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CLARISSA NETTO BLATTNER

REPERCUSSÕES HEMODINÂMICAS E METABÓLICAS DA FISIOTERAPIA RESPIRATÓRIA EM PACIENTES COM CHOQUE SÉPTICO

Orientadora: Profa. Dra. Sílvia Regina Vieira

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Projeto de pesquisa para tese de Doutorado pelo Programa de Pós Graduação da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul, aprovado pelo Comitê de Ética do Hospital São Lucas da PUC.

Orientadora: Profa. Dra. Sílvia Regina Vieira

Porto Alegre, abril 2013

DEDICATÓRIA

A todos que acreditam em mim e nos meus sonhos

À minha maravilhosa família

Aos sempre presentes Emerson, Lucas e Gustavo

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SUMÁRIO

LISTA DE ABREVIATURAS

CAP - Cateter de artéria pulmonar

CPAP - Pressão positiva contínua em vias aéreas

CVF - Capacidade vital forçada

DC - Débito cardíaco

DO_2 - Demanda de oxigênio

EGDT - Early Goal Directed Therapy

EI - Inspirometria de incentivo

EPAP - Pressão positiva expiratória na via aérea por máscara facial

ERO_2 - Taxa de extração de oxigênio

FC - Frequência cardíaca

FR - Frequência respiratória

HCO3 – Bicarbonato de sódio

HM - Hiperinsuflação manual

IC - Índice cardíaco

IPPB - Respiração com pressão positiva intermitente

IRVP- Índice de resistência vascular pulmonar

IRVS – Índice de resistência vascular sistêmica

ITSVD - Índice de trabalho sistólico do ventrículo direito

ITSVE - Índice de trabalho sistólico do ventrículo esquerdo

IVS - Índice de volume sistólico

NO – Óxido Nítrico

$PaCO_2$ - Pressão arterial de gás carbônico

PAD – Pressão arterial diastólica

PAM - Pressão arterial média

PaO_2 - Pressão arterial de oxigênio

PaO_2/FiO_2 PaO2/FiO2 – Relação pressão arterial de oxigênio/Fração inspirada de oxigênio

PAPM - Pressão média da artéria pulmonar

PCT – Procalcitonina

PEEP – pressão positiva expiratória final

pH - potencial hidrogeniônico

PIT - Pressão intratorácica

POAP - Pressão de oclusão da artéria pulmonar

PVC - Pressão venosa central

PvCO2 – Pressão venosa de gás carbônico

SaO_2 - Saturação arterial de oxigênio

$ScvO_2$ - Saturação venosa central de oxigênio

SOFA – Sequential Organ Failure Assessment

SpO_2 - saturação periférica de oxigênio

SvO_2 - saturação de mistura venosa

TBARS – Acido Tiobarbitúrico

TEMP - Terapia expiratória manual passiva

TGF-β – Fator de transformação do crescimento beta

TNF-α - fator de necrose tumoral alfa

UTI - Unidade de Terapia Intensiva

VEF1/CVF – Relação volume expiratório forçado no 1 segundo e capacidade vital forçada

VM - Ventilação mecânica

VO_2 - consumo de oxigênio

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1. INTRODUÇÃO:

A sepse grave e sua evolução para choque séptico têm sido a causa mais freqüente de óbito nas Unidades de Terapia Intensiva (UTIs) em todo o mundo. Nos últimos dez anos, dados epidemiológicos americanos mostram aumento de incidência de 91,3% de sepse nas UTIs daquele país, comprovando que a terapêutica precoce e o manejo cuidadoso com esses doentes é vital.[1]

Os efeitos da fisioterapia respiratória em Unidade de Terapia Intensiva (UTI) estão associados ao incremento de VO_2 e $SatO_2$, mas sua repercussão também tem sido associada à respostas indesejáveis tanto hemodinâmicas quanto metabólicas. Neste contexto, a atuação do fisioterapeuta na UTI vai contribuir para a prevenção primordial de complicações inerentes ao tempo prolongado de ventilação mecânica invasiva e agravamento da sepse, assim como ser utilizada como terapia complementar no manejo de pacientes criticamente enfermos. Embora diversas estratégias sejam possíveis para a atuação da fisioterapia respiratória, poucos estudos têm analisado de forma abrangente os efeitos induzidos por diferentes tipos de técnicas, bem como seus possíveis efeitos deletérios. [2,3,4]

Portanto, o presente documento inicialmente descreve o marco teórico sobre a sepse, sua evolução e a relação com a fisioterapia respiratória, abordando particularmente os efeitos promovidos por diferentes técnicas fisioterapêuticas na prevenção e tratamento da sepse grave. Em capítulos subsequentes, serão apresentados três estudos que buscam sumarizar os efeitos benéficos e/ou deletérios da assistência fisioterapêutica à pacientes com choque séptico.

2. REVISÃO DE LITERATURA:

2.1 SEPSE E CHOQUE SÉPTICO:

A sepse grave denominada infecção à disfunção orgânica aguda secundária, e sua evolução para choque séptico (sepse severa com hipotensão não reversiva com ressuscitação com fluidos) têm sido a causa mais freqüente de óbito nas Unidades de Terapia Intensiva (UTIs) em todo o mundo. Em estudo publicado em 2001[1], foi mostrado que nos Estados Unidos ocorrem aproximadamente 750.000 casos de sepse por ano, com 215.000 mortes/ano. O choque séptico possui estatísticas alarmantes também no Brasil. Dados de um estudo clínico brasileiro revelam que a incidência de sepse grave no país é em torno de 27% em pacientes com mais de 24 horas de internação em UTI, sendo a mortalidade em 28 dias de 47%.[1]

Em linhas gerais, a sepse representa uma continuidade de eventos infecciosos e interações entre patógenos com consequências hemodinâmicas causadas pela relação entre mediadores pro-inflamatórios, anti-inflamatórios e apopópticos.[1] Os estágios primários da sepse podem ser acompanhados de uma insuficiência circulatória resultante da hipovolemia, depressão miocárdica, aumento da taxa metabólica, e anormalidades de perfusão – entre a relação de demanda e reserva de oxigênio – causando uma hipóxia tecidual global.[5,6,7]

Sabe-se que aumentos na extração de oxigênio, ou diminuição da saturação venosa central ($ScvO_2$) ou saturação de mistura venosa (SvO_2) sinalizam a queda da saturação venosa de hemoglobina. Estes achados fornecem um mecanismo compensatório para atenuar o desbalanceamento da manutenção das necessidades de oxigênio. [6,8]

A SvO_2 é, sem dúvida, “padrão ouro” do balanço entre oferta e consumo global de oxigênio e tem relação fisiológica importante com o débito cardíaco (DC). A SvO_2 baixa é fortemente indicativa de falta de adequação do DC. Já seu valor de normalidade, não garante adequação da oferta à demanda de oxigênio dos tecidos. [9]

A sepse pode ser estratificada com base nos níveis séricos de lactato, e existem numerosos algoritmos de ressuscitação na sepse usando lactato como parâmetro referencial e preditor de diagnóstico. Entretanto, existem outros fatores capazes de motivar elevação do lactato sérico não necessariamente vinculados à infecção e disfunção mitocondrial. Na sepse, a acidose metabólica caracteriza-se pelo pH inferior a 7,35 e excesso de base elevado, com redução do teor do bicarbonato.[6,10]

A transição para o choque séptico pode variar de um estado hipodinâmico de demanda dependente de oxigênio (elevadas taxas de lactato e baixa saturação venosa de oxigênio) para um estado mais comumente conhecido como hiperdinâmico onde o consumo de oxigênio (VO_2) é independente da demanda de oxigênio (DO_2) – normal para o aumento das concentrações de lactato e alta saturação venosa de oxigênio. Todos estes fatores dependem do estágio da apresentação da doença e da extensão da otimização hemodinâmica.[6,7]

Na tentativa de minimizar complicações decorrentes das mais diversas patologias e do longo período de internação em Unidades de Terapia Intensiva (UTI), a assistência médica segue rotinas rígidas no cuidado destes pacientes. Dentre esses cuidados, atenção especial é dispensada ao controle da ventilação, controle circulatório e parâmetros hemodinâmicos. Para tanto, a equipe conta com um arsenal de equipamentos auxiliares na coleta de dados, mudanças de parâmetro e administração de medicamentos.[11,12]

O estresse oxidativo é um dos maiores contribuintes do aumento da mortalidade em diversas doenças, dentre elas, o choque séptico. O estresse oxidativo causado por endotoxinas pode diminuir os catalisadores ou supressores de radicais livres. Além disso, pode regular a produção do TNF-α (fator de necrose tumoral alfa), ocorrendo como um resultado de uma translocação bacteriana ou endotóxica, reduzindo a função em vários estados da doença. O óxido nítrico (NO) tem sido implicado na patogenia da hiperresponsividade vascular (hipotensão no choque séptico). Entretanto, o NO pode não ser o único mediador da lesão tecidual e citotoxicidade causadas pelas endotoxinas. Com isso, se torna influente a avaliação da potencialidade

dos radicais livres sobre pacientes com desordens metabólicas em sepse e choque séptico.[13]

