendelluft* através da TIE, mostrando o fenômeno em 40% dos pacientes e com predominância da falha ao teste de TRE no grupo dos que tinham maior volume de *pendelluft*. Houve também uma maior retenção de CO_2 no grupo de elevado *pendelluft* sugerindo maior esforço ventilatório e falha de desmame da VM(98). Santini et al. mostraram em 10 pacientes com SARA que aumentos dos níveis de fluxo inspiratório levaram a aumento do *pendelluft* enquanto diferentes níveis de PEEP não teve efeito igual(99). Esse fenômeno é difícil de ser diagnosticado com as ferramentas usuais e a TIE pode mostrar e quantificar esse fenômeno.

Entretanto, há poucos estudos clínicos na literatura sobre o real impacto do fenômeno de *pendelluft* em pacientes com SARA e desmame da VM.

Apesar dos riscos da ventilação espontânea, ainda há muitas questões controversas na literatura sobre as reais vantagens e desvantagens de manter a ventilação espontânea em pacientes com IRp. Em pacientes com IRp com necessidade de VM invasiva, os modos controlados parecem ser o ideal na fase inicial visto a necessidade de restabelecer as trocas gasosas, descanso da musculatura respiratória e tempo para correção da causa da IRp. Após essa fase inicial, a mudança de modos ventilatórios controlados para espontâneos é comum no ambiente de terapia intensiva. Estudos experimentais e clínicos sugerem os efeitos benéficos do uso de ventilação espontânea(23, 90, 100).

Wrigge et al. avaliaram 24 porcos com SARA induzida e mostraram melhora da oxigenação relacionada a recrutamento de áreas dorsais não aeradas quando preservado a ventilação espontânea(101). Neumann et al. e mostraram o efeito benéfico em porcos do *shunt* intrapulmonar e oxigenação com a preservação da ventilação espontânea em modo ventilatório *airway pressure-release ventilation* (APRV) sendo explicada pelo aumento da ventilação em áreas dependentes e abertura de regiões não aeradas(102). Moraes et al. avaliaram os suspiros em modo PSV e PCV e houve redução do colapso alveolar e pressão transpulmonar em ratos sendo que há uma redução da inflamação pulmonar em PSV e suspiros sugerindo o efeito benéfico da ventilação espontânea em SARA leve(103). Putensen et al. avaliaram 24 pacientes com SARA e mostrou melhora da relação ventilação/perfusão com a presença de ventilação espontânea em modo ventilatório APRV quando comparado a ausência de ventilação espontânea(104). No entanto, nos pacientes em modo ventilatório PSV esse

efeito não foi demonstrado(104). Radke et al. avaliaram 30 pacientes cirúrgicos com o uso da TIE e mostrou uma redistribuição da ventilação durante os modos ventilatórios PCV e PSV. Nos pacientes sem a presença da VM onde foi preservado a ventilação espontânea não houve modificação da distribuição da ventilação(105). Mauri et al. avaliaram o uso de suspiros em modo ventilatório PSV em 20 pacientes e houve melhora da oxigenação, do volume pulmonar no final expiratório das regiões não dependentes e dependentes e, consequentemente, recrutamento e redução da heterogenicidade pulmonar(106). Putensen et al. compararam ventilação controlada e espontânea em 30 pacientes com trauma em risco de SARA. Houve redução do tempo de VM e UTI, melhora hemodinâmica e das trocas gasosas nos pacientes que mantiveram ventilação espontânea e níveis de sedação menor em relação ao pacientes em ventilação controlada(22). van Haren et al. realizaram uma coorte prospectiva em 459 UTIs em pacientes com SARA e mostraram que nos pacientes que tinham ventilação espontânea preservada em VM apresentaram menos dias de VM e internação na UTI(107).

Outro efeito benéfico da ventilação espontânea durante a VM é o aumento da atividade da musculatura ventilatória ativa e redução da atrofia diafragmática. A fraqueza diafragmática está associada a desmame difícil da VM e aumento do tempo de internação e mortalidade(108). A atividade diafragmática reduz rapidamente após o início da VM e evolui para disfunção diafragmática(109). Entretanto, o excesso de carga na musculatura diafragmática pode também causar fraqueza muscular aguda e desenvolver inflamação muscular e proteólise(110). Pellegrini et al demonstraram em porcos com SARA que o diafragma age ativamente mesmo durante a expiração reduzindo a formação de

atelectasias(111). Além da preservação do tônus muscular, a ventilação espontânea preserva a expansão pulmonar e as trocas gasosas de áreas com risco de colapso pulmonar. Em situações de aumento do volume minuto pulmonar por aumento da demanda metabólica (por exemplo febre ou doença pulmonar em atividade), dor ou agitação podem desencadear aumento da atividade muscular expiratória e da contração diafragmática. Essa atividade muscular diafragmática aumentada desloca o diafragma cefalicamente e por consequência reduz o volume pulmonar expiratório final e prejudica as trocas gasosas.

2.2.5 Desmame da VM na População Geral da UTI – o que é, como avaliamos, classificamos e procedemos a retirada do suporte ventilatório

O processo de desmame da VM engloba a retirada do suporte ventilatório. Esse processo começa tão logo a causa da IRp melhora ou é resolvida(112). A falha do desmame da VM é geralmente definida quando ocorre falha ao TRE ou necessidade de reintubação e reinicio de VM dentro das primeiras 48 horas após a extubação(113, 114). A falha de desmame da VM está correlacionada direta ou indiretamente a piores desfechos como aumento do tempo de VM, internação hospitalar e mortalidade(115, 116). A causa da falha do desmame pode estar relacionada a disfunções (respiratória, muscular, cardíaca, neurológica, endócrina, metabólicas e iatrogênicas) individuais ou em associação(117, 118). Entretanto, o entendimento da fisiopatologia da falha do desmame da VM pode ser complexa em alguns casos sendo que nem sempre é entendida na sua totalidade fazendo que o seu tratamento se torne difícil. A avaliação da causa de falha do desmame da VM em alguns pacientes comparados ao grupo de sucesso

tem sido estudada desde a década de 70 e 80(119-122). Milic-Emilic alertava que o desmame da VM parecia mais arte do que ciência diante do pouco conhecimento da época e que estudos científicos deveriam ser realizados sobre o assunto(123). No final da década de 80 e início da década de 90, houve a produção de ensaios clínicos em desmame da VM voltados sobre o melhor modo de realizar a retirada do suporte ventilatório através de tubo T ou modo ventilatório PSV(124-127).

O desmame da VM pode ser classificado conforme consenso internacional em três tipos: simples, difícil ou prolongado(113). O desmame simples são os pacientes que tiveram sucesso no primeiro TRE e foram extubados sem dificuldades. O desmame difícil são os pacientes que falharam ao primeiro TRE ou precisaram até três TREs ou até sete dias para o desmame da VM. E o desmame prolongado são pacientes que necessitam mais de sete dias para o desmame da VM. Estudos clínicos que usaram essa classificação têm mostrado que nos pacientes classificados como desmame prolongado, há uma associação de aumento da morbidade e mortalidade(128-133). Em estudo multicêntrico "WIND" propôs uma nova classificação baseada na duração do processo de desmame da VM (134). Essa classificação não considera o TRE na classificação do tipo de desmame da VM. Os autores propõem essa nova classificação pois engloba todos os pacientes que recebem VM. Estudos mostram também que essa classificação inclui os pacientes que morriam antes de começar o desmame da VM, traqueostomizados, tinham uma extubação não planejada ou eram transferidos para outra instituição não contemplados na outra classificação de consenso internacional(135, 136).

Além do critério da resolução ou melhora da causa da IRp para a retirada do suporte ventilatório, são usados rotineiramente também a estabilidade hemodinâmica, habilidade de tossir e manejar secreções respiratórias pelo paciente, estado neurológico adequado e melhora da hipoxemia. A avaliação da hipoxemia é realizada através da relação pressão parcial arterial de oxigênio (PaO2) / fração inspirada de oxigênio (FiO2) adequada associados a FiO2 ≤40% e PEEP≤6 cmH2O. Durante essa avaliação o paciente é trocado de modo ventilatório controlado a volume (VCV) ou pressão (PCV) para um modo espontâneo que é geralmente o modo PSV. Após o paciente alcançar esses critérios, o paciente realiza um TRE em PSV ou tubo T durante 30-120 minutos. Após essa avaliação é definido como apto ou não a extubação(112, 137). A troca gasosa é geralmente considerada essencial na avaliação para a decisão de retirada do suporte ventilatório para exclusão da persistência da hipoxemia e falha do desmame da VM. Entretanto, ainda há poucos estudos na literatura consistentes de níveis exatos de PaO2 e relação PaO2/FiO2 que podem predizer o sucesso ou falha do desmame da VM(138-140). Assim como, essa avaliação pode ser influenciada pelos níveis de oxigênio ofertado e outros fatores na aferição não sendo considerada uma boa variável quando usada isoladamente(141). Há vários preditores para tentar avaliar o sucesso ou falha do desmame da VM(142). A frequência respiratória/volume corrente é o teste preditor mais difundido na prática clínica do desmame da VM(139). Esse preditor tem sido objeto de discussão da sua aplicabilidade e se mostra o mais sensível para avaliação do desmame da VM, porém não demonstra redução do tempo de VM(143-145). Outros preditores como volume minuto, capacidade vital, pressão inspiratória máxima, pressão de oclusão da via aérea também foram avaliados

mas com resultados variáveis e frustrantes para predizer o sucesso ou falha do desmame da VM(131, 142).

Apesar dos critérios usados acima estarem definidos em alguns guias e consensos de desmame da VM(113, 134, 146, 147), ainda há nesse processo lacunas de definição e uma larga variação de formas de abordagem na prática clínica(148). Esse problema é relevante pois há uma grande parcela de doentes críticos que passam por esse processo com riscos de complicações e prolongamento da internação. Outro aspecto é que há uma grande variedade de pacientes com diferentes patologias que levam a IRp e VM. Assim como há uma perda da individualização do processo em diferentes condições contribuintes para a IRp e desmame da VM. Por exemplo, um paciente com pneumopatia crônica em desmame da VM é diferente de um paciente com alteração neurológica em VM ou num caso de SARA.

2.2.6 Desmame da VM em pacientes com SARA - influência da ventilação espontânea no processo de desmame da VM

Diante da complexidade dos pacientes com SARA seja pelo seu fator desencadeador, patologias prévias e ajuste do respirador durante a suas fases, o desmame da VM não poderia ser menos complexo tanto na sua avaliação como na sua abordagem. Entretanto, essas particularidades tornam o assunto muito desafiador para o estudo desse grupo específico de pacientes críticos. A busca de preditores e o entendimento das particularidades do desmame da VM de pacientes com SARA se tornam necessários e relevantes para uma melhor abordagem do profissional a beira leito. No entanto, os consensos sobre desmame da VM não contemplam esse grupo específico de pacientes(113, 146,

147). Assim como, os preditores e o entendimento da falha do desmame da VM também não tem sido estudados. Consenso publicado por Sahn et al. na década de 70 citou essa subpopulação e já havia uma preocupação sobre como realizar o desmame da VM(119). Era sugerido iniciar com a melhora da complacência pulmonar, FiO2 ≤ 40% e cuidar os níveis de PEEP. A duração do desmame da VM dos pacientes com SARA estava relacionado a gravidade, doença pulmonar de base, idade e condições gerais do paciente. Os autores também ressaltavam que o período de desmame da VM era geralmente prolongado devido a resolução lenta da lesão pulmonar(119). Burns et al. em revisão de desmame da VM em SARA não mostraram dados diferentes de outros pacientes críticos em desmame da VM(149). Penuelas et al. avaliaram a população geral de pacientes em desmame da VM e, no grupo de pacientes com SARA, houve 70% de desmame difícil ou prolongado(129). Jeong et al. avaliaram o desmame da VM na UTI e encontraram 43% dos pacientes com SARA evoluíram com desmame difícil ou prolongado da VM(132). O desmame da VM dos pacientes com SARA inicia-se geralmente com a redução da sedação e troca do modo ventilatório controlado para modo ventilatório PSV quando a respiração espontânea é presente(27). Há poucos estudos de uso de PSV em pacientes com SARA. Durante o modo PSV, se o fluxo aéreo inspiratório é presente após o fim da Pmus, *swings* pressóricos durante a inspiração podem ocorrer. A falha do método ventilatório espontâneo em modo PSV pode ser ocasionado por um retardo do disparo que é causado por um atraso do início e um término precoce do suporte ventilatório(150). Outro aspecto da falha do método em modo PSV é que o nível de assistência ventilatória está frequentemente relacionado a contração diafragmática e consequente falha do desmame da VM(151, 152).

Além disso, a presença de assincronias e volumes gerados por *BS* e *pendelluft* podem levar a piora da lesão pulmonar e falha do desmame da VM(77). Pinto et al. mostraram em animais com SARA leve que no modo PSV houve maiores ΔP para um mesmo VC em comparação com o modo PCV(153). No entanto, Magalhães et al. não encontraram diferenças significativas entre os modos PSV e PCV(154). Portanto, o desmame da VM em pacientes com SARA ainda permanece um assunto a ser melhor estudado tanto os motivos da falha assim como o melhores métodos para avaliação e manejo desse subgrupo de pacientes(27).

2.2.7 Tomografia de Impedância Elétrica na SARA e Desmame da VM

Há várias formas de monitorizar os pacientes com SARA(155). A TIE é um método não invasivo, livre de radiação que avalia em tempo real e continuamente os pulmões durante a ventilação invasiva ou espontânea(28, 30, 31, 156, 157). Esse método dinâmico avalia a distribuição do ventilação em áreas pulmonares dependentes e não dependentes assim como recrutabilidade pulmonar para ajustes ventilatórios como o da PEEP(158-162). A TIE permite a visualização de diferenças regionais ocasionado por mudanças dos níveis de PEEP(163-165). Além disso, a ferramenta permite a avaliação das medidas fisiológicas pulmonares, pneumotórax, perfusão pulmonar, débito cardíaco e estado do volume intravascular(32, 166-168).