Estudos confirmam que, um estresse oxidativo severo em pacientes sépticos graves, com ressuscitação com fluídos, possui elevados níveis de substâncias ácido reativas tiobarbitúricas (TBARS), peróxidos lipídicos e a atividade da xantina oxidase. Os próprios níveis de xantina oxidase confirmam a falência do controle microcirculatório, com consequente queda da perfusão tecidual e isquemia.[13,14]

Além disso, a superóxido dismutase (SOD) tem sido evidenciada como uma molécula importante na proteção celular e tecidual contra os efeitos tóxicos destes radicais superoxidados. Uma combinação de componentes antioxidantes, como a SOD, e imunoestimulantes pode colaborar para a redução do estresse oxidativo, embora ainda haja dificuldades de se estabelecer este conceito, devido a demanda pró-inflamatória que pacientes com choque séptico apresentam em diversas ocasiões.[13,14]

Com a indução de citocinas, acompanhada de um envolvimento de mediadores pró-inflamatórios e de estresse oxidativo, torna-se claro a relação da apoptose em pacientes sépticos, aumentando-se conforme o envolvimento sistêmico na qual o paciente se envolva, como a SIRS (síndrome da resposta inflamatória sistêmica).[15]

2.2 MONITORIZAÇÃO DO DOENTE CRÍTICO:

Quando utilizada em pacientes sem doença cardiorespiratória prévia, a ventilação mecânica com volume corrente normal não apresenta consequências hemodinâmicas discerníveis. Por outro lado, a presença de doença pulmonar afetando a árvore brônquica, parênquima pulmonar, ou ambos, pode induzir a condições extremas para a ventilação mecânica. Neste momento, o efeito hemodinâmico adverso pode complicar seriamente o quadro respiratório. Essas conseqüências hemodinâmicas da ventilação mecânica são

fáceis de compreender examinado-se o impacto sobre o ventrículo direito da aplicação de uma pressão positiva na via aérea.[16]

Por outro lado, as alterações cíclicas (ventilação corrente) ou contínuas (aplicação de PEEP – pressão positiva expiratória final) na pressão transpulmonar produzidas pelo suporte respiratório afetam diretamente a impedância de saída do ventrículo direito, tendo, portanto, importante repercussão hemodinâmica sobre o doente.[16]

A avaliação precoce e a intervenção baseada em evidência são, sem dúvida, determinantes na sepse e choque séptico. Rivers et al[7], em 2001, mostraram que nas primeiras horas de ressuscitação hemodinâmica da sepse grave deve-se procurar sua otimização, num protocolo conhecido como Early Goal Directed Therapy (EGDT), que utilizava a saturação venosa central de oxigênio ($SvcO_2$), mensurada através de cateter de fibra ótica locado em veia cava superior.

A monitorização hemodinâmica atual busca a detecção precoce do desequilíbrio entre a oferta e o consumo de oxigênio, podendo definir preditores de sobrevida e incrementar a estratificação de risco, com especial importância na estimativa do prognóstico. É de fundamental importância a interação de toda a equipe para o acompanhamento da evolução clínica do paciente.[17]

O cateter de artéria pulmonar, também chamado de Swan-Ganz, é utilizado para mensurações hemodinâmicas de pacientes críticos e em pós operatório de algumas cirurgias cardíacas em pacientes de baixo ou alto risco, fornecendo informações sobre parâmetros da pressão e do fluxo tanto da circulação sistêmica quanto da pulmonar. É passado à beira do leito e o ideal é que permaneça nas artérias pulmonar central direita ou principal esquerda.[18,19]

Pode ser utilizado para determinar a etiologia do choque, acidose lática, edema pulmonar, insuficiência renal oligúrica, hipertensão pulmonar e uma variedade de anormalidades cardíacas, tais como regurgitação mitral, defeitos nos septos atrial e ventricular, tamponamento cardíaco, cardiomiopatias restritivas e taquiarritmias. [20]

O cateter de artéria pulmonar permite medidas de pressão venosa, pressões de artérias pulmonares, POAP (pressão de oclusão da artéria pulmonar) e débito cardíaco (DC). A partir destas variáveis podem ser calculadas IC (índice cardíaco), índice de volume sistólico (IVS), índice de trabalho respiratório dos ventrículos esquerdo e direito (ITSVE e ITSVD), resistência vascular sistêmica e pulmonar (RVS e RVP).[21]

Apesar das possíveis complicações e, embora não se associe à redução da mortalidade em pacientes críticos, o cateter ainda é utilizado em pacientes graves e instáveis hemodinamicamente, principalmente como orientador da prática terapêutica.[20]

Sabe-se que na sepse, a presença de disfunção cardiovascular associa-se a um pior prognóstico. No choque séptico, a dependência do consumo em ralação à oferta é mais ampla, quando comparada a outros tipos de choque, e, por esta razão, uma condição hiperdinâmica se faz necessária para atender a demanda do paciente. Diante dessa necessidade, o cateter de artéria pulmonar (CAP) fornece informações que permitem otimizar a reposição volêmica e drogas vasoativas, visando à restauração das variáveis de perfusão tecidual. Um estudo americano demonstrou uma menor mortalidade quando se utilizou, de forma mais frequente, o CAP durante o suporte hemodinâmico de pacientes com choque séptico.[22,23,24]

A associação do CAP com mortalidade, morbidade e custos hospitalares é controversa. Sabe-se que o benefício com o emprego do CAP depende muito da qualificação dos profissionais que indicam e interpretam os dados, bem como da tomada de decisões baseadas nesses achados. Portanto, é difícil avaliar a relação direta do uso do CAP com mortalidade, morbidade, custos e tempo de internação. Existem estudos que sugerem aumento da mortalidade e tempo de internação, mas sem justificar diretamente esse achado ao uso do CAP. De outra forma, outros ensaios clínicos correlacionam o uso do CAP com melhor prognóstico e outros que não encontram diferenças. [25,26]

2.3 FISIOTERAPIA NA SEPSE

A fisioterapia respiratória resulta em mudanças fisiológicas com alterações significantes nos parâmetros hemodinâmicos, respiratórios e intracranianos. Entretanto, a literatura não permite que se conclua quais são os principais efeitos da fisioterapia respiratória sobre pacientes internados em uma unidade de terapia intensiva. A fisioterapia tem demonstrado ser um importante componente no manejo de pacientes em unidade de terapia intensiva e tem demonstrado beneficios a curto e médio prazo. [27,28]

As técnicas mais comuns usadas pelos fisioterapeutas em uma unidade de terapia intensiva são os posicionamentos, a hiperinsuflação manual (HM), as técnicas percussivas manuais passivas torácicas, as vibrações torácicas, sendo que todas estas técnicas podem estar ou não associadas à pressão positiva nas vias aéreas.[27,29]

Muitos estudos avaliam os efeitos hemodinâmicos, entretanto, nenhum se torna conclusivo a afirmar os potenciais efeitos que a fisioterapia provoca em pacientes críticos, principalmente pelo número pequeno amostral ou pelas variadas técnicas utilizadas num mesmo estudo, dificultando a análise dos resultados.[30,31]

A extensão na qual é possível prevenir estas anomalias fisiopatológicas e o desenvolvimento subseqüente de atelectasias e infecção tem sido base de muitas pesquisas e é a premissa básica por trás da ação da fisioterapia em pacientes que foram submetidos à cirurgias abdominal ou cardíacas, por exemplo. A maior parte da literatura que examina o uso de medidas profiláticas na prevenção de complicações pulmonares pós-operatórias apresenta um quadro confuso, frequentemente com evidências contraditórias sobre a aceitação ou rejeição de um regime de tratamento em particular. Existem muitos problemas inerentes na comparação destes estudos devido à grande variabilidade nas modalidades de tratamento, grupos de pacientes e medidas de resultado. Não há um ‘padrão ouro’ no qual os tratamentos possam ser comparados ou concordância sobre os critérios de diagnóstico a serem utilizados para avaliação das complicações pulmonares.[32]

Uma variedade de técnicas fisioterapêuticas respiratórias tem sido usadas em pacientes ventilados mecanicamente. A terapia expiratória manual passiva (TEMP) é mais conhecida no Japão como “squeezing” (compressão leve). No entanto, o paciente submetido à cirurgias torácicas e/ou cardíacas tem incisões anteriores ou laterais além de fraturas e instabilidades ósseas, de costelas e esterno, que podem comprometer a eficácia da manobra por dor.[33]

Na maioria dos estudos, os adjuntos mecânicos, principalmente EI (inspirometria de incentivo) ou IPPB (respiração com pressão positiva intermitente), tem sido comparados com exercícios respiratórios.[30] Com exceção do estudo de Oulton et al.[31] não foram observadas diferenças entre os grupos de tratamento. Stock et al.[34] compararam exercícios respiratórios, EI, e uso de CPAP (pressão positiva contínua em vias aéreas) aplicado por máscara facial em 38 pacientes submetidos a cirurgia cardíaca ou substituição de válvula. Embora o CPAP tenha falhado em acelerar a recuperação dos volumes pulmonares e PaO_2, estes autores sugeriram que o CPAP pode ser preferível comparado a EI ou respiração profunda pois este é aplicado independente do esforço do paciente. Vraciu e Vraciu[35] relataram uma menor incidência de complicações respiratórias em pacientes de alto risco (história recente de tabagismo, Capacidade vital forçada (CFV) < 80% do previsto normal, VEF_1/CVF < 75% ou acima de 60 anos de idade), quando foram adicionados exercícios respiratórios supervisionados duas vezes ao dia na rotina de enfermagem, consistindo de EI a cada duas horas e exercícios respiratórios e tosse a cada hora. [30,31,34,35]