A avaliação regional através da TIE durante a presença de esforços ventilatórios espontâneos pode mostrar alterações com a visualização da ventilação e aeração em regiões pulmonares. Elevados níveis de PSV ou VCs aumentam a

ventilação ventral e hiperdistensão das regiões não dependentes(27, 33). Mauri et al. avaliaram 10 pacientes em recuperação de SARA com diferentes níveis de PEEP e PSV(169). Em níveis baixos de PSV houve maior esforço da contração diafragmática visto na TIE através aumento do VC em áreas dependentes em relação as não dependentes. A falha do desmame da VM pode ser atribuído a situações de intensa contração da musculatura diafragmática e na presença de *swings* de pressão(77). Blankman et al. avaliaram 20 pacientes em pós-operatório de cirurgia cardíaca com o uso de TIE e mostrou resultados similares com uso de PSV(170). Houve também uma ventilação mais homogênea quando usado VC < 8ml/kg de peso predito em relação a VC maiores. Radke et al. em estudo com seis pacientes cirúrgicos em PSV e TIE mostraram também uma redistribuição da ventilação ventral com a mudança desse modo em relação ao modo controlado(171). Blankman et al. avaliaram 10 pacientes com SARA e houve uma melhor ventilação das regiões dependentes e assistência da VM com modo NAVA em relação ao modo PSV vistas através da TIE(172). Becher et al. demonstraram ser possível avaliar diferentes níveis de PEEP em 18 pacientes em PSV através do uso de TIE(173).

Bickenbach et al. avaliaram 31 pacientes em desmame prolongado da VM com o TIE e há durante TRE uma perda de homogeneidade pulmonar nos pacientes que falham no desmame da VM(174). Esse dado foi visto através do índice de não-homogenidade com uma sensibilidade de 85% e os autores sugerem que esse achado poderia auxiliar na decisão do desmame da VM. Lima et al. avaliaram com TIE 42 pacientes que realizaram TRE e os pacientes que se submeteram a teste com tubo T ocorreu perda da aeração em comparação ao TRE com modo PSV principalmente nos pacientes que falharam o TRE(175).

Zhao et al. avaliaram 30 pacientes com o uso TIE e mostrou associação de sucesso de desmame da VM há uma redistribuição de ventilação nas regiões dorsais com baixos níveis de PSV(176). Hsu et al. mediram em 16 pacientes o uso de compensação automática do tubo durante o TRE através da TIE sendo que, quando usado, foi efetivo para ativação da ventilação(177). Longhini et al. avaliaram 78 pacientes que realizaram TRE e houve mais perda de recrutamento e heterogenicidade pulmonar no grupo com falha ao teste(178).

A TIE permite também a visualização da plestimografia e as curvas do respirador(29). Como já discutido acima, essa ferramenta pode avaliar as assincronias e *BS* secundário a duplo disparo e disparo reverso. Além disso, a avaliação da plestimografia poder estimar a capacidade residual funcional e a avaliação do VC gerado também poderia ser uma ferramenta para estimar sua variabilidade durante o tempo. Estudos tem relacionado a variabilidade com evolução do desmame da VM(179-182). Outro ponto também já discutido é a avaliação do *pendelluft* através da TIE e risco de hiperdistensão regional de regiões dependentes vistas pela TIE(77).

Desde a inicial descrição dos 12 pacientes por Ashbaugh e colegas em 1967(1), a SARA tem sido um assunto ao mesmo tempo interessante e desafiador. O estudo do seu desmame da VM não tem sido menos oportuno visto as múltiplas particularidades da sua fisiopatologia e a influência da VM e respiração espontânea(183). Por isso, diante da atual discussão das repercussões da ventilação espontânea em pacientes com SARA, novos estudos relacionados ao tema devam ser realizados visando o estudo dessa lacuna no desmame da VM de pacientes com SARA.

3. MARCO CONCEITUAL

O marco conceitual do estudo mostra a sequência do desmame da VM dos pacientes com SARA evoluindo com aumento do VC e ΔP, pendelluft e P-SILI. Essas alterações levam a piora da lesão pulmonar inicial e, consequentemente, piora da hipoxemia e da mecânica pulmonar e falha do desmame da VM.

Figura 2: Marco Conceitual Esquemático
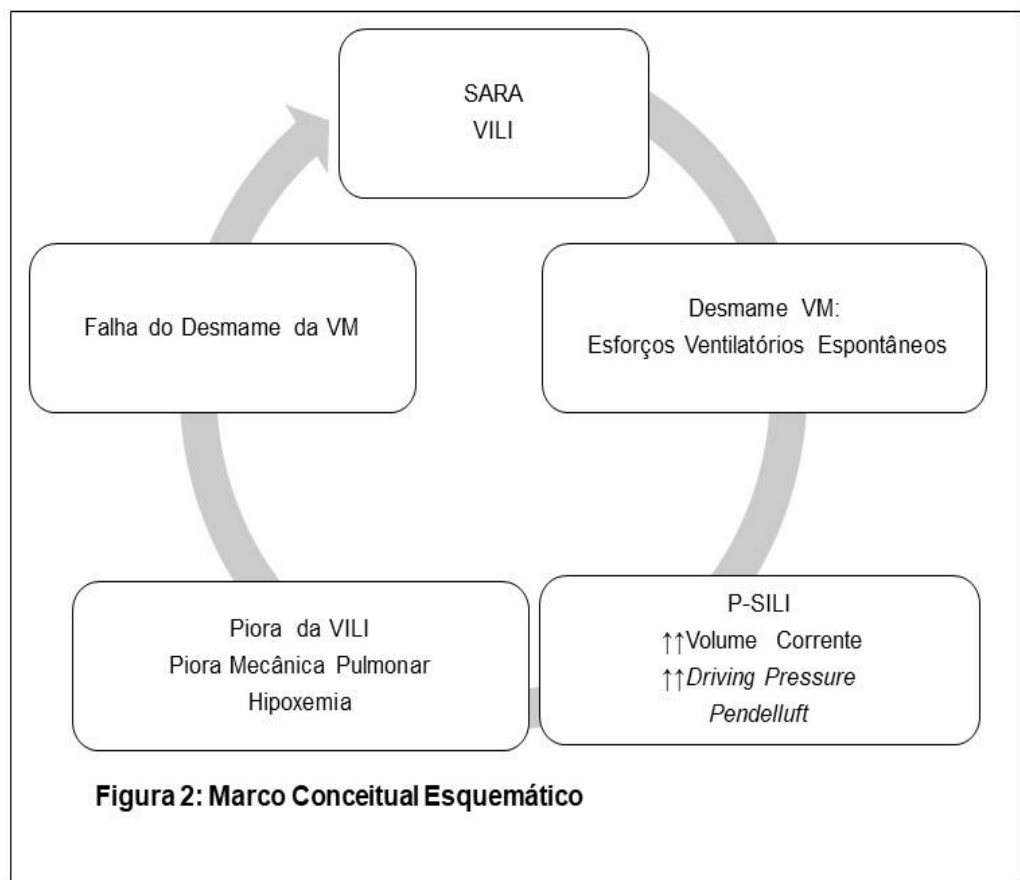
4. JUSTIFICATIVA

A SARA é uma síndrome de fisiopatologia complexa e a influência da VM e esforços espontâneos podem ser deletérios em alguns pacientes através da VILI e P-SILI. O desmame da VM ainda é um tema que requer mais estudos para entendimento da falha do processo e melhores estratégias para ajudar esse grupo de pacientes. Por isso, o estudo do desmame da VM de pacientes com SARA é um tema pertinente e necessita de estudos para permitir um entendimento melhor da sua avaliação visto que há poucos dados na literatura sobre esse processo nesse estágio da SARA e suas repercussões clínicas. Além disso, o presente estudo propôs o emprego de TIE como uma nova ferramenta para avaliar melhor a repercussão da ventilação espontânea no processo de desmame dos pacientes com SARA. Também foram avaliados os métodos usuais para o desmame da VM para fornecer dados adicionais de uma avaliação mais precoce das alterações pulmonares dos pacientes com SARA em desmame da VM.

5. OBJETIVOS

5.1   Objetivo Primário

- Avaliar o desmame da VM em pacientes com SARA e suas repercussões através do uso da TIE associados a parâmetros clínicos e ventilatórios.

5.2   Objetivos Secundários

- Avaliar o processo de desmame da VM(simples, difícil e prolongado) nos pacientes com SARA com o uso da TIE;

- Medir a mecânica pulmonar dos pacientes na SARA durante os estágios do processo de desmame da VM;

- Avaliar os volumes pulmonares usuais e causados por assincronias e *pendelluft* através do emprego da TIE durante o processo de desmame da VM em pacientes com SARA;

- Mensurar com a TIE a quantidade de assincronias e pendelluft durante o desmame da VM dos pacientes com SARA;

- Comparar os dados clínicos e da mecânica pulmonar dos tipos de desmame da VM de pacientes com SARA;

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7. ARTIGO

O artigo será enviado para a revista: "American Journal of Respiratory and Critical Care Medicine"

Evaluation of Electrical Impedance Tomography with Clinical and Ventilatory Patterns That Influence Weaning from Mechanical Ventilation in ARDS Patients

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ABSTRACT

Background: The acute respiratory distress syndrome (ARDS) is characterized by an intense inflammatory response and protective mechanical ventilation (MV) is essential. The presence of spontaneous breathing has beneficial effects, however, it can be harmful in more severe cases. The repercussion of spontaneous breathing and its repercussion during weaning from MV in patients with ARDS is still poorly understood and studied.

Objective: Evaluate weaning from MV in patients with ARDS using electrical impedance tomography (EIT) with clinical and ventilatory parameters.

Methods: Prospective cohort study of patients with ARDS who presented improvement criteria and were judged by the attending team to be able to suspend the use of neuromuscular blocker (NMB) and sedatives, and start weaning from MV. The EIT and pulmonary mechanics data were collected at baseline (Tpre) and after 30 minutes (T30min), 2 hours (T2h) and 24 hours (T24h) after changed from controlled mode (VCV or PCV) to spontaneous mode (PSV).

Results: The study included 25 patients between July,2017 and February,2019. The patients were 09 simple, 08 difficult and 08 prolonged weaning. The duration of MV, delirium, agitation, intensive care unit–acquired weakness (ICU-AW), tracheostomy, length of stay (LOS) and mortality of the ICU were higher difficult and prolonged weaning group. The tidal volume (TV) and driving pressure(ΔP) increased when changing from controlled to spontaneous mode, mainly in the prolonged weaning group when compared with simple weaning group (p time=0.0001). The patients with prolonged weaning presented larger total volumes after begin of the spontaneous ventilation (p=0.02). The prolonged

weaning group had a tendency more posterior region ventilation and reduction of the ventral/dorsal(V/D) ratio visualized by EIT.

Conclusion: The weaning from MV of patients with ARDS has a high proportion of difficult and prolonged weaning associated with worse clinical outcomes. The pulmonary changes seen by EIT and assessment of pulmonary mechanics showed to be relevant in the prolonged and difficult weaning group and could be monitored routinely. Further studies should be realized to evaluate the spontaneous breathing and weaning from MV in ARDS to continue to protect the lung.

Key Words: Respiratory Distress Syndrome, Adult; Ventilator Weaning; Respiratory Mechanics; Electric Impedance Tomography

Introduction

Protective mechanical ventilation (MV) is a supportive therapy in critically ill patients and during the last decades reduced mortality mainly with acute respiratory distress syndrome (ARDS)[1, 2]. The use of neuromuscular blocker (NMB) to abolish the presence of spontaneous breathing during early stages of ARDS has been widely debated[3-5]. The spontaneous breathing show beneficial effects as a homogeneous distribution of pulmonary aeration, improvement of gas exchange, increases contraction and reduces diaphragmatic inactivity, need of sedation and, consequently, decreased time of the MV and intensive care unit(ICU)[6-9]. However, the deleterious effect of uncontrolled spontaneous breathing can cause or worsen lung and diaphragmatic injury by ventilator-related mechanisms (ventilator-induced lung injury - VILI) and by the patient-related mechanisms (patient self-inflicted lung injury -P-SILI)[10-13].

Nevertheless, the effects of spontaneous breathing and its repercussion on the weaning of the MV of patients with ARDS is still poorly studied and need studies to better assess its consequences. Therefore, we postulate that some patients with ARDS may fail the weaning process of MV due to partial or complete loss of well-defined protective ventilatory strategy control at the beginning of MV. Epidemiological studies of MV weaning poorly differentiate patients with ARDS and consequently the understanding of the pathophysiology of ventilatory support discontinuation failure in patients with ARDS is not fully understood[14, 15]. In addition, weaning from MV in ARDS patients has been used conventional methods for any critically ill patient[16, 17]. However, there has been great progress in understanding of pulmonary behavior through imaging methods such as the use of chest tomography and electrical impedance tomography (EIT)[18,

19]. Therefore, the study of these tools associated with conventional methods may allow better understanding, monitoring and management of cases of ARDS during weaning from MV[19, 20].

Therefore, the study of the influence of spontaneous ventilation and its repercussions at the time of weaning from the ventilatory support of patients with ARDS is necessary and essential to avoid damage related to VILI and P-SILI. The present study aims to evaluate the weaning from MV in patients with ARDS and its repercussions through the use of EIT and clinical and ventilatory parameters of pulmonary mechanics.

Methods

Study design and Setting

A prospective observational cohort study was conducted between July 2017 and February 2019 in the ICU of the Hospital de Clínicas de Porto Alegre, Brazil. The ethical committee of Hospital de Clínicas de Porto Alegre approved the study (Project number:15-0571). The study was submitted to Brazilian Registry of Clinical Trials – ReBEC (Id number: RBR-35qvjy). The STROBE tool was used for the study development[21].

Participants

All patients diagnosed with ARDS defined by the Berlin criteria were followed[22]. Consecutively, the patients defined by the ICU team who were considered ready to begin the MV weaning process were included. Informed consent was obtained from the family member. Exclusion criteria were: patients who were already in

spontaneous ventilatory mode, family member or legal representative who did not consent to participate in the study, pulmonary fistulas that made it difficult to measure respiratory mechanics, use of cardiac pacemaker, damage to the rib cage that makes it impossible to place the EIT electrodes or inability to perform the evaluation for reasons that may hinder the patient's evolution.

Date Collection

The following data were collected from the patient's record: age, gender, height, ideal weight, body mass index, source of hospitalization, comorbidities, Simplified Acute Physiology Score 3 (SAPS 3), etiology and severity of ARDS, time of diagnosis of ARDS start of MV weaning, use of sedatives and NMB, vasoactive drugs, prone position, dialysis and *extracorporeal membrane oxygenation.* During follow-up were collected: MV dates, the number of spontaneous breathing trial (SBT), weaning type (easy, difficult or prolonged)[23], MV weaning success or failure (reintubation within 72 hours after extubation), delirium[24], agitation, intensive care unit–acquired weakness (ICU-AW), tracheostomy, length of stay (LOS) in ICU and hospital, time of the MV and mortality in ICU and hospital. Agitation was defined as the need for sedation or mechanical restraint to control patient agitation during weaning from MV and whether or not they had criteria for delirium. Muscle strength was evaluated with the use of the Medical Research Council (MRC) scale and ICU-acquired paresis was an MRC score of less than 48[25].

Study Protocol

After the initial screening, a basal collection (Tpre) was performed in a controlled ventilatory mode (Volume Controlled Ventilation - VCV or Pressure Controlled

Ventilation - PCV) during 30 minutes before changed to spontaneous mode (Pressure Support Ventilation - PSV). Arterial blood gases and MV data were collected. After EIT installation, 10 minutes was recorded for later offline analysis of the file. The EIT electrodes were positioned on the thorax in the supramamilar position and continuous acquisition was started image acquisition was done using a 32-electrode EIT device (Timpel Enlight 1800®) composed of 32 electrodes and with 50Hz acquisition frequency. The data obtained were analyzed in offline mode through specific program in Labview environment developed by our group. EIT parameter analysis was performed (Delta Z (ΔZ), ventilation distribution in the zones 1-4, ventral and dorsal ratio (V/D ratio), pendelluft volume and analysis of the ventilation curves acquired in the device to identify and quantify breath staking (BS), reverse triggering, double-triggering and asynchrony index.

After this initial evaluation period, the ICU team performed switching from controlled to spontaneous ventilation mode (PSV 8-12 cm H2O), with the patient in a semirecumbent position and fractional inspired oxygen concentration set at the same level. Arterial blood gases, MV and EIT data were collected after 30 minutes (T30min) and two hours (T2h), 24 hours (T24h). Data related to EIT images were collected in real time over 10-minute periods. For the evaluation of pulmonary mechanics, small doses of sedatives and short-acting NMB (propofol 10mg IV and if necessary, succinylcholine 20mg IV) may be given by the medical team according to the researchers.

The criteria used by the medical staff were based on the MV institutional weaning protocol according to the current guidelines (see Appendix 1)[16, 17]. The initial

SBT lasted 30 minutes and consisted of breathing with a T-tube or using 5–8 cmH2O pressure support with positive end expiratory pressure (PEEP) 5-8 cmH2O was performed. When a patient successfully passed the SBT according to the criteria, extubation was performed. The final decision to extubate was made by the attend physician. When a patient failed the initial SBT, MV was reinstituted and reviewed the possible reversible causes for the failure. The spontaneous breathing trial was repeated on the next day, if the patient was again ready-to wean. The a priori criteria for weaning failure were tachypnea, increased accessory muscle activity, diaphoresis, facial signs of distress, cyanosis, tachycardia, arrhythmias, and hypotension. Patient-related decisions were all made by the medical staff and researchers did not influence decisions.

Statistical analysis

We defined to collect consecutively 25 cases as there were no specific ARDS weaning studies for sample calculation. Variables categories were presented as relative and absolute frequencies. Continuous variables are reported as mean ± sd or median and interquartile ranges for nonnormal distributions. In nonparametric data was performed Mann-Whitney and Kruskal-Wallis test. Quantitative continuous variables were compared among the three groups (simple, difficult and prolonged weaning) using one-way analysis of variance, with Tukey post hoc comparisons. To compare categorical variables, the $\chi 2$ test was used, except when expected frequencies in contingency tables were less than 5, in which case the Fisher exact test or the Monte Carlo method was used. The generalized linear mixed models were used to evaluate interaction weaning type with time of weaning (TPre, T30min, T2h and T24h). All *P*-values were two-sided,

with *P*-values less than 0.05 considered as statistically significant. Statistical analyses were performed with SPSS 17.0 program (SPSS, Chicago, IL).

Results

Population

During the study period, 37 patients were evaluated and 25 patients were consecutively enrolled in the study (Figure 1). The patients were classified according to the type of MV weaning: 09 simple, 08 difficult and 08 prolonged weaning. The general characteristics and outcomes of the patients according each type of weaning were shown in Table 1. This table showed duration of MV, delirium, agitation, ICU-AW, tracheostomy, LOS and ICU mortality higher difficult and prolonged weaning group (others dates see Appendix 2).

Gas Exchange, Ventilatory, and Respiratory Mechanics.

The table 2 and figure 2 showed parameters during MV weaning. The tidal volume(TV) increased when changing from controlled to spontaneous mode, mainly in the prolonged weaning group. The during time of controlled to spontaneous mode showed differences with TV, respiratory rate(RR) and driving pressure(ΔP). The TV and ΔP levels were higher mainly in difficult and prolonged weaning groups (see figure 2 and figure 2).The values of DP in the simple weaning had not higher values than 13.9. Blood gas and MV data during hospitalization and weaning previous were shown in Appendix 3.

Asynchronies e Pulmonary Volumes

Table 3 showed the amount of the double trigger, reverse trigger and BS during MV weaning. The asynchronous numbers are high in prolonged weaning in the initial time. After to change to spontaneous mode, the asynchronies had a reduction with increasing pulmonary volumes paradoxically. In the figure 3 showed evaluation of the total, normal pulmonary, BS and pendelluft volumes generated every 10 minutes. The patients with prolonged weaning presented larger total volumes during all times. The volumes generated by BS secondary asynchronies were more prolonged compared simple weaning. The pendelluft volumes were more difficult and prolonged compared simple weaning(Figure 3).

Imaging Dates

The figure 4 showed the ventilation distribution by EIT the groups of the type weaning during ARDS weaning. Patients on prolonged weaning have greater posterior ventilation seen in the lower V/D ratio compared to the difficult and simple weaning. When divided into slices 1-4, ventilation on slice 4 was greater in this region in patients with prolonged weaning.

Discussion

Our study showed the behavior weaning from MV of the ARDS patients during changing from controlled to spontaneous ventilation mode after withdrawal of the sedation and NMB. We studied a specific subpopulation of patients with ARDS who could have influenced spontaneous breathing in the MV weaning process. Our results suggest that patients with ARDS have a higher proportion of difficult and prolonged weaning (64% cases studied). Peñuelas et al. showed almost 70% difficult and prolonged weaning in the ARDS patients in the study of the MV weaning[15]. Previous studies show a higher proportion of simple weaning

because they evaluated only general ICU patients weaning from MV[26]. However, the patients with prolonged weaning had higher mortality and worse others outcomes as previous studies[15, 26, 27].

Our study showed mainly in patients with prolonged weaning the loss of protective ventilation during weaning of the MV with higher TV and ΔP. The recommended levels of protective ventilation are lost during weaning in some patients who show high values of VT and ΔP, causing a risk of VILI due to volutrauma and barotrauma[11, 28]. Initially, the patients showed the presence of high asynchrony indices into 26% any patients that correlate with previous study of increased mortality with asynchrony index higher 10%[29]. The presence of excessive asynchrony seen in our data generated volumes by BS and consequent additional volumes of the adjusted for protective values. After the beginning of the spontaneous ventilatory mode a reduction of the asynchrony occurred. However, there was a significant increase in TV and ΔP to non-protective levels in complicated weaning. These findings may be complex understanding. One explication may be increased "inappropriate" respiratory drive especially in the prolonged weaning group and ARDS[30, 31]. The respiratory drive abnormally high may be resulting high inspiratory effort, dyspnea, patient–ventilator dyssynchrony, lung (i.e. P-SILI) and respiratory muscles injury (i.e, myotrauma) and consequently adverse clinical outcomes[12, 13, 32, 33]. These findings have also been shown during the COVID-19 pandemic with the potential difficulty of weaning from MV[34]. We assessed total lung volume during and showed a significant increase in patients with prolonged weaning. There are no reports of studies that globally assessed volume and its correlation with weaning from MV. In addition, our study showed the volumes

produced by pendelluft that are most prominent in groups with complicated weaning. These volumes can lead to dorsal hyperinflation, large swings and cause negative pressures that can be deleterious in lungs with solid-like behavior[35]. Coppadoro et al. showed that the phenomenon of pendelluft through EIT is frequent (40%) and more failure to wean from MV due to increased ventilatory effort as well as in our patients[36].

Our results showed increased TV during ventilatory mode change (PCV or VCV to PSV) with increased ventilation in dorsal visualized by the EIT. Blankman et al. showed similar results by the EIT[37]. However, our cases had more severe ARDS and a higher risk of unfavorable outcome related with spontaneous breathing during MV weaning. The levels of the PSV or PEEP can influence diaphragmatic contraction and ventilation in dependent areas viewed by EIT and the use higher PEEP strategy could be help spontaneous breathing in severe ARDS [38-40]. Additionally, when TV values lower than 8ml/kg of predicted weight show more homogeneous ventilation when there are higher TV[37]. Our study demonstrated higher TVs with a lower V/D ratio showing increased risk of the dorsal injury influenced by increased diaphragmatic contraction, more negative pleural pressures with increased degree of swing and risk of pulmonary edema and overuse injury diaphragmatic.[41, 42] The features visualizable by EIT could be to influenced the failure and success weaning. Furthermore, sedation and NMB strategies could reduce muscle overload and use of higher PEEP could be beneficial for stabilizing unstable alveoli and ventilation in more dorsal regions[20, 43, 44].

The use of EIT to assess weaning from MV has still been poorly evaluated and studies suggest loss of pulmonary homogeneity during weaning from MV[45, 46].

The present study suggests that monitoring of the weaning from ARDS could be reassessed. The creation of better tools for assessing weaning in ARDS as well as the proper evaluation of the resolution of the cause of hypoxemia and pulmonary inflammation are necessary[13, 47]. The present study showed occult findings by EIT that the bedside clinical evaluation has not been performed routinely. The EIT tool could be potential to use in ARDS weaning by real-time monitoring, optimize MV settings and detect complications[19]. Early studies on weaning from MV already suggested that patients with ARDS could be better evaluated and the time to recover from the injury respected[48]. Given the current understanding of the influence of spontaneous breathing on this group of patients, weaning from MV may be complicated. Since it is an evaluation of heterogeneous patients, weaning has multiple causes of weaning failure that are related to the complex pathophysiology of ARDS. This pathophysiology does not only include the pulmonary aspect but there are other aspects such as the presence of delirium and ICU-AW shown in our population as well as in other studies[49, 50].

The aspects studied related to weaning from MV in patients with ARDS have proved to be important, such as large lung volumes, increased ΔP, asynchrony and change of ventilation to posterior regions secondary to intense inspiratory effort. These findings in weaning from MV could cause lung injury and consequently lead to failures in spontaneous breathing tests and worsening outcomes, especially in patients with ARDS. Therefore, weaning from MV could progress to a lung injury that is not well resolved, which could be called "Weaning Induced Lung Injury - WILI" added to the well-known VILI and P-SILI. However, more studies in multiple centers could be performed to identify this related phenomenon of weaning from MV causing worsening of lung injury. In addition,

through a better understanding of the pathophysiology of weaning failure, more individualized strategies could be developed to address this clinical context.

Limitations

First, this study was observational and there was a risk that the selection of cases could influence the results of the study. However, patients were selected consecutively according to the inclusion and exclusion criteria. Second, the study was conducted at a single center and the management of patients could be different when compared to other centers. However, patient care protocols were based on the guidelines of the main intensive care societies, and researchers did not influence patient therapy decisions. Third, there was no consideration of the use of non-invasive ventilation or high-flow oxygen therapy in the study. This could have less severe patients and change study outcomes. In our study, we had few patients with mild ARDS and the impact of the spontaneous breathing could be not dangerous as severe types of ARDS. The other factor may be influence of the results that most of sample was primary cause of ARDS and pneumonia. Our ICU is reference center for clinical patients and not trauma and surgical center. Fourth, other factors could cause failure in weaning such as obstructed tubes, sedatives, diaphragmatic dysfunction, respiratory drive, phenotypes in addition to the heterogeneity of patients with ARDS. Fifth, the definition of the type of weaning from VM could not include all aspects of weaning from VM including its outcomes. However, when the study was designed, it was the classification used in the current literature at the time to assess weaning from MV.

Conclusions

The present study evaluated weaning from MV of patients with ARDS. The patients with difficult and prolonged weaning were associated with worse clinical outcomes. Patients with worse outcomes had larger lung volumes and pressures and more ventilation in dorsal regions related to excessive spontaneous effort viewed by EIT and mechanics pulmonary. The findings of pulmonary changes could be monitored mainly EIT and assessment of pulmonary mechanics. Further studies should be realized to evaluate the spontaneous breathing and weaning from MV in ARDS to continue to protect the lung.

Acknowledgments

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Table 1. Main Characteristics of the All Patients and Simple, Difficult and Prolonged Weaning Groups

Characteristics	All (n=25)	Simple (n=9)	Difficult (n=8)	Prolonged (n=8)	P value
Age - yr	43.9±19.5	36.8±20.7	42.8±17.2	53.1±19	0.28
Male sex	32%	33.3%	37.5%	25%	0.87
SAPS 3	64.7±15.4	63.6±21.4	58.1±8.2	72.5±10.1	0.13
Body mass index, kg/m2	26.5±6.4	27.5±5.4	26.9±5.8	25.3±8.2	0.52
Clinical	96%	100%	87.5%	100%	0.35
Comorbidity					-
Cardiovascular disease	24%	33.3%	12.5%	25%	0.62
COPD	8%	0%	12.5%	12.5%	0.56
Cancer	16%	0%	12.5%	37.5%	0.11
SIDA	16%	11.1%	25%	12.5%	0.71
Hematologic disease	16%	0%	25%	25%	0.28
Imussupresion	32%	0%	37.5%	62.5%	0.02
Etiology of ARDS					0.35
Primary, infectious	96%	100%	87.5%	100%	-
Extrapulmonary, noninfectious	4%	0%	12.5%	0%	-
ARDS Severity					0.35
Mild	12%	22.2%	12.5%	0%	-
Moderate	60%	55.6%	75%	50%	-
Severe	28%	22.2%	12.5%	50%	-
PaO2/FiO2 initial, mmHg	141.8±50	147.1±51	152.3±48	125.4±55	0.46
Cstat/PBW initial, ml/cmH2O/kg	0.53±0.1	0.44±0.1	0.57±0.2	0.58±0.1	0.2
T_ARDSweaning, days	4.9±2	4.1±1.6	4.8±1.3	6.0±2.8	0.23
Prone Position	40%	33.3%	37.5%	50%	0.78
ECMO	8%	11.1%	12.5%	0%	0.61
Neuromuscular Blocker	84%	77.8%	87.5%	87.5%	0.82
Delirium	56%	22.2%	75%	75%	0.04
Agitation	76%	44.4%	100%	87.5%	0.02
ICU-AW	44%	22.2%	25%	87.5%	0.01
Duration of MV, days	12.8±9.3	6.3±2.3	10.9±5.1	22.0±10.4	0.00
Tracheostomy	12.5%	0%	0%	37.5%	0.03
LOS ICU, days	16.4±10.4	9.2±3.2	14.1±5.2	26.8±11.8	0.00
LOS Hospital, days	32.4±19.4	21.2±13.6	27.6±10.4	49.8±20.9	0.01
Mortality ICU	20%	0%	12.5%	50%	0.03
Mortality Hospital	24%	11.1%	12.5%	50%	0.12

Legend: SAPS 3 = Simplified Acute Physiology Score 3; COPD= *Chronic obstructive pulmonary disease*; SIDA = Acquired Immunodeficiency Syndrome; ARDS= Acute Respiratory Distress Syndrome; PaO2/FiO2 = pressure arterial oxygen/fractional inspired oxygen concentration; Cstat/PBW = Static Compliance/Predict body weight; T_ARDSweaning = time of ARDS diagnosis to initiation of weaning from MV; ECMO= *extracorporeal membrane oxygenation*; MV= Mechanical Ventilation; ICU-AW = intensive care unit–acquired weakness; ICU=Intensive Care Unit; LOS=Length of stay; Valor p compare simple versus difficile versus prolonged weaning; Data are expressed as mean ± SD or %. Kruskal-Wallis Test or Chi-Square or Fisher Test. This table shows all patients and simple, difficult and prolonged weaning groups. Subgroups were divided according weaning classification. The duration of MV, delirium, agitation, ICU-AW, tracheostomy, length of stay and mortality ICU higher with difficult and prolonged weaning.