A pressão positiva expiratória final, também conhecida como PEEP, é uma forma de aplicação de resistência a fase expiratória, que reflete-se em aumento das pressões alveolares, podendo recrutar unidades alveolares colapsadas, diminuindo o “shunt” e melhorando a relação ventilação-perfusão, resultando em melhora das trocas gasosas. No uso com o paciente cardiopata, esses efeitos redundam em diminuição do trabalho respiratório que, adicionado à melhora do desempenho cardíaco, provoca redução da carga imposta à musculatura respiratória, o que predispõe a um maior controle da hipoxemia[16]. Sabe-se que a pressão intratorácica pode interferir no desempenho cardíaco, principalmente no paciente com insuficiência cardíaca congestiva[17]. A PEEP

tem efeitos benéficos sobre o desempenho cardíaco através da redução da pré carga, em função da diminuição do retorno venoso e de redução da pós carga, através da redução da pressão transmural do ventrículo esquerdo.[36,37,38]

Em 2000[39], um estudo utilizou o CPAP como recurso terapêutico durante e após o procedimento cirúrgico, em 14 pacientes, e destacou a eficácia da PEEP, tendo em vista que, 18h após a cirurgia todos os pacientes ventilados em CPAP foram extubados e transferidos a uma unidade de tratamento intermediária. Neste mesmo estudo, alguns pacientes do grupo controle, que não utilizaram o CPAP, desenvolveram síndrome de disfunção multiorgânica durante a noite após a operação e requiseram cuidados de terapia intensiva e permaneceram em ventilação mecânica por mais seis dias antes de serem desmamados.

A avaliação de parâmetros hemodinâmicos durante ou após a fisioterapia respiratória tem papel terapêutico importante. Porém, sua mensuração requer instrumentos específicos, por vezes caros e invasivos. Com o objetivo de avaliar as alterações hemodinâmicas causadas por pressão positiva expiratória na via aérea por máscara facial (EPAP), um estudo randomizado, em pacientes estáveis no pós-operatório de cirurgia cardíaca concluiu que a terapêutica foi bem tolerada, porém demonstrou aumento nas medidas de pressão de enchimento ventricular direito e esquerdo, assim como, na pressão arterial média.[40]

As evidências sobre fisioterapia respiratória e uso terapêutico de resistência expiratória demonstram repercussões ventilatórias positivas, incluindo reexpansão e deslocamento de secreções. No entanto, no que tange repercussões hemodinâmicas e metabólicas, os estudos utilizam combinações variadas de técnicas, não sendo possível atribuir resultados específicos a uma técnica em particular.[29,41]

A fisioterapia motora sob forma de movimentação passiva dos membros, também foi estudada, visando avaliar possíveis efeitos hemodinâmicos e metabólicos. Apesar da amostra reduzida, concluíram que as mobilizações cíclicas podem influenciar a condição hemodinâmica e metabólica de pacientes

sedados e dependentes da ventilação mecânica (VM). Isso foi demonstrado através de aumento do consumo de oxigênio (VO_2), da taxa de extração de oxigênio (O_2ER) e índice cardíaco (IC). Concomitantemente, houve queda na saturação de oxigênio no sangue venoso (SvO_2).[42]

Embora o uso de técnicas de fisioterapia respiratória no tratamento de pacientes submetidos à cirurgia cardíaca seja amplo, existem poucas avaliações científicas detalhadas. Em um estudo de 2002[40], foram avaliados e comparados 269 pacientes quanto ao teste de função pulmonar pré e pós operatório com os efeitos do longo período de intubação. Todos os pacientes submetidos a esse estudo realizaram um programa de reabilitação cardiopulmonar, incluindo exercícios pulmonares diafragmáticos, educação de tosse, técnicas de drenagem postural e exercícios de mobilização geral durante sua internação, iniciando no primeiro dia de extubação. Os resultados foram positivos quanto ao tempo de intubação e internação, demonstrando potencial efeito da fisioterapia sob a evolução clínica pós operatória.[43]

A hiperinsuflação manual ("bagging") pode ser usada como uma técnica de ventilar um paciente ou durante a fisioterapia. Ao ventilar manualmente os volumes correntes normais são distribuídos de forma geral, enquanto que, como método fisioterápico, respirações mais longas ou alternância entre hiperinsuflações rápidas e mais lentas serão necessárias. O "bagging" pode ser oferecido usando tanto um circuito de bolsa de água quanto um hiperinsuflador manual. Em casos de pacientes dependentes de PEEP ou, que se beneficiariam com seus efeitos, uma válvula de *spring loaded* deve ser instalada na saída exalatória a fim de manter a pressão expiratória final positiva durante o procedimento.[44]

A HM foi definida como a insuflação pulmonar utilizando oxigênio e compressão manual para proporcionar um volume corrente que excede o volume basal, e utilizando um volume que é 50% maior que o aplicado pelo ventilador (quando utiliza-se ambas as mãos para compressão da "bolsa"), exigindo um pico de pressão inspiratória de 20 a 40cmH_2O. O uso de um volume corrente maior, proporcionado por uma respiração com maior volume durante um período, pode aumentar o percentual de fluxo expiratório,

auxiliando assim na mobilização de secreções em direção às vias proximais. A frequência com que o hiperinsuflador manual é comprimido, ao invés da resistência do circuito em si, é o principal fator que influencia o percentual de pico de fluxo inspiratório.[45]

Em um estudo realizado em 2005[46], foram analisados diversos fatores como aspecto da secreção, capacidade do sistema respiratório e relação PaO_2/FiO_2, em dois grupos, onde um recebia técnicas de hiperinsuflação manual três vezes ao dia, durante 5 dias e o grupo controle recebia o tratamento convencional, estando também ventilando mecanicamente, porém sem técnicas de hiperinsuflação adicionais. Segundo esse estudo, houve melhora significativa no que diz respeito a sinais radiográficos (melhora das atelectasias) e incremento da relação PaO_2/FiO_2 no grupo com HM.

Uma análise prospectiva, em 2005[47], analisou dez fisioterapeutas com experiência em unidades de terapia intensiva e, utilizando um sistema simulador pulmonar, avaliou se o uso de PEEP de 0-15cmH_2O associado a HM promove benefícios à complacência pulmonar e à higiene brônquica. Como resultado, sugeriu que a HM é um método efetivo para mobilização de secreções e que, diminui significativamente o pico de fluxo expiratório quando associado à PEEP maior que 10cmH_2O. Esse estudo sugere, porém, que mais estudos clínicos são necessários para definir a efetividade da manobra de hiperinsuflação manual quando associada aos efeitos da PEEP.

Um ensaio clínico randomizado, em 2008, encontrou benefícios significativos sob o tempo de extubação, complacência estática e oxigenação, quando comparou o uso de hiperinsuflação manual associado à PEEP no pós operatório imediato de cirurgia de revascularização do miocárdio. No entanto, não encontrou efeitos deletérios e repercussões hemodinâmicas do uso da técnica.[48]

Entretanto, sabe-se que alguns autores documentaram importantes respostas indesejáveis, tanto hemodinâmicas quanto metabólicas, quanto submetiam pacientes à sessões de fisioterapia. Ao investigar esse tipo de efeitos, formulou-se a hipótese de que o aumento da demanda metabólica

durante a fisioterapia, independente das técnicas utilizadas, era similar à resposta a exercícios, resultante do aumento da atividade muscular. Já o aumento das respostas hemodinâmicas seria, provavelmente, causado pela resposta ao estresse associada ao aumento do tônus simpático.[3,49]

Cabe salientar, que há uma infinidade de estudos que questionam a efetividade da técnica no que diz respeito à segurança da aplicação e alterações hemodinâmicas. Já foi demonstrado que, em modelos animais, a ventilação com elevado volume corrente e altas pressões de pico de induzem ou ampliam a lesão pulmonar. Além disso, o uso de HM acarreta alterações hemodinâmicas relacionadas à diminuição do débito cardíaco com vasoconstrição compensatória evidente pelo aumento da resistência vascular sistêmica e pressão arterial média.[50]

Sabe-se que as alterações na pressão intratorácica (PIT) podem afetar a performance cardíaca, e a ventilação mecânica por pressão positiva está associada com redução da pré-carga no ventrículo esquerdo e débito cardíaco. Se a HM gera uma substancial PIT, sugere-se que há comprometimento da performance cardíaca. Além disso, em se tratando de pacientes com choque séptico, instabilidade hemodinâmica e, consequente dependência de drogas vasoativas, talvez a HM possa ser contra-indicada ou utilizada com muita cautela. Acredita-se, que os efeitos hemodinâmicos da HM em pacientes com choque séptico são relativamente pequenos e insignificantes, e parecem estar relacionados à condição cardiovascular antes do procedimento. [3,37,51,52,53]

Tendo em vista a escassez de dados no que diz respeito à benefícios e eficácia da fisioterapia e, além disso, à possíveis repercussões hemodinâmicas inerentes a determinadas técnicas fisioterapêuticas em pacientes ainda em ventilação mecânica, esse estudo busca analisar as repercussões hemodinâmicas e metabólicas decorrentes da aplicação de hiperinsuflação manual associada à PEEP em pacientes com choque séptico, internados em uma unidade de terapia intensiva afim de comprovar, ou não, que a atuação do fisioterapeuta de forma cada vez mais precoce vem a acrescentar à boa evolução do quadro funcional do paciente crítico, sem ocasionar efeitos deletérios. Associado a isto, como as complicações respiratórias representam

importante mortalidade e morbidade no âmbito da terapia intensiva, todo o esforço deve ser empreendido no sentido de reduzi-las.

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3. HIPÓTESE PRINCIPAL:

A fisioterapia respiratória, seja através de manobras torácicas, ou por uso de pressão positiva expiratória final (PEEP) associada à hiperinsuflação manual, não implica em repercussões hemodinâmicas deletérias que prejudicam a evolução clínica do paciente com choque séptico e contribuem com benefícios ventilatórios e metabólicos nesses doentes.

4. OBJETIVOS

Os objetivos listados abaixo estão divididos de acordo com os estudos que serão apresentados nos capítulos seguintes.

4.1 Estudo I

Objetivo geral: analisar as repercussões cardiorrespiratórias decorrentes da aplicação de fisioterapia respiratória padrão em pacientes com choque séptico.

Objetivos específicos:

- Analisar variáveis de oxigenação no pré atendimento fisioterapêutico (5 minutos antes) e logo após.
- Analisar e comparar amostras de sangue arterial para análise de pH, PaO_2, $PaCO_2$, HCO_3 e SaO_2.
- Avaliar Variáveis hemodinâmicas não invasivas de FC (frequência cardíaca) e PAM (pressão arterial média) conforme rotina da unidade.

4.2 Estudo II

Objetivo geral: Verificar as repercussões hemodinâmicas decorrentes da aplicação de hiperinsuflação manual associada à PEEP em pacientes com choque séptico, internados em Unidade de Terapia Intensiva Adulta através da mensuração por catéter de artéria pulmonar, comparando com um grupo que realizará fisioterapia respiratória convencional, com manobras torácicas manuais.

Objetivos específicos:

- Verificar as repercussões hemodinâmicas das variáveis pressão arterial média (PAM), pressão média da artéria pulmonar (PMAP), pressão venosa central (PVC), pressão de oclusão da artéria pulmonar (POAP), índice cardíaco

(IC), índice de volume sistólico (IVS), índice de trabalho sistólico do ventrículo direito (ITSVD), índice de trabalho sistólico do ventrículo esquerdo (ITSVE), índice de resistência vascular sistêmica (IRSV), índice de resistência vascular pulmonar (IRVP), saturação periférica de oxigênio (SpO_2), freqüência cardíaca (FC) e freqüência respiratória (FR) decorrentes da aplicação de hiperinsuflação manual associada à PEEP e compará-las com um grupo que realizará fisioterapia respiratória convencional, com manobras torácicas manuais.

- Realizar essas mensurações em três momentos, sendo eles, no pré manobra, imediatamente após e 15 minutos depois.

3.3 Estudo III

Objetivo Geral: avaliar o efeito imediato da fisioterapia respiratória em parâmetros hemodinâmicos, metabólicos, inflamatórios e de estresse oxidativo em pacientes com choque séptico.

ARTIGO I

CARDIORESPIRATORY REPERCUSSIONS OF PHYSIOTHERAPY IN PATIENTS IN SEPTIC SHOCK

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ABSTRACT:

Questions: What are the cardiorespiratory repercussions resulting from applying standard respiratory physiotherapy to patients in septic shock? Does the technique provide an immediate clinical benefit?

Design: Prospective experimental study.

Participants: patients diagnosed with septic shock and using vasopressors in an Intensive Care Unit.

Outcome: The cardiorespiratory variables (HR –heart rate), MAP – mean arterial pressure, pHA hydrogen ion potential, PaO2 – partial pressure of oxygen , PaCO2 – partial pressure of carbon dioxide -, SaO2 – oxygen saturation, HCO3 – sodium bicarbonate) were collected 5 minutes before the intervention and immediately afterwards.

Results: The PaO_2, HR and SaO_2 levels rose significantly after physiotherapy (0.001; 0.017; 0.048). On the other hand, the $PaCO_2$ levels were significantly reduced (0.003).

Conclusion: The respiratory physiotherapy approach in patients in septic shock in an Intensive Care Unit was safe and well-tolerated and did not present deleterious efects and hemodynamic deterioration with clinical decompensation during care.

Key-words: Septic shock; respiratory physiotherapy

INTRODUCTION:

Severe sepsis and the development of septic shock have been the most frequent cause of death in Intensive Care Units (ICUs) worldwide.[1] Described as

the evolutionary phase of severe sepsis, in which, despite adequate volemic resuscitation, the patient continues to show signs of tissue hypoperfusion, septic shock presents alarming statistics also in Brazil. Data from a Brazilian clinical study reveal that the incidence of severe sepsis in the country is around 27% in patients who are over 24 hours in the ICU, and the 28-day mortality is 47%.[2]

To minimize complications resulting from the pathologies and the long length of stay of the patient in ICUs, medical care of these patients follows strict routines, mainly in controlling ventilation and circulation, and in hemodynamic parameters.[3]

Various respiratory physiotherapy techniques have been used in mechanically ventilated patients, including the use of positive end expiratory pressure (PEEP) as a way of applying resistance to the expiratory phase. This is reflected as an increase of the alveolar pressures, which can recruit collapsed alveolar units, diminishing shunt and improving the ventilation-perfusion ratio, resulting in improved gas exchanges.[4]

In 2008, a randomized controlled trial (RCT) (ECR)[5] found significant benefits in extubation time, static compliance and oxygenation, comparing manual hyperinflation associated with PEEP immediately after myocardial revascularization surgery. No deleterious effects and hemodynamic repercussions were found using the technique.

Several studies question the effectiveness of physiotherapy concerning safety of application and hemodynamic changes. It has already been demonstrated that, in animal models, ventilation with a high tidal volume and high peak inflation pressure induces or increases the pulmonary lesion. Moreover, the use of manual hyperinflation, for instance, causes hemodynamic alterations related to diminished cardiac output with compensatory vasoconstriction evidenced by the increased systemic vascular resistance and mean arterial pressure.[6]

Current findings, however, characterize the hemodynamic alterations resulting from physiotherapeutic procedures as small, insignificant and related to the cardiovascular status before the procedure.[7]

Due to the scarcity of data regarding benefits and efficacy of physiotherapy, and also possible hemodynamic repercussions inherent to certain physiotherapy techniques in patients who are still undergoing mechanical ventilation, this study seeks to analyze the cardiorespiratory repercussions resulting from the use of standard respiratory physiotherapy in patients in septic shock.

METHOD:

Design:

This study was developed in the General ICU at Hospital São Lucas of the Pontifical Catholic University of Rio Grande do Sul (PUCRS), Brazil, between August 2010 and November 2012. Patients with a diagnosis of septic shock, independently of infection site, who were using a vasopressor, without a dose limitation but with a medical indication for physiotherapy, were allocated to this study. Free and informed consent was obtained from the family member responsible. The patients were kept on invasive mechanical ventilation in a pressure controlled mode. The standard medical treatment was not influenced by the study. When participating in the study, the patient received respiratory physiotherapy care according to the unit protocol, which consisted of thoracic maneuvers and ventilatory patterns with manual hyperinflator and PEEP (using an inspiratory pressure of 40cmH_2O and a PEEP of 10cmH_2O), besides tracheal aspiration. Physiotherapy was done once per shift (morning, afternoon and evening), until the patient was extubated, maintaining standard physiotheraphy. The patients received a physiotherapy intervention in order to collect data for the study. (Fig 1)

The ventilatory (PaO_2, $PaCO_2$, SaO_2), metabolic (pHa, HCO_3) and hemodynamic variables (HR, MAP) were collected 5 minutes before the intervention and immediately afterwards.