Table 2: Gasometric, Ventilatory, and Respiratory Mechanics During Mechanical Ventilation Weaning

Parameters	Simple(n=9)	Difficult (n=8)	Prolonged (n=8)	p type	p time	p interaction
PaO2/FiO2 ratio, mmHg				0.2	0.3	0.3
TPre	348.4±27	322.9±29	290.5±29			
T30min	332.7±34	337.8±36	285.0±36			
T2h	329.8±36	318.1±38	277.6±38			
T24h	398.4±38	346.8±39	261.0±39			
TV/ideal weight, ml				0.02	0.000	0.8
TPre	5.9±0.4	6.9±0.3	7.5±0.4			
T30min	8.4±1.0	10.4±1.1	10.5±1.1			
T2h	7.9±0.9	10.3±1.0	10.1±1.0			
T24h	7.7±0.7	9.6±0.8	10.0±0.8			
Respiratory rate, breath/min				0.2	0.001	0.15
TPre	26.2±1.4	21.2±1.5	23.3±1.5			
T30min	17.4±2.1	16.9±2.2	19.0±2.2			
T2h	19.1±2.8	16.0±3.0	25.9±3.0			
T24h	24.3±2.3	20.9±2.4	23.3±2.4			
Plateau pressure, cm H2O				0.7	0.048	0.15
TPre	19.8±1.1	18.5±1.2	19.3±1.2			
T30min	20.8±1.8	23.0±1.9	21.8±1.9			
T2h	19.0±1.6	22.8±1.7	21.4±1.7			
T24h	20.0±1.9	22.5±1.9	20.1±1.8			
PEEP, cm H2O				0.1	0.9	0.34
TPre	9.0±0.5	8.4±0.6	8.5±0.6			
T30min	8.2±0.5	8.4±0.6	8.4±0.6			
T2h	8.2±0.5	8.4±0.6	8.3±0.6			
T24h	8.1±0.5	7.9±0.6	7.5±0.5			
Static compliance, ml/cm H2O				0.6	0.7	0.1
TPre	35.1±4.1	40.6±4.1	34.8±4.4			
T30min	37.1±4.8	43.0±4.8	36.7±5.2			
T2h	36.3±4.7	42.9±4.7	36.0±5.0			
T24h	37.7±5.0	40.1±5.0	36.5±5.4			
ΔP, cm H2O				0.5	0.000	0.8
TPre	10.4±0.9	10.6±0.9	11.5±1.0			
T30min	13.9±1.5	15.6±1.5	15.5±1.6			
T2h	13.0±1.3	15.4±1.3	15.3±1.4			
T24h	12.7±1.6	15.6±1.5	15.0±1.7			

Legend: TV=tidal volume; RR=respiratory rate; PEEP = Positive End Expiratory Pressure; ΔP=Driving pressure; Tpre = baseline collection performed in a controlled ventilatory mode (VCV or PCV). T30min = 30 minutes after changed to spontaneous mode PSV; T2h= two hours after changed to PSV; T24h= 24 hours after changed to PSV. Data are reported as mean ± std. error (SE). Valor p compare the type of weaning (simple versus difficile versus prolonged) and time of weaning (Tpre versus T30min versus T2h versus T24h) and interaction type with time weaning; This table shows parameters of the gas exchange, ventilatory, and mechanical respiratory for the types of the weaning (simple, difficult and prolonged). The type of simple compared difficult and prolonged weaning showed more higher TV. The during time of controlled to spontaneous mode showed differences with TV, RR and DP.

Table 3: Asynchronies, Breath Staking and Pendelluft During Mechanical Ventilation Weaning

Parameters	TPre	T30min	T2h	T24h	p
Asynchrony Index %					NS
Simple Weaning	0.5[0-7.9]	0.8[0-1.4]	0.8[0-3.2]	0[0-0.2]	
Difficult Weaning	0.5[0-15]	0[0-5]	0[0-1.6]	1.1[0-3.7]	
Prolonged Weaning	15.4[0-26]	0.5[0-1.6]	2.0[0-6.9]	0[0-3.6]	
Double Trigger, n					NS
Simple Weaning	1[0-3]	0[0-2]	0[0-3]	0[0-7]	
Difficult Weaning	0[0-2]	0[0-3]	0[0-2]	1[0-1]	
Prolonged Weaning	33[1-52]*	0[0-0.2]	3[0-7]	0[0-1.5]	
Reverse Trigger, n					NS
Simple Weaning	0[0-25]	0[0-2]	0.5[0-3]	0[0-0]	
Difficult Weaning	0[0-20]	0[0-1.5]	0[0-0]	1[0-5]	
Prolonged Weaning	0[0-5]	0[0-1]	0[0-2]	0.5[0-5]	
Breath Staking, n					NS
Simple Weaning	3[0-33]	1[0-3]	2[0-3]	0[0-10]	
Difficult Weaning	4[0-33]	2[0-6]	9[0-4]	5[1-10]	
Prolonged Weaning	51[2-73]	1[0-3]	6[0-18]	5[0-14]	
Pendelluft, n					NS
Simple Weaning	0[0-0]	0[0-0]	0[0-0]	0[0-0]	
Difficult Weaning	0[0-0]	0[0-0]	0[0-5.8]	0[0-13]	
Prolonged Weaning	0[0-0]	0[0-5.3]	2[0-11.8]	0[0-15.8]	

Legend: Tpre = baseline collection performed in a controlled ventilatory mode (VCV or PCV). T30min = 30 minutes after changed to spontaneous mode PSV; T2h= two hours after changed to PSV; T24h= 24 hours after changed to PSV. Data are reported as Median/IQ interval. Kruskal-Wallis Test. Valor p compare simple versus difficult versus prolonged weaning; This table shows asynchronies index, types of asynchronies, breath staking, pendelluft during 10 minutes each time of the study; *=p<005; NS = non-significant.
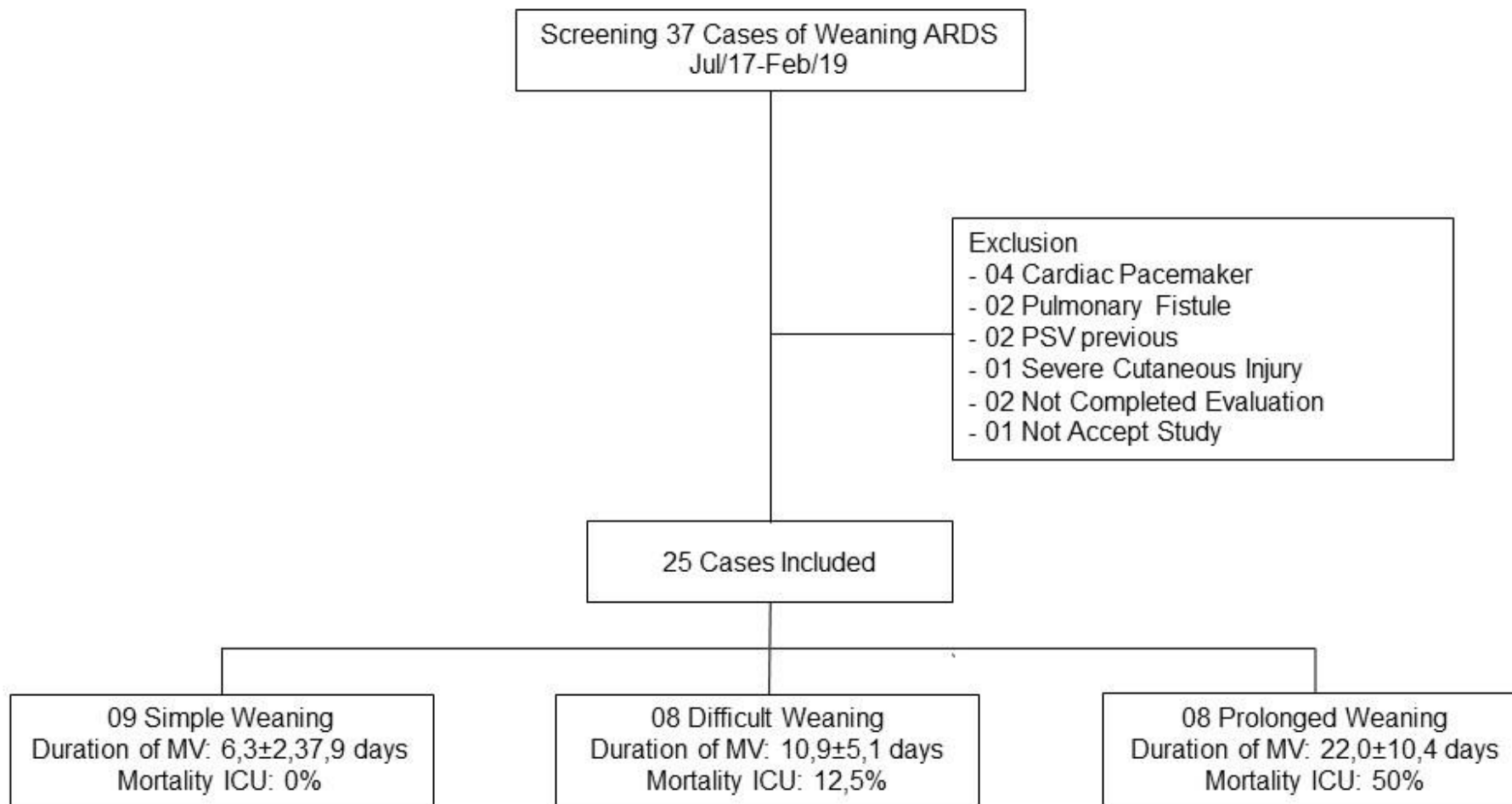
Figure 1: Study flowchart
Legend: ARDS= Acute Respiratory Distress Syndrome; PSV = Pressure Support Ventilation; MV= Mechanical Ventilation; ICU= Intensive Care Unit

Figure 2: Ventilatory Parameters During Mechanical Ventilation Weaning

Legend: TV=tidal volume; RR=respiratory rate; PEEP = Positive End Expiratory Pressure; ΔP=Driving pressure; Cstatic=Static compliance; Tpre = baseline collection performed in a controlled ventilatory mode (VCV or PCV). T30min = 30 minutes after changed to spontaneous mode PSV; T2h= two hours after changed to PSV; T24h= 24 hours after changed to PSV. Data are reported as mean ± std. error (SE). Valor p compare the type of weaning (simple versus difficile versus prolonged) and time of weaning (Tpre versus T30min versus T2h versus T24h) and interaction type with time weaning; This figure shows parameters of the gas exchange, ventilatory, and mechanical respiratory for the types of the weaning (simple, difficult and prolonged). The type of simple compared difficult and prolonged weaning showed more higher TV. The during time of controlled to spontaneous mode showed differences with TV, RR and ΔP.