Research:

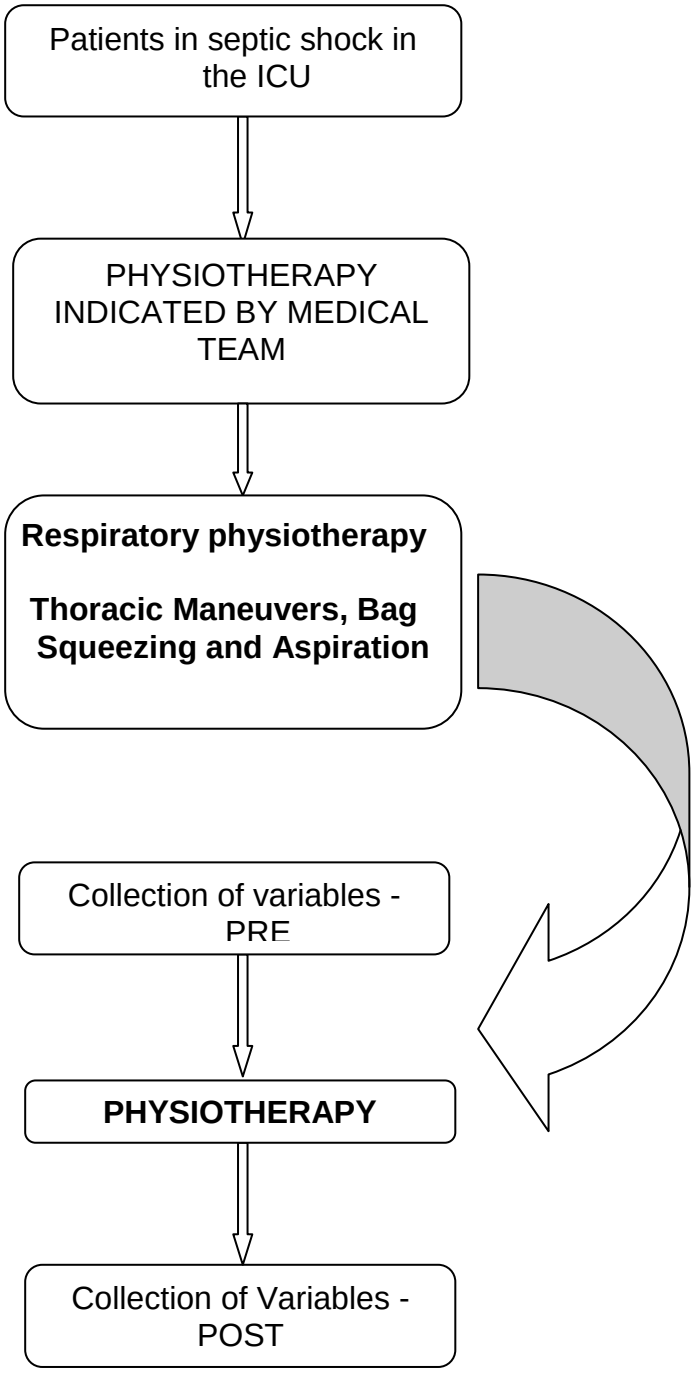

Fig. 1: Design and flow of the study

Participants:

All patients with a diagnosis of septic shock and using a vasopressor who did not present any exclusion criterion were invited to participate in this study. Patients below the age of 19 years or over the age of 80 years, pregnant, with acute myocardial infarction 3 months before the study, septic shock secondary to pulmonary disease, severely ill cardiac patients, with an ejection fraction < 30%, and life expectancy less than 24 hours were excluded.

Intervention:

Mechanical ventilation values were adjusted according to the unit's routine pressure controlled mode, tidal volume of 8 ml/kg, and variable FiO_2. The main objective for patients treated with physiotherapy was to clear and reexpand the lungs. Care consisted of thoracic maneuvers (vibrocompression and redirecting flux, besides decubitus exchanges) according to the routines protocol of the unit, besides 20 minutes of manual hyperinflation using a spring loaded valve to keep the positive end expiratory pressure at 10 cmH_2O. A 3-litre self-inflating bag was connected to a 15 l/min flow and was used to deliver an inspiratory pressure of 40 cmH_2O. A manometer was connected to the system to monitor pressures. Exhaled and inhaled tidal volumes and manual hyperinflation frequencies were not measured. Manual hyperinflation was performed according to ventilation patterns in which long breaths or alternance of rapid and slow hyperinflation were performed at a frequency that varied from 18 to 30rpm. Inspiratory time and inspiratory hold varied between participants. The endotracheal tube and upper airways were suctioned immediately after manual hyperinflation. Suctioning was performed with a closed system.

Outcomes:

Oxygenation variables were analyzed before physiotherapy (5 minutes before) and immediately afterwards. Arterial blood samples were collected to analyze pH, PaO_2, $PaCO_2$, HCO_3 and SaO_2.

Non invasive hemodynamic variables of HR (heart rate) and MAP(mean arterial pressure) were collected according to the unit routine.

Statistical Analysis:

The quantitative variables were described by mean and standard deviation or median and range of variation. The categorical variables were described by absolute and relative frequencies.

The Student t test for paired samples was used to compare the means of the parameters before and after physiotherapy.

The associations between variables were evaluated using the Pearson or Spearman correlation coefficients.

The level of significance adopted was 5% ($p \leq 0.05$) and the analyses were performed in program SPSS version 18.0.

RESULTS:

The characteristics of all participants and of each group before intervention in the table 1.

The results obtained during the pre respiratory physiotherapy period and immediately afterwards are shown in table 2.

Table 1: Characteristics of all participants before intervention

Variables	n=56
Age (years) - Mean ±SD [min – max]	56,9 ± 17,9 [20 – 87]

Weight (kg) - Mean ±SD [min – max]	77,9 ± 15,6 [50 – 140]
Length of stay in ICU (days) – Md [min – max]	8,5 [1 – 58]
Sex – n(%)	
Male	21 (37.5)
Female	35 (62.5)
Vasopressor – Md [min – max]	10 (0 – 50)
Vasopressor (dose/kg/min) – Md [min – max]	0.10 (0.00 – 0.56)
Site of Sepsis	Urinary 11 (19.65%)
	Abdominal 15 (26.85%)
	Pulmonary 30 (53.5%)

Table 2: Comparison between pre and post-physiotherapy

Variables	Pre (n= 56)	Post (n=56)	p*
pHa	7.30 ± 0.40	7.40 ± 0.13	0.077
PaO_2	**99.4 ± 37.5**	**115.4 ± 43.2**	**0.001**
$PaCO_2$	**39.5 ± 12.7**	**36.1 ± 10.6**	**0.003**
MAP	83.6 ± 15.3	85.4 ± 14.0	0.227
HR	**99.5 ± 18.4**	**102.3 ± 18.9**	**0.017**
HCO_3	21.3 ± 4.6	22.0 ± 5.5	0.257
SaO_2	**94.5 ± 6.5**	**96.2 ± 3.8**	**0.048**

* Student t test for paired samples.

Legend: pHa: hydrogen ion potential; PaO_2: partial pressure of oxygen; $PaCO_2$ – partial pressure of carbon dioxide; MAP: mean arterial pressure; HR: heart rate; HCO_3: sodium bicarbonate; SaO_2: oxygen saturation.

The duration of physiotherapy was 567±98 seconds (mean ±SD). The maximum inspiratory peak pressure generated by HM was 40cmH2O, and maintaining a PEEP of 10cmH2O. A manometer was connected to the system to measure pressures.

The PaO_2, HR and SaO_2 levels increased significantly after physiotherapy. On the other hand, the $PaCO_2$ levels were significantly reduced after physiotherapy.

The changes in the parameters were not associated with the vasopressor dose, age, sex and length of stay in ICU ($p>0.10$).

DISCUSSION:

The results of this study showed that physiotherapy in patients with septic shock was well tolerated clinically, with a reduction of the PCO_2 and increase of

PO_2 and SaO_2. As a non invasive hemodynamic variable, HR became significantly higher, but this information was not translated into clinical relevance when the state before the technique for septic patients is analyzed.

Physiotherapy in ICUs has been increasing and has proved of great importance, essentially in developed countries.[8] Outstanding among its benefits are bronchial clearance, prevention and resolution of atelectasis, increased gas exchanges, improved inspiratory muscle performance, culminating in reduction of length of stay in hospital and in ICUs.[9,10,11]

In the unit where the study was performed, all patients on mechanical ventilation had respiratory and motor physiotherapy three times a day with visible clinical and functional effects, especially concerning ventilatory weaning.

The increment in PaO_2 and SaO_2 reflected the benefit of reexpansion and clearance maneuvers to respiratory mechanics. Bronchial hygiene improves with the reduction of $PaCO_2$.

The blood gas and hemodynamic effects of respiratory physiotherapy in patients on mechanical ventilation have been gradually investigated. Clearance and reexpansion maneuvers in the form of thoracic mobilization did not present a significant increase in the hemodynamic condition or the VO_2, which may indicate greater metabolic expenditure.[12]

In this study, patients in septic shock were evaluated. This was defined as the presence of hypotension refractory to volemic replacement, clearly secondary to an infection process, according to the 1992 consensus[13]. In this way, our sample consisted of very ill patients in critical hemodynamic and ventilatory conditions.

It should be recalled that hyperdynamic or septic states course with low values of arteriovenous difference, and therefore low extraction and poor arterial oxygen saturation. This justifies the fact that our patients present altered blood gas, often with the presence of major respiratory acidosis.

In severe sepsis, tissue hypoperfusion characterized by hyperlactatemia or low venous oxygen saturation indicates the need for hemodynamic

resuscitation guided by pre-established goals, and this oxygenation variable should remain greater than or equal to 70%.[14]

During the maneuvers, hypoxemia episodes occurred, although they were transient and had no clinical repercussions, which allowed maintenance and further development of care.

Several clinical studies have related the oxygenation parameters to predictors of results in sepsis. Possibly an additional process that could exacerbate sepsis is the adrenergic stimulation provoked by blood flow reduction, with increased oxygen consumption.[15]

Although in this methodology we do not measure the SvO_2, considered a "gold standard" indicator of the balance of overall offer and consumption of oxygen, we concerned ourselves with showing that it is possible to submit a severely ill septic patients to physiotherapy interventions, with the immediate result of improving oxygenation and gas exchanges, and no apparent short term deleterious effects.

The effects of positive pressure in heart patients have already been well-defined and can be expressed from the standpoint of cardiac performance as diminished pre-loading, by reduction of the venous return, and diminished post-loading by reduction of the transmural pressure of the left ventricle. As to ventilatory mechanics, there is an outstanding recruitment of collapsed alveolar units, reduction of pulmonary shunt with increased oxygenation and reduction of the cardiovascular overload .[16,17]

Early physiotherapy in patients submitted to heart surgery, especially myocardial revascularization, can help remove tracheobronchial secretions, reexpand pulmonary areas with atelectasis and increase gas exchange, incrementing oxygenation, clinical progression and diminishing postoperative complications.[5,18] Motor physiotherapy, in the form of early passive mobilization of patients on mechanical ventilation for more than 48 hours showed a marked reduction of SVO_2 by increased consumption.[19]

During the period of the study, no participant developed atelectasis and pneumonia associated with MV.

In 2000, a randomized clinical trial sought to analyze the efficacy of HM (manual hyperinflation) used alone, without adding PEEP and investigating effects on pulmonary compliance and the proportion of arterial oxygen to inspired fraction of oxygen (PaO_2:FiO_2). The results showed a significant increase of both variables, but, according to the study, the significance of this improvement has not been determined.[20]

It is known that in an ICU it is essential to take an early approach. In sepsis it is no different, and care must be quick and feasible. Positioning, alveolar recruitment maneuvers and prone position are strategies to be evaluated safely and early.[21] And these are part of a multi and interdisciplinary process that must be applied including the physiotherapist.

The limitations of this study include the small number of patients and the variation of the septic site. Certainly, in a population with pulmonary septic shock, the effects of respiratory physiotherapy would be overestimated. Besides, the absence of variable SvO_2 may not specifically show the degree of metabolic expenditure of patients during the procedure.

Studies should be performed to prove the effects of respiratory physiotherapy in critical patients, especially if they seek to analyze ventilatory and hemodynamic variables through more faithful invasive methods.

It is concluded that, in the form of thoracic maneuvers assocuated with HM and the use of PEEP, the respiratory physiotherapy approach in patients in septic shock in an ICU was safe and beneficial, and did not present any deleterious effects, specially considering hemodynamic state during care.

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ARTIGO II

HEMODYNAMIC EFFECTS OF RESPIRATORY PHYSIOTHERAPY ON PATIENTS IN SEPTIC SHOCK : RANDOMIZED CLINICAL TRIAL

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ABSTRACT:

Objective: Despite the positive effects of physiotherapy already described in critically ill patients, hemodynamic changes inherent to the procedure have already been reported. This study aimed at verifying the hemodynamic repercussions resulting from applying respiratory physiotherapy to patients in septic shock.

Methods: Thirty-two sedated patients on mechanical ventilation in an adult intensive care unit at a university hospital were evaluated. The patients were randomized into a control group (respiratory physiotherapy using chest maneuvers) and an intervention group (ventilatory exercises with manual hyperinsuflator associated with PEEP – positive end expiratory pressure – with an inspiratory pressure of 40cmH_2O and PEEP of 10cmH_2O, besides the chest maneuvers). The hemodynamic and oxigenation data were recorded through a pulmonary artery catheter before the procedure, immediately after and 30 minutes after.

Results: A significant effect of time was observed in the variables: HR heart rate (HR), cardiac output (CO) and mean pulmonary arterial pressure ((MPAP) in the intervention group. In analyses of oxygenation, the arterial oxygen saturation (SaO_2) tends to increase over time in both groups, while oxygen consumption (VO_2) increases 30min after physiotherapy in the intervention group. The vasopressor dose was higher in the patients who died.

Conclusion: Respiratory physiotherapy can alter hemodynamic parameters when evaluated immediately after the procedure. These effects do not result in instability or clinical deterioration, independent of the type of technique used.

Key-words: Septic shock; respiratory physiotherapy

INTRODUCTION:

Sepsis is a continuum of infectious events and interactions between pathogens with hemodynamic consequences caused by the relationship between pro-inflammatory, anti-inflammatory and apoptotic mediators which, in their primary presentation, are accompanied by circulatory failure, myocardial depression, increased metabolic rate and abnormalities in the oxygen demand/reserve ratio with consequent global tissue hypoxia.[1,2]

Physiotherapy has become a major component in managing patients in intensive care units and has shown short and medium term benefits. The primary benefit results from the physiological effects of early mobilization and easier drainage of bronchial secretions, resulting in significant alterations in the hemodynamic, respiratory and intracranial parameters..[3,4,5]

Hemodynamic alterations must be constantly evaluated to minimize risks. Studies report significant alterations in reduction of cardiac output, compensatory vasoconstriction, and increased systemic vascular resistance, which may have deleterious repercussions on the patients.[6]

Moreover, metabolic responses have been described, showing increased oxygen consumption (VO_2), as well as a drop in venous oxygen saturation (SvO_2) due to an increased oxygen extraction rate (ERO_2) and cardiac index (CI).[7]

The purpose of this study is to look at the hemodynamic repercussions resulting from applying two physiotherapeutic techniques – manual hyperinsuflation associated with PEEP and conventional respiratory physiotherapy with manual chest maneuvers in patients in septic shock in an Adult Intensive Care Unit.

METHODS:

The study is a randomized clinical trial, approved by the Ethics and Research Committee at Hospital São Lucas at PUCRS. The randomization system was done using Random Allocation Software. The patients were allocated into a control group ("conventional" respiratory physiotherapy using chest maneuvers) and an intervention group (ventilatory patterns with manual insuflator associated with PEEP, with an inspiratory pressure of 40cmH_2O and a PEEP of 10cmH_2O, besides the chest maneuvers).

Population and Sample:

The study was performed in the Intensive Care Unit at Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), during from August 2009 to February 2013. Patients with a pulmonary artery catheter associated with septic shock were considered eligible for the study. The exclusion criteria were: being younger than 19 years or older than 80 years, pregnancy, acute myocardial infarction three months before the study, septic shock secondary to pulmonary disease, severely ill cardiac patients, with an ejection fraction < 30%, life expectancy less than 24 hours and impossibility of the family member or guardian signing the Free, Informed Consent. The Informed Consent was obtained by inserting the pulmonary artery catheter (Swan Ganz) through contact with the patient's family.

The variables studied were: heart rate (HR); mean arterial pressure (MAP); mean pulmonary artery pressure (MPAP); pulmonary vascular resistance index (PVRI); cardiac index (CI); right ventricular ejection fraction (RVEF); end diastolic volume index (EDVI); arterial oxygen saturation (SpO_2); venous oxygen saturation (SVO_2); Oxygen Consumption Rate (VO_2); Oxygen extraction rate (ERO_2); Oxygen delivery rate (DO_2).

Statistical analysis:

The quantitative variables (hemodynamic variables, ages) were described using mean and standard deviation. The qualitative ones (sex, % of septic focus) were described by absolute and relative frequencies.

The Student t test was applied for independent samples and Mann-Whitney test to compare the quantitative parameters of the groups. Pearson's Chi-square test was applied to compare the qualitative parameters of the groups.

For intra and inter group comparisons, Analysis of Variance (ANOVA) was applied, for repeated measures with a correction using the Bonferroni test. To control confounding factors (age and weight), Analysis of Covariance (ANCOVA) for repeated measures was used.

The level of significance was considered 5% and the analyses were performed using program SPSS (Statistical Package for the Social Sciences) version 18.0.

RESULTS:

There were no losses in the sample. The patients whose families agreed to participate finished the study, without dropouts or deaths inherent to applying the techniques. No untoward events occurred in any patient during the procedures. Fifteen of the 32 patients were male.

The comparison between the control and intervention groups did not show any major hemodynamic alterations. The clinical characteristics of the patients are described in Table 1, where it is seen that the groups are similar in practically all variables, except age (p=0.025) and weight (p=0.034).The intervention group consists of younger patients who weigh less.