Figure 3: Volume Produced During Evaluation of Weaning Mechanical Ventilation
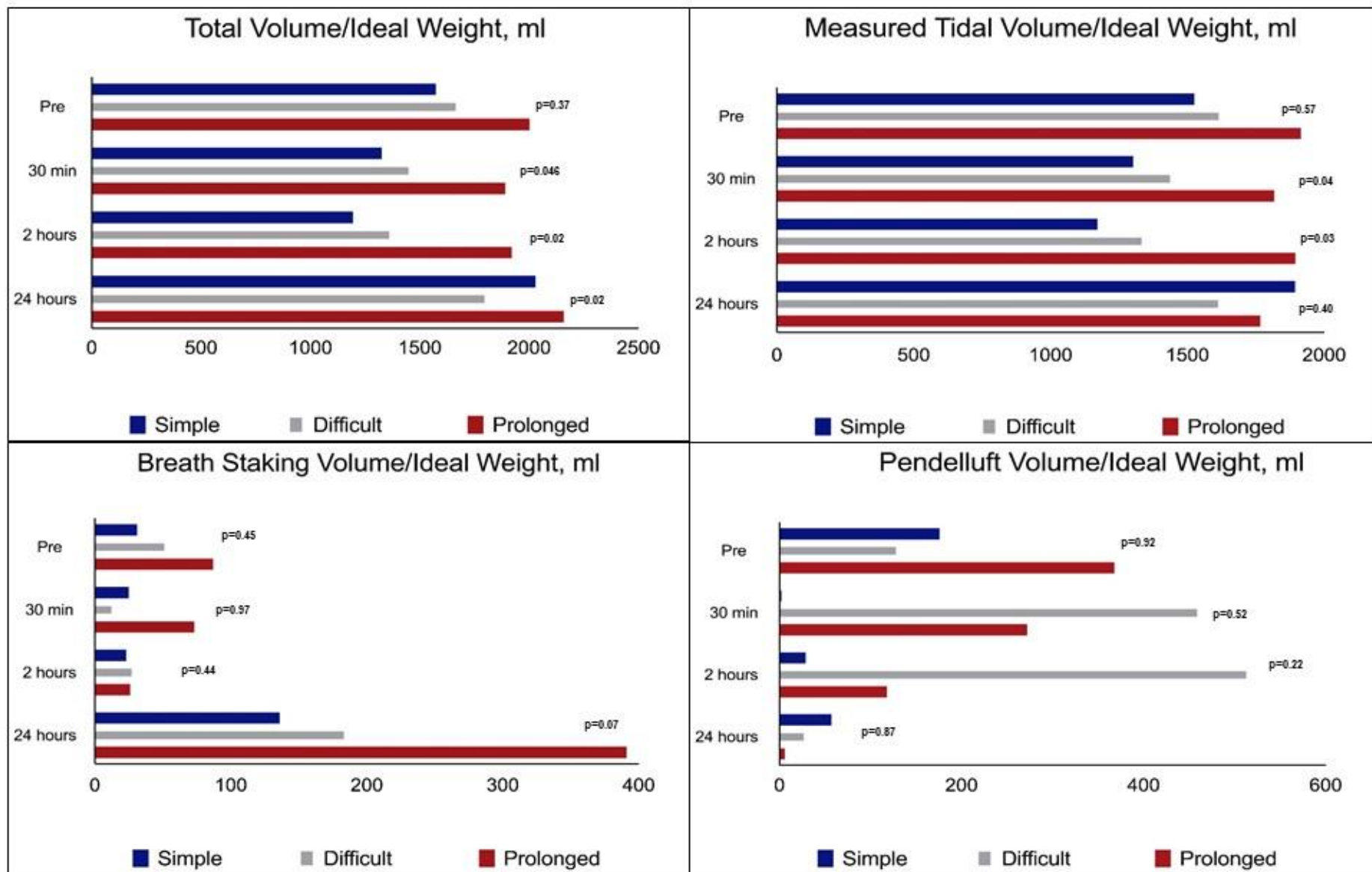
Legend: Tpre = baseline collection performed in a controlled ventilatory mode (VCV or PCV). T30min = 30 minutes after changed to spontaneous mode PSV; T2h= two hours after changed to PSV; T24h= 24 hours after changed to PSV. Data are reported as mean. Kruskal-Wallis Test. Valor p compare simple versus difficult versus prolonged weaning; This figure shows volumes during 10 minutes each time collected of the evaluation. The types of the weaning (simple, difficult and prolonged) showed tidal volume measured and breath staking providing of asynchronies (double trigger and reverse trigger) and pendelluft. The group with more volumes produced were prolonged and difficult weaning.
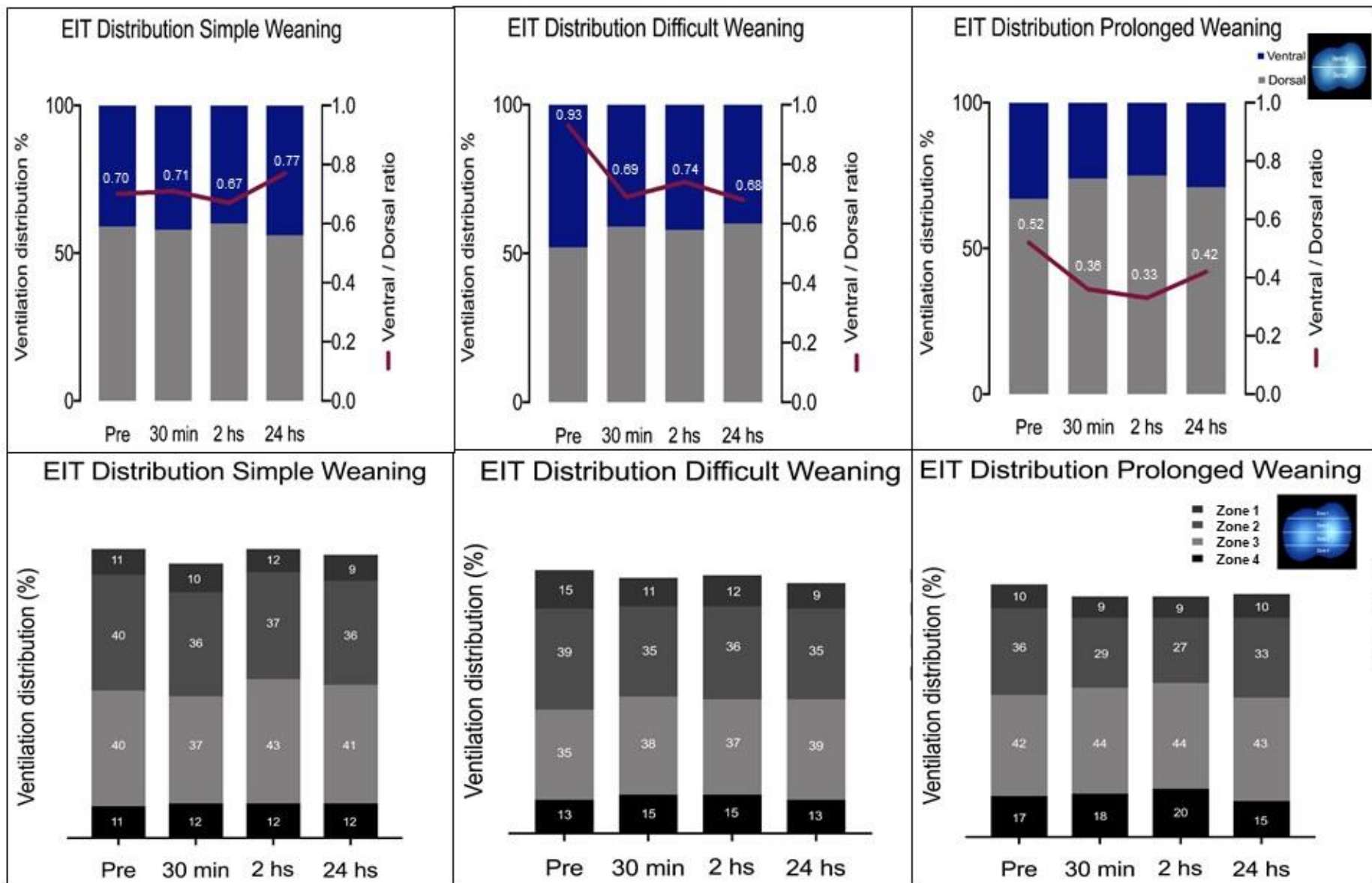
Figure 4: Ventilation Distribution by Electrical Impedance Thomography

Legend: EIT = Electrical impedance thomography; Tpre = baseline collection performed in a controlled ventilatory mode (VCV or PCV). T30min = 30 minutes after changed to spontaneous mode PSV; T2h= two hours after changed to PSV; T24h= 24 hours after changed to mode PSV. The Ventral/Dorsal represents the 50% border. The EIT image was divided in four zones (zone 1 = ventral, zone 2 = mid-ventral, zone 3 = mid-dorsal and zone 4 = dorsal). Prolonged weaning has higher posterior ventilation seen in the Ventral/Dorsal ratio compared to difficult and simple. When assessed by zones 1-4, ventilation on zone 4 is greater in this region in patients with prolonged weaning.

8. CONSIDERAÇÕES FINAIS

O presente estudo demonstrou que os pacientes com SARA apresentaram uma grande proporção de desmame prolongado e difícil com piores desfechos clínicos. No grupo de desmame prolongado houve um aumento significativo dos volumes e pressões pulmonares quando comparado ao desmame simples sugerindo grande comprometimento pulmonar e não resolução do processo inflamatório da SARA. A TIE demonstrou que os pacientes que evoluíram com desmame prolongado apresentaram maiores ventilações em regiões dorsais e aumento relação V/D sugerindo intenso esforço ventilatório espontâneo e comprometimento das regiões pulmonares dependentes. Esses achados mostraram o quanto foi relevante a avaliação da perda da ventilação protetora e a influência da ventilação espontânea nos casos mais graves de desmame da VM. O estudo permitiu através das alterações pulmonares um melhor entendimento na fisiopatologia da falha do desmame da VM em pacientes com SARA. Apesar das limitações já descritas do estudo, poderiam ser desenvolvidos novos estudos utilizando a TIE associados a avaliação rotineira da mecânica pulmonar para uma nova abordagem mais detalhada desse momento crucial da retirada do suporte ventilatório

9.PERSPECTIVAS FUTURAS

O estudo apresentado nesta tese de doutorado mostrou novos dados pertinentes ao assunto do tema da pesquisa. Os achado principais da TIE associado aos dados clínicos e da mecânica pulmonar foram de grande valia para a formulação de novas pesquisas sobre o assunto. As alterações pulmonares do aumento do VC e DP deveriam ser melhor testadas em novos estudos de forma multicêntrica para confirmar os resultados mostrados nessa amostra de pacientes. O emprego da TIE em pacientes mais graves que estão evoluindo com desmame prolongado e que apresentaram redução da relação V/D com aumento da ventilação em regiões posteriores deveria também ser testada num número mairo de pacientes. Durante a coleta foi também obtido amostras de plasma que possibilitariam a dosagem de biomarcadores e possível hipótese que o desmame da VM pode ter efeito na inflamação pulmonar gerando risco da piora do quadro inflamatório da SARA. Outra perspectiva bem plausível é a formulação de um escore com o uso da TIE associado a outros dados clínicos para desmame em pacientes com SARA baseado nos principais achados do estudo (aumento do VC, DP e redução da relação VD associados assincronias e achados clínicos como delirum e fraqueza adquirida na UTI) que poderiam identificar de forma mais precoce os pacientes que irão falhar no desmame da VM. Essa identificação precoce é pertinente para formulação de um plano terapêutico mais adequado e individualizado para essa parcela de pacientes.

10.ANEXOS E/OU APÊNDICES

Appendix 1 - Protocol of the Weaning from MV in Adults HCPA

Patient ≥ 48 hours of MV with resolution of the cause of respiratory failure through the clinical julgment and daily suspension of sedation

Conditions to progress weaning?

Consider extubation with the use of NIV in patients at high risk for reintubation:
-COPD and CHF
-Age> 65 years
- Previous T-tube test failure or extubation
-Chronic or acute petraluropathy
-Airway stridor that does not need immediate intubation
-Morbid obesity

Those with tolerance to PSV ≤10cmH2O and PEEP 5cmH2O and FiO2 ≤0.4 for 30-120minutes.

Conditions for T-tube testing:
-Tolerance of MV in assisted mode
- Adequate oxygenation: PaO2> 60mmHg and FiO2≤0.4 and PEEP≤8 cmH2O and pH>7.25
-Hemodynamic stability: HR <120 and absence of significant hypotension (norepinephrine≤0.1mcg / kg / min)
- Adequate neurological status.

Yes

Patient at high risk for reintubation?

Yes → No

No

NIV Protocol

Test T tube for 30 minutes with O2 5l/min in order to maintain SpO2> 90%

Consider:
RSBI (1st and final test) <105
PiMax (1st test) <-20 cm H2O
Cuff-leak test (before starting test) Δ≥ 12%
SvO2 (1st and final test) Δ≤4.5

Return to MV with adequate PSV level for patient comfort for 24 hours (use of sedation if necessary) OR until resolution of the cause of the test failure. Investigate causes of intolerance to the T-tube test

Tolerance to the test

No

Yes

Signs of intolerance to the test:
-use of accessory musculature
-sweating
-changing level of consciousness (drowsiness / agitation)
-RPM> 35rpm
-HR> 120 or cardiac arrhythmia
-Hypertension or hypotension
-SpO2 <88%
-RSBI> 105
-PiMáx> -20cmH2O-consider TMV

Extubation

Appendix 2: Main Characteristics of the Study Population

Patient No.	Age*	Gender	BMC	SAPS III	Etiology of ARDS	ARDS Type	PaO2/FiO2 diagnosis**	PaO2/FiO2 weaning**	Weaning Type	MV Time	Outcome ICU	Outcome Hospital
#1	20	M	19,9	76	Primary, infectious	Moderate	126	337	Simple	10	Survivor	Survivor
#2	18	F	16,1	81	Primary, infectious	Severe	56	350	Prolonged	28	Suvivor	Survivor
#3	23	M	26,5	48	Primary, infectious	Severe	50	372	Difficult	9	Survivor	Survivor
#4	15	F	21,8	39	Primary, infectious	Moderate	146	387	Simple	5	Survivor	Survivor
#5	61	F	26,7	73	Primary, infectious	Severe	95	280	Prolonged	29	Survivor	Survivor
#6	29	F	29,4	54	Primary, infectious	Mild	228	225	Simple	6	Survivor	Survivor
#7	37	F	43	56	Primary, infectious	Moderate	183	407	Prolonged	14	Died	Died
#8	75	F	28,9	73	Primary, infectious	Severe	96	349	Prolonged	16	Died	Died
#9	76	F	33,1	80	Primary, infectious	Moderate	120	540	Simple	7	Survivor	Survivor
#10	21	F	28,7	39	Primary, infectious	Severe	87	343	Simple	6	Survivor	Survivor
#11	51	M	20	77	Primary, infectious	Mild	222	280	Prolonged	11	Survivor	Survivor
#12	19	F	24,8	74	Primary, infectious	Moderate	191	247	Difficult	9	Survivor	Survivor
#13	36	M	24,1	76	Primary, infectious	Moderate	137	229	Prolonged	15	Survivor	Survivor
#14	46	F	28,1	64	Primary, infectious	Moderate	180	420	Difficult	23	Died	Died
#15	72	F	22,3	85	Primary, infectious	Moderate	134	209	Prolonged	21	Died	Died
#16	38	M	25,9	54	Primary, infectious	Mild	226	223	Simple	5	Survivor	Died
#17	50	F	20,5	59	Primary, infectious	Severe	80	220	Prolonged	42	Died	Died
#18	29	M	23,1	92	Primary, infectious	Moderate	162	397	Simple	4	Survivor	Survivor
#19	57	M	19,4	56	Primary, infectious	Mild	203	330	Difficult	8	Survivor	Survivor
#20	41	F	30	55	Primary, infectious	Moderate	124	307	Difficult	10	Survivor	Survivor
#21	32	M	38,4	53	Primary, infectious	Moderate	153	233	Difficult	7	Survivor	Survivor
#22	39	F	37,4	47	Primary, infectious	Moderate	138	298	Simple	4	Survivor	Survivor
#23	66	F	21	62	Primary, infectious	Moderate	160	366	Difficult	9	Survivor	Survivor
#24	58	M	26,5	53	Extrapulmonary,noninfectious	Moderate	157	308	Difficult	12	Survivor	Survivor
#25	64	F	28,6	91	Primary, infectious	Severe	91	295	Simple	10	Survivor	Survivor
Mean±SD	43,9±19	9M/16F	26,6±6	64,7±15	24 primary/1 extrapulmonary; 24 infectious/1 noninfectious	4 Mild 14 Moderate 7 Severe	141,8 ± 50,8	321,7 ± 82,4	09 Simple 08 Difficult 08Prolonged	12,8 ± 9,3	20 survivor 5 Died	19 Survivor 6 Died