Table 1: General characteristics of the patients:

Variables	Intervention Group (n= 19)	Control Group (n=13)	p value
Age - Mean ±SD	46.4 ± 18.6	61.2 ± 15.4	0.025
Weight - Mean ±SD	75.6 ± 12.3	86.7 ± 15.9	0.034
Height – Mean ±SD	170.5 ± 8.6	171.2 ± 11.9	0.863
Sex – n(%)			0.770
Male	8 (42.1)	7 (53.8)	
Female	11 (57.9)	6 (46.2)	
Time MV – Mean ± SD	7.00 ± 4.48	6.31 ± 2.63	0.587
Type of sepsis – n(%)			0.261
Urinary	4 (21.1)	5 (38.5)	
Pulmonary	10 (52.6)	3 (23.1)	
Abdominal	4 (21.1)	5 (38.5)	
Liver	1 (5.3)	0 (0.0)	
Vasopressor (mcg/kg) – Mean ± SD	0.20 ± 0.09	0.22 ± 0.09	0.647
Death – n(%)	10 (52.6)	9 (69.2)	0.567

MV – mechanical ventilation

The baseline values (before physiotherapy) of SaO2 (94.2 ± 3.6), HR (106.1 ± 13.7), MAP (84.0 ± 9.3) and VO2 (146.0 ± 70.3) show the clinical and hemodynamic stability of the patients before the procedure is performed.

The comparison between the three moments of the research is shown in Table 2. A significant effect isolated from time can be seen in variable HR, CO, and MPAP, which does not remain significant when adjusted by the age and weight of the patient. In the variables HR, MAP and MPAP without adjustment, in both groups there is an increase immediately after the intervention, that

diminishes 30 minutes later. For CO there is a significant decrease over time in both groups.

Table 2: Hemodynamic variables according to group and moment evaluated

Variables	Intervention Group (n= 19)			Control Group (n=13)		
	Before	Immediately after	30' after	Before	Immediately after	30' after
HR	106.1 ± 13.7	113.8 ± 17.6	109.7 ± 15.0	109.3 ± 20.0	113.4 ± 22.3	106.9 ± 19.2
CO	5.76 ± 1.16	5.28 ± 0.91	5.15 ± 0.79	5.66 ± 1.26	5.20 ± 0.84	5.09 ± 0.64
MAP	84.0 ± 9.3	91.8 ± 12.8	84.7 ± 12.8	76.7 ± 14.1	80.4 ± 15.5	78.8 ± 13.0
MPAP	27.9 ± 3.7	28.8 ± 4.7	27.1 ± 3.4	29.7 ± 7.7	30.9 ± 7.3	29.5 ± 6.5
PVRI	469.9 ± 272.8	503.4 ± 275.3	460.9 ± 285.7	526.6 ± 261.7	612.9 ± 293.5	566.0 ± 270.7
CI	2.53 ± 0.98	2.37 ± 1.10	2.51 ± 1.18	2.41 ± 1.13	2.28 ± 1.27	2.54 ± 1.19
RVEF	24.1 ± 8.5	22.5 ± 9.0	24.0 ± 8.3	26.9 ± 11.1	24.9 ± 11.5	27.4 ± 11.8
EDVI	112.1 ± 40.3	109.2 ± 32.7	115.4 ± 44.4	93.8 ± 31.9	94.2 ± 33.2	93.4 ± 30.2
Effects	p value			Adjusted p-value*		
	Group	**Time**	**Group x time**	**Group**	**Time**	**Group x time**
HR	0.999	0.004	0.502	0.934	0.674	0.440
CO	0.807	<0.001	0.985	0.869	0.406	0.973
MAP	0.069	<0.001	0.172	**0.029**	0.647	0.318
MPAP	0.260	0.028	0.899	0.685	0.739	0.959
PVRI	0.346	0.089	0.319	0.968	0.313	0.316
CI	0.869	0.522	0.873	0.540	0.412	0.666
RVEF	0.370	0.292	0.920	0.331	0.663	0.909
EDVI	0.153	0.813	0.702	0.575	0.772	0.590

Legend: HR: Heart rate; CO: cardiac output; MAP: mean arterial pressure; PMAP: pulmonary mean arterial pressure; PVRI: pulmonary vascular resistance index; CI: cardiac index; RVEF: right ventricular ejection fraction; EDVI: end diastolic volume index. Values expressed as means ± standard deviation.

There is an isolated group effect when adjusted for age and weight in MAP (p=0.029). Patients belonging to the intervention group present higher pressure levels than the control group, independent of the moment evaluated.

Data on oxygenation are described in Table 3. There is an isolated effect of time on variable SAO_2 (p<0.001), which becomes borderline when adjusted for age and weight (p=0.054). Saturation tends to increase over time in both groups.

In variable VO_2 there is significant effect of time, that does not remain after adjustment of age and weight. Without the adjustment, the intervention group has a significant increase of VO_2 30 minutes after the intervention (p=0.011) while in the control group there is no significant difference (p=0.399).

Table 3 – Oxygenation variables according to group and moment evaluated.

Variables	**Intervention Group (n= 19)**			**Control Group (n=13)**		
	Before	**Immediately after**	**30' after**	**Before**	**Immediately after**	**30' after**
SAO_2	94.2 ± 3.6	96.5 ± 4.2	97.6 ± 2.1	94.5 ± 3.8	96.1 ± 3.9	97.1 ± 2.4
SVO_2	69.8 ± 7.5	71.8 ± 9.8	75.7 ± 7.8	72.7 ± 12.0	72.7 ± 10.2	71.9 ± 8.3
VO_2	146.0 ± 70.3	147.1 ± 70.8	165.9 ± 72.9	158.1 ± 101.8	145.9 ± 60.8	156.1 ± 56.7
ERO_2	24.1 ± 6.6	25.8 ± 7.9	26.2 ± 9.8	24.1 ± 11.6	26.5 ± 8.9	27.0 ± 8.5
DO_2	512.8 ± 120.3	536.3 ± 119.7	538.2 ± 120.3	516.2 ± 195.2	492.2 ± 141.6	491.7 ± 135.4
Effects	**p value**			**Adjusted p value***		
	Group	**Time**	**Group x time**	**Group**	**Time**	**Group x time**
SAO_2	0.791	<0.001	0.772	0.847	0.054	0.742
SVO_2	0.992	0.212	0.052	0.308	0.270	0.319
VO_2	0.988	0.030	0.447	0.264	0.286	0.832

ERO_2	0.861	0.179	0.948	0.249	0.374	0.910
DO_2	0.522	0.994	0.456	0.622	0.793	0.489

Arterial oxygen saturation (SAO_2); venous oxygen saturation (SVO2); Oxygen Consumption Rate (VO2); Oxygen extraction rate (ERO2); Oxygen delivery rate (DO2). Values expressed in means ± standard deviation.

It was observed that both in the patients in the intervention group and in the controls, the vasopressor dose was significantly higher in those who died. However, there was no association of the variation of oxygenation and hemodynamic variables with death ($p>0.10$).

There is no significant association between the changes obtained in the CO with those obtained in SVO_2 ($p=0.813$).

DISCUSSION:

This study showed that, independent of the respiratory physiotherapy technique adopted in patients in septic shock, a benefit was found in oxygenation by the increase of SaO_2 and the hemodynamic alterations observed were not very relevant.

Physiotherapy in ICUs has been growing and has proved to be of prime importance, essentially in developed countries. Among its benefits is bronchial clearance, prevention and resolution of atelectases, increased gas exchanges, improved inspiratory muscle performance culminating in decreased length of stay in hospital and in ICUs .[8,9,10,11]

In the unit where the study was developed, all patients on mechanical ventilation undergo respiratory and motor physiotherapy three times a day, and the clinical and functional effects are visible, especially for ventilatory weaning and bronchial hygiene.

Analyzing the significant data, we find that there is a significant isolated effect of time on the variables HR, MAP and PMAP immediately after the intervention which, however, decreases after 30 minutes. Besides not being a

clinically relevant increase, this alteration is no longer significant when adjusted by patient age and weight.

Besides, there is an isolated group effect when adjusted for age and weight in MAP (p= 0.029), i.e., in this analysis, patients in the intervention group presented higher pressure levels than the control group, independent of the moment when it is evaluated, which showed a certain tendency to the heterogeneity of the sample in this variable.