Legend: M=male; F=female; BMC= Body Mass Index (Kg/m2); SAPS3 = Simplified Acute Physiology Score 3; ARDS= Acute Respiratory Distress Syndrome; MV= Mechanical Ventilation; ICU=Intensive Care Unit; *years; **mm Hg; This table showed main characteristics of the all patients included of the study;

Appendix 3: Ventilator Parameters during ICU

Parameters	General (n=25)	Simple(n=9)	Difficult (n=8)	Prolonged (n=8)	P value
pHD1	7.29±0.1	7.25±0.11	7.31±0.08	7.30±0.08	0.41
pHD3	7.33±0.1	7.35±0.04	7.32±0.07	7.31±0.06	0.18
pHD7	7.39±0.1	7.33±0.01	7.41±0.04	7.38±0.09	0.12
PCO2D1	50.1±13	55.7±18.2	46.8±6.2	48.4±10.8	0.32
PCO2D3	48.9±10	49.7±13.5	45.9±3.6	51.1±11.2	0.61
PCO2D7	45.6±9	52.5±12.0	40.9±6.7	47.9±10.5	0.18
PaO2/FiO2D1	141.8±51	147.1±51.3	152.3±48.1	125.4±55.5	0.46
PaO2/FiO2D3	263.7±117	316.0±140.6	296.3±80.1	172.4±58.4	0.03
PaO2/FiO2D7	288.7±97	234.0±107.5	339.4±99.3	258.0±83.6	0.38
PaO2D1	81.9±32	81.8±11.3	85.8±45.4	78.1±34.4	0.84
PaO2D3	102.2±35	116.5±49.2	106.3±22.3	82.0±13.1	0.12
PaO2D7	96.0±39	78.1±21.1	119.0±40.9	80.3±32.0	0.11
FiO2D1	62.4±22	61.6±23.5	61.3±26.3	64.4±19.6	0.81
FiO2D3	41.8±12	38.4±9.1	37.5±10.4	50.0±10.4	0.03
FiO2D7	35.9±13	30.3±9.5	33.3±6.2	40.3±17.0	0.50
TVD1	6.4±0.8	5.9±0.6	6.6±0.6	6.8±0.9	0.02
TVD3	6.3±1.2	5.5±1.3	6.6±0.9	6.9±1.0	0.05
TVD7	7.9±2.3	8.0±4.3	7.9±1.8	7.9±2.0	0.85
RRD1	28.9±4.3	29.2±3.2	28.5±5.9	28.9±4.3	0.57
RRD3	27.6±4.9	25.3±5.3	27.9±4.7	30.0±3.8	0.09
RRD7	25.0±6.2	25.3±4.2	24.1±6.8	25.8±6.9	0.87
PPlatôD1	24.8±5.2	26.3±5.5	23.3±4.9	24.6±5.5	0.58
PPlatôD3	23.0±3.8	22.6±4.2	22.5±3.7	24.0±3.9	0.37
PPlatôD7	21.0±4.9	24.5±0.7	20.4±4.2	20.7±5.9	0.39
PEEPD1	11.6±2.7	11.4±2.4	11.0±2.4	12.3±3.5	0.50
PEEPD3	10.9±2.8	11.2±3.3	10.3±2.3	11.3±3.0	0.65
PEEPD7	8.6±2.4	8.7±4.6	7.9±1.7	9.3±2.2	0.48
PIPD1	31.4±7.1	30.0±6.9	31.1±8.7	33.3±6.0	0.39
PIPD3	30.7±5.9	28.0±6.7	30.1±6.1	32.6±4.6	0.18
PIPD7	24.9±6.1	22.0±10.0	26.4±4.0	25.0±5.9	0.71
CStatD1	29.8±9.7	25.1±6.6	35.0±12.6	29.8±7.5	0.28
CStatD3	31.0±9.8	28.6±9.1	35.6±11.8	29.0±7.6	0.29
CStatD7	43.6±30	27.5±2.1	42.2±17.7	49.3±40.2	0.38
CDynD1	19.8±6.2	20.1±7.2	21.5±6.7	17.6±4.1	0.39
CDynD3	19.7±6.6	21.3±8.0	21.3±7.9	16.9±2.6	0.41
CDynD7	26.5±9.3	20.5±3.5	26.4±7.3	28.7±12	0.49
ΔPD1	13.2±3.4	14.7±3.7	12.3±3.1	12.4±3.1	0.27
ΔPD3	12.0±2.4	11.6±2.1	12.0±2.9	12.5±2.3	0.81
ΔPD7	12.0±4.5	12.5±2.1	12.4±5.4	11.6±4.8	0.93

Legend: MV = mechanical ventilation; D1 = day 1 MV, D3 = day 3 MV; D7 = day 7 MV; FiO2 = inspired oxygen fraction; RR = respiratory ratio; PEEP = positive end-expiratory pressure; CStat = Static Compliance; Cdyn = Dynamic Compliance; ΔP = driving pressure

Apêndice 4: Review Article: "Weaning from Mechanical Ventilation in ARDS: Aspects to Think about for Better Understanding, Evaluation, and Management"

Review Article

Weaning from Mechanical Ventilation in ARDS: Aspects to Think about for Better Understanding, Evaluation, and Management

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Acute respiratory distress syndrome (ARDS) is characterized by severe inflammatory response and hypoxemia. The use of mechanical ventilation (MV) for correction of gas exchange can cause worsening of this inflammatory response, called "ventilator-induced lung injury" (VILI). The process of withdrawing mechanical ventilation, referred to as weaning from MV, may cause worsening of lung injury by spontaneous ventilation. Currently, there are few specific studies in patients with ARDS. Herein, we reviewed the main aspects of spontaneous ventilation and also discussed potential methods to predict the failure of weaning in this patient category. We also reviewed new treatments (modes of mechanical ventilation, neuromuscular blocker use, and extracorporeal membrane oxygenation) that could be considered in weaning ARDS patients from MV.

1. Introduction

Since the creation of the intensive care unit (ICU), the use of mechanical ventilation (MV) has been evaluated basically with regard to three aspects of debate [1]. The first is when should MV be started, either invasive or noninvasive. The second is after the start of MV, when the choice of ventilation mode is made and ventilation parameter settings are evaluated. These adjustments were better understood after the description of "ventilator-induced lung injury" (VILI), where adjustments made only for the correction of gas exchange may worsen pulmonary and extrapulmonary injury [2–4].

The third subject of debate, which is no less challenging, is when would be the best time for withdrawal of ventilatory support, so-called weaning from MV [5]. MV weaning has been studied for several years and has gone from a state of the art to a science after formulating more defined concepts and conducting clinical studies. MV weaning can be simple in most cases, but there may be cases of difficult or

prolonged weaning. In these groups, the outcomes are worse when compared to simple weaning from MV [6]. This more complicated MV weaning scenario has been seen more in the last years after the best initial care of the critical patient, which has provided a reduction in mortality, but a portion of patients progress to chronic critical illness [7, 8].

Studies and guidelines for MV weaning have little concern for distinguishing the peculiarities of the critical patient [9–13]. There is no individualization of a patient with chronic obstructive pulmonary disease (COPD) or acute respiratory distress syndrome (ARDS). The first shows the changes of a chronic lung disease, while the second displays various acute peculiarities related to intense inflammatory response. New approaches could be considered in MV weaning with the evolution of intensive care [14].

This study proposes a review of the main aspects for the understanding of ARDS during weaning of MV as well as evaluating and managing this phase of withdrawal of ventilatory support. The review of the literature was carried

out aiming at the aspects related to the evaluation of weaning of MV in patients with ARDS. Search was conducted in the period from 1967 to 2018 and the following electronic databases: MEDLINE, EMBASE, LILACS, and Cochrane Central Register of Controlled Trials (CENTRAL) and relevant science sites. The following "Mesh terms" are from MEDLINE: "Respiratory Distress Syndrome, Adult"[Mesh], "Ventilator Weaning"[Mesh]. After the results, the articles of relevance to the theme of the proposed study were selected.

2. Mechanical Ventilation in ARDS: Start, Transition, and End of Weaning Process

The initial evaluation and treatment of the patient with ARDS begin with the correction of the inflammatory mechanism that triggered the process, i.e., sepsis and the decision to start ventilatory support [17, 18]. This ventilatory support can be provided as supplemental oxygen, high-flow nasal oxygen therapy, and noninvasive MV and in most cases invasive MV [19–21]. Another important initial aspect of ventilatory support is the choice of ventilatory mode (controlled versus spontaneous) and parameter settings to adopt the "lung-protective ventilation" strategy. This protective ventilation consists in the adjustment of low tidal volume (TV) on the basis of predicted weight and elevated levels of positive end-expiratory pressure (PEEP) with respiratory regulation (RR), considering not only the correction of hypoxemia, but in the care of the targets of pulmonary pressures and volumes to avoid volutrauma and atelectrauma [22–24]. In the most severe cases, the use of neuromuscular blockade (NMB), prone position, and extracorporeal membrane oxygenation (ECMO) will be evaluated when there is refractory hypoxemia [25–29]. These initial strategies are key to successful treatment of patients with ARDS and therefore weaning success and reduction in MV time.

After a few days with assumed improvement in inflammatory status and gas exchange, the clinician at bedside begins to think of withdrawing ventilatory support. First, NMB and sedation are provided until spontaneous ventilation movements are detected. Afterwards, spontaneous breathing trials (SBTs) are conducted to evaluate the withdrawal of MV. The T tube test or pressure support ventilation (PSV) modalities are useful for all types of MV weaning patients [12]. In recent years, the influence of spontaneous ventilation has been better evaluated in patients with ARDS. Initial studies suggest the beneficial effect of spontaneous ventilation in both improvement of hypoxemia and pulmonary compliance and reduction in atrophy of respiratory muscles, mainly diaphragmatic [30–33]. However, animal studies show the opposite with increased transpulmonary pressure, worsening of asynchrony (flow starvation, short cycling, and double-triggering), breath stacking, pendelluft phenomenon, diaphragmatic injury, and worsening of inflammatory response and VILI (Figures 1 and 2) [15, 16, 34–37]. Spontaneous efforts may cause swings and heart-lung imbalances with worsening of pulmonary edema and injury, mainly due to excessive negative pleural pressure (Ppl) [38, 39]. During weaning, excessive respiratory drive and high ventilatory demands increase dyspnea and may lead to
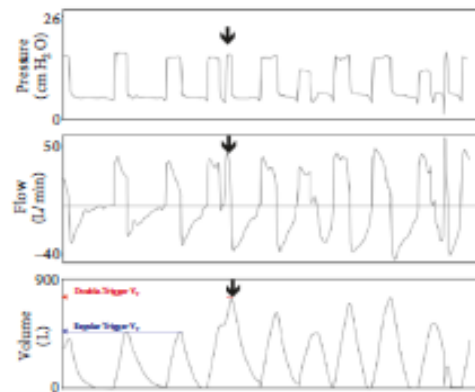
FIGURE 1: Double-triggering occurs when a spontaneous effort triggers a (second) ventilator breath before the initial breath has completely exhaled (arrow). The pressure-time trace (upper panel) and flow-time trace (mid panel) demonstrate the occurrence of the additional breath, but do not give a sense that both inspirations are summed; this is apparent from the volume-time (lower panel) trace indicating that the double-triggering results in a substantially larger (potentially injurious) VT (red) compared with regular triggering (blue). Legend: VT: tidal volume. With authors permission [15].

weaning failure and/or failure to intubate and may present "air hunger" [40]. The high respiratory drive leads to vigorous inspiratory efforts that result in excessive global or regional pulmonary distension due to a nonhomogeneous distribution of stress and strain. A mechanism recently termed "patient self-inflicted lung injury" (P-SILI) may create a vicious circle of worsening injury, resulting in higher TVs and injurious lung stress [19]. Papazian et al. showed a reduction in mortality and inflammation in moderate and severe ARDS with the use of NMB in the early stages, suggesting the attenuation of lung injury with NMB [25, 41]. These findings related to the presence of spontaneous movements in injured lungs should be considered in patients with ARDS, who are starting weaning from MV. Despite the great interest in this area, there are few studies that definitively assess the true impact of spontaneous ventilation during weaning from MV in patients with ARDS (Figure 3).

3. Monitoring MV Weaning in ARDS

The usual parameters for the evaluation of MV weaning are in regard to clinical, gasometry, ventilatory mechanics, and radiological data. These parameters can assess the overall improvement in the cause of respiratory failure. However, they may be unable to predict patients with MV weaning failure.

The use of frequency-to-tidal volume ratio (f/VT) is the most widespread predictor of weaning and has better prediction than other prediction methods. However, the f/VT as well as the other methods have failures to predict the withdrawal of the MV. New applications of weaning
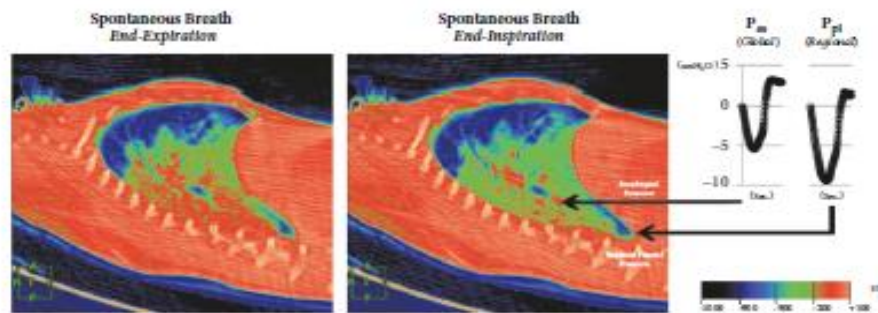
FIGURE 2: Dynamic CT scan in end-expiration (left panel) demonstrates that the aerated lung (blue) is nondependent, while the dependent lung is densely atelectatic (red). At end-inspiration during a spontaneous breath (mid panel), there is little change in the nondependent aerated lung (blue); the dependent lung, previously densely atelectatic (red) is now partially aerated (green/red). The inspiratory pleural pressure traces (right panel), measured at the arrow tips, show the negative deflections ("swings") in regional Ppl and global Pes during inspiration. However, the "swing" in regional Ppl is greater (x2) than the "swing" in Pes, indicating that diaphragm contraction results in greater distending pressure applied to the regional lung near the diaphragm compared with the pressure transmitted to the remainder of the lung (i.e., Pes). Ppl: pleural pressure; Pes: esophageal pressure; HU: Hounsfield Units, with authors permission [15].
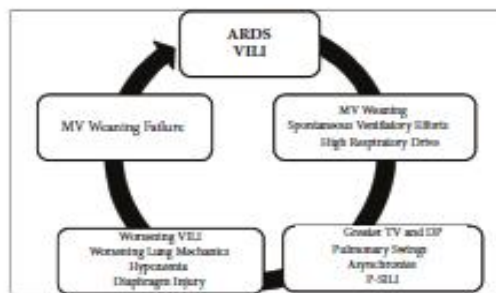

FIGURE 3: Weaning failure in ARDS. ARDS: "Acute Respiratory Distress Syndrome"; VILI: "Ventilator-Induced Lung Injury"; MV: "Mechanical Ventilation"; TV: "Tidal Volume"; DP: "Driving Pressure"; P-SILI: "patient self-inflicted lung injury".

predictors in this scenario must be explored in future studies [65]. During the weaning of ARDS patients in PSV, it was observed in a pilot study in ARDS patients with weaning failure that TV increases without changes in RR patients as generally described by Tobin [5, 58]. These alterations—reduced TV and increased RR—associated with other signs of failure—arterial hypertension, sweating, accessory musculature utilization, and drowsiness—usually occur in later phases of MV weaning failure.

The evaluation of hypoxemia is generally used to classify the severity of ARDS and monitor the progression of lung injury [66, 67]. At weaning from MV, usually a PaO_2/FIO_2 ratio over 200 is considered the criterion for the start of the MV weaning process [13]. Nevertheless, hypoxemia is not a specific marker of the inflammatory response [68].

Another point to emphasize is that, during spontaneous ventilation tests, there is the inability to evaluate transpulmonary pressure or driving pressure (DP) [56, 69]. During spontaneous ventilation after withdrawal of NMB, other pressures involved—pleural and muscular pressure—influence the evaluation of pulmonary mechanics [70]. Pilot study for early weaning evaluation was seen to be increased DP. For the evaluation of pulmonary mechanics during study, small doses of sedatives or short-acting NMBs (propofol 10mg IV and if necessary succinylcholine 2-4mg IV) may be given [58].

The evaluations of airway pressures usually employed in MV weaning assessment are the levels of PEEP and peak and plateau pressures. The target generally recommended to start weaning from MV is a PEEP level of 5-8 cmH$_2$O and pressure support levels to maintain adequate ventilation.

In patients with ARDS there is a wide variation of radiological findings seen on conventional chest radiography compared with computed tomography [71]. There is also a discrepancy of the observers in the interpretation of the presence of edema seen in the chest radiograph [18].

4. Potential Methods for Predicting MV Weaning in ARDS

The purpose of this topic is to present some methods that have been the subject of debate in the literature and that could be better evaluated for weaning prediction in ARDS patients (Table 1). However, the magnitude of weaning from MV specifically in patients with lung injury as well as new methods should be further studied. However, clinicians need new parameters at bedside to better predict MV weaning because of the unique pathophysiology of patients with ARDS compared to other causes of respiratory failure.

TABLE 1: Potential methods for predicting weaning in ARDS.

Potential Method	Advantages	Disadvantages
Esophageal pressure[42, 43]	Pressure measurements with spontaneous ventilation Quantification of pulmonary swings Help in the visualization of asynchrony	Difficulty in positioning the catheter and its accuracy for measuring esophageal pressure Minimally Invasive
P0.1[44, 45]	Evaluation of ventilatory drive	Failure of previous studies as a predictor of general weaning failure
Lung ultrasound [46–48]	Non-invasive Quantification of aeration and collapse during weaning	Operator dependent Skin lesions may make it impossible to perform the test
Echocardiography[49]	Evaluation of the heart-lung interaction Measures left and right ventricular function	Same as above Cardiac images are difficult to visualize in some patients
Asynchrony[36, 50]	Quantification of asynchrony and better adjustment of parameters and modes of mechanical ventilation during weaning	Automatic devices that are validated for clinical use are missing
EIT[51–54]	Non-invasive and radiation-free Real-time visualization of aeration and collapsed lung and swings during weaning Evaluation of pulmonary perfusion	Artifacts caused by changes in thoracic shape, providing three-dimensional absolute/relative images with better resolution
Biomarkers[55]	Evaluation of VILI and P-SILI worsening during mechanical ventilation weaning	Influence by extrapulmonary inflammatory response

EIT: Electrical Impedance Tomography; VILI: Ventilator-Induced Lung Injury; P-SILI: patient self-inflicted lung injury.

4.1. Monitoring Mechanical Ventilation Parameters. The monitoring of pulmonary pressures through the usual pressure curves shown by ventilators during weaning is mixed by the presence of spontaneous ventilation. The pressures abolished by the effect of the BNM appear after their withdrawal and can influence the lung lesion as well as during the transition from controlled to spontaneous [70, 72]. Amato et al. in a large retrospective analysis showed the increase in DP as a worse predictor of outcome in patients with ARDS [56]. At weaning from MV, the persistence of the inflammatory response could increase DP. This alteration could be better evaluated as a new marker of complicated weaning in lungs that still had unresolved "occult" lung injury.

The use of esophageal manometry has been used in respiratory physiology research, but its clinical use is not common. The evaluation of esophageal pressure (Pes) using esophageal manometry helps in the estimation of pleural pressures because its measurement can be influenced by the effects of the chest wall and lungs [42]. There is a gradual reduction in ventilatory support and increased patient effort during weaning from MV. The Pes increases progressively in patients who fail weaning, while the success of weaning does not occur significant changes in Pes [73, 74]. The continuous evaluation of Pes variations predicts a better success or failure at MV weaning than f/TV [74]. Yoshida et al. suggest the use of the esophageal manometry to guide PEEP settings to reduce VILI [57]. Pes monitoring may be a useful tool and part of the intensivist's clinical armamentarium to show oscillations of pulmonary pressures during weaning from MV [42, 43].

The pressure developed in the occluded airway 100 ms after the onset of an inspiratory effort (P0.1) is another measure that could help as a weaning predictor in patients with ARDS. P0.1 was initially described more than 40 years ago [75] and may be used to assess simply and noninvasively the increased ventilatory drive in ARDS and its deleterious consequences in injured lungs [40]. P0.1 is independent of respiratory mechanics and the patient's reaction, and it is, importantly, unaffected by respiratory muscle weakness. The optimal target range for respiratory drive and inspiratory effort during MV is uncertain. In healthy subjects breathing at rest, P0.1 varies between 0.5 and 1.5 cmH_2O [44]. P0.1 can be useful to adjust the level of ventilatory support due to its close correlation with inspiratory effort. Higher values of P0.1 indicate insufficient levels of support, while lower values correspond to excessive assistance. P0.1 has been extensively studied as a predictor of weaning success or failure [5]. A high P0.1 during a spontaneous breathing trial is associated with failure, suggesting that a high respiratory drive could predict weaning failure. P0.1 alone can provide clinicians with information regarding their patient's drive, where it is sensitive to ventilator settings and may be useful during weaning [45].

4.2. Imaging Monitoring. Lung ultrasound can be a good alternative to chest radiography or computed tomography scan in many cases. Bedside lung ultrasound in the evaluation of patients with respiratory failure has been well established [76, 77]. In ARDS there are several findings in the pulmonary ultrasound [71]. The evaluation of aeration can predict the success or failure of weaning from MV [46–48]. Bouhemad

showed to be accurate the use of the lung ultrasound reaeration score for the use of antibiotics in ventilator-associated pneumonia [60]. Haji et al. showed parameters lung (loss of aeration score of the left and right anterior and lateral regions) and parameters cardiac through diastolic dysfunction (left atrial area, E/E', interatrial septal rightward fixed curvature) to help predict failed extubation [49]. Echocardiography should be further explored in this population because the risk of swings and changes in heart-lung interaction can influence the success of weaning from MV [38, 78]. The lung ultrasound examination has some limitations: it cannot detect lung overinflation; subcutaneous emphysema and the presence of large thoracic dressings may preclude propagation of ultrasound beams to the lung surface, with severe chest trauma or burns; it may be limited by the patient's pain and discomfort; training is required to correctly perform the examination and interpret its findings and it is not a continuous monitoring tool [71]. Lung ultrasound and echocardiography are still uncertain methods in the evaluation of weaning in ARDS and require more specific studies for their present application.

Another imaging tool to use at bedside is electrical impedance tomography (EIT), which is a noninvasive imaging method [79]. EIT is a radiation-free, noninvasive technique for continuous monitoring of lung volume during ventilation and possibly a guide for the weaning process [51, 52, 80]. The dynamic real-time evaluation of aerated and nonaerated areas could show the pulmonary swings and their correlation with the course of MV weaning (see Figure 2). Blankman et al. compared the effects of pressure control ventilation (PCV) and PSV on the distribution of ventilation with the use of EIT. There was improved ventilation of the dependent lung region during PSV due to the contribution of the diaphragm resulting in a distribution shifted to the nondependent lung with elevated TV [81]. Bickenbach et al. showed changes in regional ventilation of the lung and heterogeneity in prolonged weaning undergoing T-piece trials in real time [53]. Regional EIT monitoring during edema formation reveals a decrease in lung aeration in dorsal regions, associated with a decrease in regional ventilation. In association with such changes, EIT typically discloses compensatory increases in regional ventilation of ventral regions. The presence of spontaneous ventilatory movements causes increased ventilation in dorsal regions. This ventilation is an effect of apposition of the dorsal diaphragm and also gravitational effect, leading the dependent lung to a greater regional complacency [54]. In contrast, high pressure support levels or TVs are associated with increased ventral ventilation and signals of nondependent lung overdistension (Figures 4 and 5). When pendelluft occurs, the possibility of overstretch of the dependent lung is strongly suggested by EIT, even in patients subjected to low TV ventilation [82]. Impedance properties are sensitive to the difference between blood and air; therefore, EIT has also been studied to assess the regional distribution of perfusion and its relationship with ventilation. The lung pulsatility method has so far been shown to provide qualitative information about lung perfusion, e.g., following the activation of hypoxic pulmonary vasoconstriction [83].

Another evaluation during weaning from MV is the use of plethysmography, a tool to assess functional residual capacity, TV, and variability over time. Studies with pulmonary variability have correlated with success or failure of MV weaning in patients in general [84–86]. Studies have been carried out recently with the use of EIT, but there is still a need to improve image reconstruction and to create algorithms for applications in weaning evaluation at bedside [87].

4.3. Monitoring Asynchrony. Ventilator asynchrony is associated with increased ICU stay and mortality. During episodes of asynchrony may occur worsening hypoxemia and increased respiratory muscle work [50, 59, 88]. There is also increasing concern that asynchrony may cause large transpulmonary pressure swings and inappropriately large TV that may be especially harmful in critically ill patients who are receiving lung-protective ventilation [36]. The presence of asynchrony during the weaning of ARDS patients from MV could be better quantified and distinguished. In addition, the types of asynchrony could also be evaluated. The presence asynchrony, both quantity and type, could be considered at bedside as a predictor MV weaning failure in patients with ARDS.

4.4. Biomarkers. ARDS is characterized by intense inflammatory response with release of several inflammatory mediators during the course of this response, exudative, proliferative, and fibrotic phases of ARDS [18]. Increased levels of plasma biomarkers, including markers of systemic inflammation (interleukin-6 and interleukin-8), epithelial and endothelial injury, along with markers of dysregulated coagulation, have been associated with adverse outcomes of ARDS [18, 89, 90]. During the weaning process, SBTs involve cardiopulmonary stress for ventilated patients; interleukin-6, a major modulator of the stress response, has been shown to be higher in COPD patients during weaning failure [91]. Yang et al. showed reduced levels of serum inflammatory cytokines, especially IL-6, with successful weaning in septic patients on ventilators [55]. Other more specific lung biomarkers could also be evaluated during weaning from MV in patients with ARDS, i.e., amphiregulin and type III procollagen [92, 93]. However, there are still no studies that define the role of biomarker measurement in the evaluation of MV weaning in ARDS patients.

5. Innovative Therapies to Treat ARDS with Complicated Weaning

There have been few studies specifically on the subject of weaning ARDS patients from MV and on their approach as well [94, 95]. Table 2 has future potential suggestions to resume the actual moment in research that is waiting research to confirm this evaluation in VM weaning for ARDS. Weaning that does not progress should be evaluated for any factors that perpetuate the inflammatory response, e.g., uncontrolled infection. Invasive ventilation itself can lead to iatrogenic damage to the lungs already with lung injury, and therefore, caution with the influence of spontaneous ventilation can lead to more lung injury and diaphragmatic dysfunction. New occult mechanisms increasing the risk of VILI during assisted spontaneous breathing (e.g., occult pendelluft and
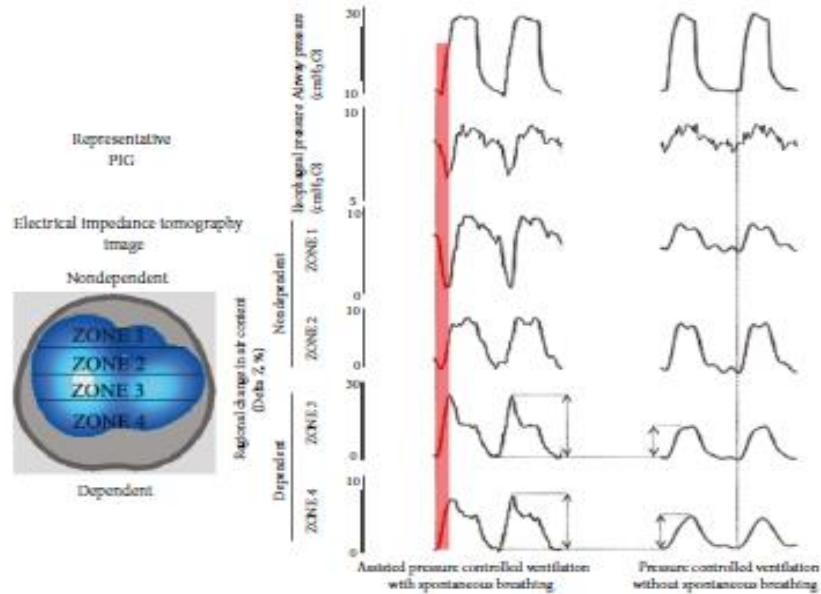
FIGURE 4: Electrical impedance tomography (EIT) waveforms in experimental lung injury, spontaneous versus ventilator breaths. In an anesthetized pig model of acute lung injury assist pressure-controlled ventilation (IP, 15 cm H2O; f, 25 min21; PEEP–13 cm H2O; triggering threshold, 22 cm H2O) was used. The EIT image was divided into four zones, each covering 25% of the ventrodorsal diameter (zones 1–4). During controlled ventilation (under muscle paralysis), simultaneous inflation of each of the different lung regions was observed, although at different inflation rates. In contrast, when spontaneous efforts were present, two observations were noted. First, in the initial stages of the breath, spontaneous efforts caused inflation of dependent lung regions (red in zones 3 and 4), which was greater with controlled breaths. Second, the early inflation in the dependent region was accompanied by concomitant (transient) deflation of nondependent region (red in zone 1), indicating movement of gas from nondependent to dependent lung regions, because this was not associated with alterations in tidal volume it indicates a pendelluft phenomenon. This finding was always present during spontaneous breathing efforts in all animals with experimental lung injury: f – respiratory frequency; IP: inspiratory pressure; PEEP: positive end-expiratory pressure, with authors permission [16].
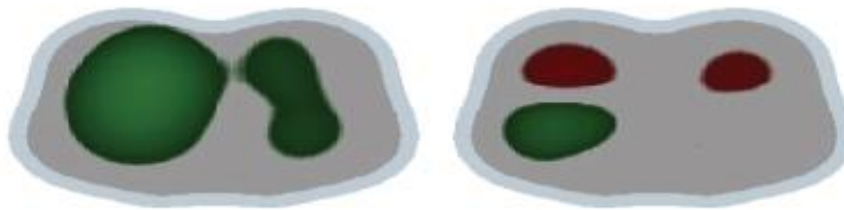

FIGURE 5: Electrical Impedance Tomography. Example of the visualization of the variation in pulmonary ventilation seen through EIT of MV weaning in two ARDS patients in the first 2 hours. Image on the left indicates the gain in ventilation in green with an increase in TV from 6 to 12 ml/kg. The patient on the right showed weaning failure and prolonged weaning from MV. Image displays an increase in TV from 6 to 8 ml/kg and loss of ventilation variation in red; the patient showed simple weaning from MV.

TABLE 2: Future potential suggestions to evaluation in VM weaning for ARDS.

WEANING IN ARDS
(1) Control of the Illness (reducing inflammation)
(2) PaO2/FiO2>200 and PEEP≤10 cmH2O
(3) Evaluate:
(a) Pulmonary mechanics during the spontaneous ventilation test:
(i) Measure TV e DP – caution TV>8ml/kg and/or DP>13 [56]
(ii) If available – monitoring Pes [42, 57]
(iii) Bedside alternative for the evaluation of pulmonary mechanics: Administration of small doses of sedatives and short-acting NMB (propofol 10mg IV and if necessary succinylcholine 2-4mg IV) and change to VCV to measurements [58]
(b) Asynchrony and Ventilatory Drive:
(i) Asynchrony Index (failure if>10%)[59]
(ii) P0.1 (consider high drive if>3.0)[44, 45]
(c) Imaging Monitoring:
(i) EIT (tidal variation of impedance (TIV), the changes in end-expiratory lung impedance (ΔEELI) – failure if global inhomogeneity index (GI) value> 40 [53]
(ii) US (lung score >17 is predictive of postextubation distress [49, 60])
(iii) Echocardiography (qualitative right ventricular failure and diastolic dysfunction)[49]
(4) Management with High TV, DP, Asynchrony Index, P0.1 or worse of regional aeration:
(i) Eliminate stress factors (pain, anxiety and delirium) and sedation adjustment – try dexmedetomidine or propofol. Avoid bolus of fentanyl (can lower RR and increase TV)
(ii) Test increment in PEEP to 12cmH2O
(iii) Alternative ventilatory modes to improve asynchronies – PAV [61] or NAVA [62]
(iv) Patients with refractory weaning: use partial NMB [63] and ECMO [64]

ARDS: acute respiratory distress syndrome; MV: mechanical ventilator; PEEP: positive end-expiratory pressure; TV: tidal volumes; DP: driving pressure; Pes: esophageal pressure; P0.1: pressure 100 ms after the onset of an inspiratory effort; EIT: electrical impedance tomography; VCV: volume control ventilation; US: ultrasound; IPAV: proportional-assist ventilation; NAVA: neurally adjusted ventilator assist; NMB: neuromuscular blockade; ECMO: extracorporeal membrane oxygenation.

solid-like lung behavior) are extremely difficult to recognize at bedside, but clinically, they should be suspected in patients with more severe lung injury (e.g., patients with extremely low compliance) and/or with strenuous inspiratory effort [72].

5.1. New Ventilatory Modes. The ventilation mode should be evaluated to improve patient-ventilator synchrony. When pressure support is added to spontaneous breathing, the same principles apply, but total pressure across the respiratory system and transpulmonary pressure increase, generating additional flow and volume. During pressure support, if inspiratory airflow exists after the end of respiratory muscular pressure, Pes/Ppl can result in positive swings along inspiration, where ventilation is a hybrid of active (during the first part) and passive (towards the end) phenomena [70].

An alternative ventilatory mode that the ventilator generates pressure in proportion to the patient's effort is the proportional-assist ventilation (PAV) mode. The synchrony can improve because the RR is determined by the patient's own respiratory drive of the patient and the ventilatory assistance terminates with the end of the inspiratory effort. The different approaches used in PSV and PAV to pressurize the lung could theoretically lead to marked differences in

response to these variations in respiratory system impedance. Respiratory loading has often been used to stimulate changes in respiratory impedance and to evaluate the consequences of such changes on ventilatory patterns and respiratory muscle performance [61].

Another ventilatory mode that is adjusted to the neural output of the patient's respiratory center is neurally adjusted ventilator assist (NAVA). The pressure is regulated by the integral of the electrical activity of the diaphragm (EAdi) and therefore better synchrony between the patient and the ventilator. Studies show that NAVA protects against excess pressure and TV when compared to PSV. The Hering-Breuer reflex may be implicated in the absence of a TV increase with NAVA levels [96]. Terzi et al. evaluated ARDS patients and showed recovery and improved the synchrony compared PSV [62]. Therefore, NAVA is another ventilation mode that improves patient-ventilator synchrony in these patients during the weaning process [63, 97–99].

5.2. Partial Neuromuscular Blockade. An alternative but still experimental approach with "partial neuromuscular blockade" proposed by Doorduin et al. in 10 patients with ARDS during PSV is innovative and deserves attention [100]. This study showed a reduction in TV, EAdi, and transpulmonary

pressure with subtherapeutic doses of rocuronium without changes in pH and diaphragm activity. In other words, strong spontaneous breathing efforts were abolished, but a significant degree of diaphragm activity was maintained. An assist-controlled mode under these conditions resulted in severe breath stacking, which is associated with high TV [31]. A change of mode of ventilation to controlled ventilation and adjustment of sedatives (propofol or dexmedetomidine, for example) could help in controlling the high respiratory drive.

5.3. Extracorporeal Membrane Oxygenation. Another device that has gained ground in intensive therapy is ECMO. After a series of cases with H1N1 and the CESAR study, its use has been more widespread and studied [27]. Authors suggest that ultra-protective MV can be better performed with this device especially in patients with spontaneous ventilatory movements and control of ventilatory drive in patients with ARDS [64, 101–104]. Its use in patients with difficulty in weaning needs to be better studied because there is physiological and protective rationale as a whole. However, the risks of the procedure and the absence of robust studies in this situation do not allow its routine use in weaning patients with ARDS.

6. Conclusion

Weaning ARDS patients from MV still needs to be better debated and studied. New knowledge related to the presence of spontaneous ventilation and the risk of inflammatory worsening are important in this debate. Practitioners could consider weaning in ARDS to continue to protect the lung. New methods to evaluation of weaning of the patients with ARDS as well as more rational approaches based on pathophysiology should be performed for success in withdrawal of ventilatory support and improvement of their outcomes.

Abbreviations

ARDS: Acute respiratory distress syndrome
MV: Mechanical ventilator
VILI: Ventilator-induced Lung Injury
COPD: Chronic obstructive pulmonary disease
TV: Tidal volumes
PEEP: Positive end-expiratory pressure
RR: Respiratory rate
NMB: Neuromuscular blockade
ECMO: Extracorporeal membrane oxygenation
SBT: Spontaneous breathing trial
PSV: Pressure support ventilation
Ppl: Pleural pressure
P-SILI: Patient self-inflicted lung injury
f/VT: Frequency-to-tidal volume ratio
DP: Driving pressure
Pes: Esophageal pressure
P0.1: Pressure 100 ms after the onset of an inspiratory effort
EIT: Electrical impedance tomography
PCV: Pressure control ventilation

PAV: Proportional-assist ventilation
NAVA: Neurally adjusted ventilator assist
EAdi: Electrical activity of the diaphragm.

Data Availability

The data used for this review were consulted through the availability of journal access.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Iuri Christmann Wawrzeniak reviewed the literature and wrote the article. Silvia Regina Rios Vieira conducted a review of the article. Josué Almeida Victorino reviewed the articles and wrote the article. All authors read and approved the final manuscript.

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Apêndice 5: Termo de Consentimento Livre e Eclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Nº do projeto CAAE: 51678415.8.0000.5327

Título do Projeto: Avaliação da Mecânica Pulmonar em Pacientes com SARA no Processo de Desmame da Ventilação Mecânica.

A pessoa pela qual você é responsável está sendo convidada a participar de uma pesquisa cujo objetivo é avaliar a mecânica pulmonar, ou seja, o funcionamento dos pulmões em pacientes com SARA (Síndrome da Angústia Respiratória Aguda que é uma inflamação de ambos os pulmões) durante o processo de desmame da ventilação mecânica. Esta pesquisa está sendo realizada pelo Serviço de Medicina Intensiva do Hospital de Clínicas de Porto Alegre (HCPA).

O paciente pelo qual você é responsável está atualmente dependendo de aparelhos para respirar e irá iniciar o processo de tentar retirar o respirador (desmame), de acordo com a indicação do médico responsável. Normalmente, durante este processo de retirada podem ocorrer falhas e até piora nos casos mais graves. Atualmente essa avaliação é realizada de rotina através de coletas de sangue e raio X de tórax, assim como utilizando os dados no monitor do respirador, os quais nem sempre mostram as causas de falha da retirada do respirador.

Se você concordar com a participação na pesquisa, os procedimentos envolvidos são os seguintes: iremos consultar nos dados de prontuário os resultados dos exames realizados de rotina do paciente e realizar uma coleta de sangue adicional, que será realizada preferencialmente através de cateteres que o paciente já tenha implantado para outros procedimentos assistenciais. Para melhor avaliação da mecânica pulmonar poderá ser realizada a administração de pequenas doses de sedativos, o que será conduzido pela equipe de pesquisadores e em caso de qualquer complicação será interrompida a avaliação. Também será realizada uma tomografia de impedância elétrica. A tomografia é um método para coleta de imagens do pulmão, sendo que as tomografias tradicionais usam radiação e são realizadas em locais fora da UTI, aumentando os riscos e desconfortos do transporte. A tomografia por impedância elétrica é um método que mede as correntes elétricas naturais do corpo e não causam danos conhecidos. É realizada no próprio leito, usando tiras parecidas com os pequenos adesivos que já são utilizados para a verificação dos batimentos do coração. O paciente permanecerá com estas tiras por um período de 2 (duas) horas para coletar as imagens do pulmão.

Durante a coleta de dados não serão modificados ou interrompidos nenhum procedimento de rotina que o paciente possa estar realizando de acordo com a indicação médica, como coletas de sangue, uso de medicamentos ou aparelhos já em uso. Se o paciente apresentar alguma intercorrência durante o estudo, todo o procedimento será interrompido. Quanto ao uso da tomografia de impedância elétrica, trata-se de um procedimento livre de radiação, indolor e sem qualquer sensação desagradável conhecida ao usuário. Os adesivos com gel aplicado na pele do paciente também não causam nenhum dano esperado ao paciente, se houver qualquer reação, como por exemplo, alérgica, o procedimento será imediatamente interrompido. A coleta de sangue pode causar algum desconforto como o causado para coleta de exames de rotina, que será minimizado por utilizar acessos que o paciente já tenha para coletas. A utilização adicional de sedativos poderá causar sonolência, queda da pressão arterial, necessidade de ficar no respirador o que geralmente são transitórias e de curta duração e serão cuidados pela equipe.

Rubrica do responsável _____   Rubrica do pesquisador _____   Página 1 de 1

CEP Hospital de Clínicas de Porto Alegre (MR 05/11/2015)

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

A participação na pesquisa não trará benefícios diretos aos participantes, porém, contribuirá para o aumento do conhecimento sobre o assunto estudado, e poderá beneficiar futuros pacientes com este mesmo quadro.

A participação na pesquisa é totalmente voluntária, ou seja, não é obrigatória. Caso você decida não autorizar a participação, ou ainda, retirar a autorização após a assinatura desse Termo, não haverá nenhum prejuízo ao atendimento que o participante da pesquisa recebe ou possa vir a receber na instituição.

Não está previsto nenhum tipo de pagamento pela participação na pesquisa e não haverá nenhum custo com respeito aos procedimentos envolvidos.

Caso ocorra alguma intercorrência ou dano, resultante da pesquisa, o participante receberá todo o atendimento necessário, sem nenhum custo pessoal.

Os dados coletados durante a pesquisa serão sempre tratados confidencialmente. Os resultados serão apresentados de forma conjunta, sem a identificação dos participantes, ou seja, os nomes não aparecerão na publicação dos resultados.

Caso você tenha dúvidas, poderá entrar em contato com o pesquisador responsável Dr. Iuri Christmann Wawrzeniak, pelo telefone (51) 33598639 ou com o Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre (HCPA), pelo telefone (51) 33597640, ou no 2º andar do HCPA, sala 2227, de segunda à sexta, das 8h às 17h.

Esse Termo é assinado em duas vias, sendo uma para o participante e seu responsável e outra para os pesquisadores.

_____
Nome do participante da pesquisa:

_____
Nome do responsável

_____
Assinatura

_____
Nome do pesquisador que aplicou o Termo

_____
Assinatura

Local e Data: _____

Apêndice 6:The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		Case-control study—If applicable, explain how matching of cases and controls was addressed
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.