Hemodynamic monitoring has been the subject of research aiming at avoiding the deleterious effects of certain techniques in severely ill patients.[6,12] In 2010, a randomized clinical trial evaluated the hemodynamic changes caused by the use of positive expiratory pressure in the airway by face mask (EPAP), and observed an increased MAP (mean arterial pressure), MPAP (mean pulmonary artery pressure), CVP (central venous pressure), and PAOP (pulmonary artery occlusion pressure). However, despite the statistical significance for these variables, this did not translate into clinical relevance when analyzed against each other . [13] The benefits of respiratory physiotherapy are a constant reason for clinical studies and advances. The evidence regarding the therapeutic use of expiratory resistance show positive ventilatory repercussions, including re-expansion and displacement of secretions.[14] In similar studies, an increment was shown in PaO2 and SaO2 reflecting a benefit to respiratory mechanics, and improved bronchial clearance with an effect on reducing PaCO2.[15]

In the present study, there was an isolated effect of time in variable SAO2 ($p<0.001$), which is borderline when adjusted for age and weight ($p=0.054$). Saturation tends to increase over time in both groups, agreeing with data in the literature..[16]

In variable VO_2 there is a significant effect of time which does not remain after adjustment of age and weight. Without the adjustment, the intervention group has a significant increase of VO_2 30 minutes after the intervention ($p=0.011$) while in the control group there is no significant difference ($p=0.399$). It is known that clearance and re-expansion maneuvers in the form of chest

mobilizations did not show a significant increase in the hemodynamic condition or in VO2, which might indicate a greater metabolic expenditure.[16] Although they do not present statistically significant data, SvO2 and ERO2 are important variables in the metabolic context. Hyperdynamic or septic states course with low values of arteriovenous difference, and consequently with a low extraction and poor arterial oxygen saturation. This justifies the fact that our patients present altered blood gas, often with the presence of high respiratory acidosis. Several clinical studies have related the oxygenation parameters to predictors of result in sepsis. Possibly an additional process that can lead to the exacerbation of sepsis is adrenergic stimulation, provoked by a blood flow reduction, culminating in increased oxygen consumption.[17]

SvO_2 is certainly the “gold standard” in the balance between global supply and demand of oxygen, and it has a major physiological relationship with cardiac output (CO). Low SvO_2 is a strong indication of lack of adequacy of CO. On the other hand, its normal value does not ensure that the supply is adequate to the oxygen demand in the tissues.[18] The patients in the study presented baseline CO values higher than normal. And, although the SvO_2 values presented an increase, according to time ($p=0.119$), the CO values presented a decrease ($p<0.001$), which confirms the theory of adequacy of the cardiovascular function.

Septic patients have high oxygen consumption (VO_2) and are highly dependent on its supply. The increase of VO_2 associated with the reduction of oxygen extraction through the peripheral tissues and with profound changes in microcirculation are related to progressive tissue hypoxia and progressive organ dysfunction. The diminished arteriovenous difference in oxygen suggests that the oxygen is not reaching or is not being used by the cells. The most plausible possibility is that the vascular abnormalities observed lead to diminished tissue perfusion, similar to what happens in patients with a very low cardiac output, as in the cases of cardiogenic or hypovolemic shock. Another possibility is that tissue perfusion is adequate, and that the cellular metabolism is diminished, which is common in sepsis.[19,20]

Although not significantly, the increased VO_2 did not show this inversely proportional relationship with the oxygen extraction rate. The only really effective way of quantifying alterations in oxygen consumption and in the production of carbonic gas in sepsis, is by using indirect calorimetry at the bedside. This method allows a serial follow up of the patient's treatment, with volume replacement, vasoactive drugs and nutritional support. And, possibly in this way we might be able to quantify the matter of tissue demand and supply.[21]

It can be seen that, both in the intervention group patients and in the controls, the vasoactive drug dose was significantly higher in those who died. It is known that the hemodynamic instability characteristic of septic shock is what makes the therapeutic process difficult and limits the multidisciplinary team management.

An increment was observed in terms of patient oxygenation. $SatO_2$ presented an increase (<0.001), and so did VO_2 (p=0.017). However, there was no association of oxygenation and hemodynamic variables with death (p>0.10).

Although there are specific indications for the use of the pulmonary artery catheter, and it is not standardized for all septic shocks, this tool is highly relevant to measure the hemodynamic condition of critically ill patients, and without it our objective would not be achieved. The limitations of the present study include the small number of patients and the inclusion of patients with distinct septic foci, which could lead to overestimating some findings, such as improved oxygenation in patients with pulmonary sepsis. Besides, metabolic measures such as lactate and calorimetry could add data for analysis and understanding of the pathophysiological mechanisms involved during physiotherapy.

Concluding, the use of manual hypeinsuflation associated with positive pressure, and also the chest maneuvers during respiratory physiotherapy were well tolerated, and did not lead to deleterious effects. The alterations found were similar in both groups and did not represent clinical deterioration. As to oxygenation, there is an isolated effect of time in the SAO_2 variable, that tends

to increase over time in both groups, as well as in VO_2, which presented a significant benefit of time.

New studies should definitely be developed to perform a precise analysis of the effects of physiotherapy on septic patients. Our research group has been developing a similar model, with and without invasive parameters, but adding metabolic and ecographic variables at the bedside.

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ARTIGO III

IMMEDIATE EFFECTS OF RESPIRATORY PHYSIOTHERAPY ON HEMODYNAMIC, METABOLIC AND OXIDATIVE STRESS PARAMETERS IN PATIENTS WITH SEPTIC SHOCK

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ABSTRACT:

Introduction: Septic shock is one of the greatest health problems worldwide, affecting millions of people a year. It presents as a continuum of infectious events and interactions between pathogens caused by the relationship between apoptotic, anti-inflammatory and inflammatory mediators, generating tissue hypoxia and hypovolemia, and increased oxidative stress. Respiratory physiotherapy can help increase oxygenation and improve gas exchanges. The purpose of this study was to evaluate the immediate effect of respiratory physiotherapy on hemodynamic, metabolic, inflammatory and oxidative stress parameters in patients with septic shock.

Methods: Before and after *quasi-experimental* study in thirty patients in septic shock, who underwent respiratory physiotherapy, without associated heart diseases and with vasopressors less than 0.5 mL/Kg/min. Venous and arterial blood gas, clinical and hemodynamic data, inflammatory data, lactate and oxidative stress were evaluated before and 15 minutes after physiotherapy.

Results: Thirty patients with a mean age of 61.77±15.91 years and SOFA of 7.9±3.1 were included. Respiratory physiotherapy caused a reduction of pH (p=0.003), $PaCO_2$ (p=0.009), lactate (p=0.0002) and TBARS (p=0.04) and an increase of PaO2 (p=0.026), SaO_2 (p=0.018) and PaO_2/FiO_2 (p=0.04) ratio, 15 minutes after it was applied.

Conclusion: The results indicate that respiratory physiotherapy has immediate effects, improving oxygenation, reducing lactate and oxidative damage in patient in septic shock. However, it does not cause alterations in the inflammatory and hemodynamic parameters.

Key-words: Septic shock; respiratory physiotherapy; oxidative stress; lactate; oxygen.

INTRODUCTION

Severe sepsis (an infection that leads to secondary acute organic dysfunction) and septic shock (severe sepsis with irreversible hypotension and resuscitation with fluids) are two of the greatest health problems, affecting millions of individuals worldwide every year [1].

Sepsis is a continuum of infectious events and interactions between pathogens with hemodynamic consequences caused by the relationship between apoptotic, anti-inflammatories and pro-inflammatories mediators [1]. The primary stages of sepsis can be accompanied by circulatory failure resulting from hypovolemia, myocardial depression, increased metabolic rate and abnormalities of perfusion – between the oxygen demand and reserve ratio – causing global tissue hypoxia [2,3].

In septic shock, metabolic acidosis is characterized by a pH less than 7.35 and high base excess, with a reduction of the bicarbonate content. There may be an elevation of the serum lactate levels which give these patients a worse prognosis. However, there are other factors that can cause the elevation of serum lactate and are not necessarily connected to infection and mitochondrial dysfunction [2].

Oxidative stress is one of the main contributing factors to increased mortality in several diseases, including septic shock. Oxidative stress caused by endotoxins can diminish the free radical catalysts or suppressors. Besides, oxidative stress, induced by endotoxins, may regulate the production of tumor necrosis factor alpha (TNF-α), occurring as the result of bacterial or endotoxic translocation, reducing the function in several states of the disease. Nitric Oxide (NO) has been implicated in the pathogeny of vascular hyperresponsivity (hypotension in septic shock). However, NO may not be the only mediator of tissue injury and cytotoxicity caused by the endotoxins. Therefore it is important

to evaluate the potential of free radicals in sepsis and septic shock patients with metabolic disorders [4]. Indeed, the mitochondrion also plays an important role in cellular energy and its structure and function are markedly affected by the physiopathology of sepsis. Its high reactivity, in particular, composes the peroxynitrite, generated by the reaction of nitric oxide and superoxidase anions, mitrochondrial inhibition enzymes and nucleic acids, proteins and injured lipids [5].

Physiotherapy has proved to be an important component in the management of patients in intensive care units, and has shown short and medium-term benefits. Respiratory physiotherapy results in physiological changes such as significant alterations in the hemodynamic, respiratory and intracranial parameters. However, so far, the literature does not allow any conclusions about the main effects of respiratory physiotherapy on patients in an intensive care unit [6,7].

Although many studies evaluate the hemodynamic effects of respiratory physiotherapy, their repercussion in critical patients is not yet clear, either because the sample size is small, or because many different techniques are used [7,8]. Considering these limitations, the purpose of this study is to evaluate the immediate effect of respiratory physiotherapy on the hemodynamic, metabolic, inflammatory and oxidative stress parameters, in patients with septic shock hospitalized in an adult intensive care unit.

MATERIALS AND METHODS

This study is characterized as *quasi-experimental*, of the before and after type, in which the hemodynamic, metabolic, inflammatory and oxidative stress variables of patients in septic shock who received conventional respiratory physiotherapy were evaluated.

The study included 30 patients in the adult intensive care unit at Hospital São Lucas at the Pontifical Catholic University of Rio Grande do Sul, under invasive mechanical ventilation, sedated, aged 30 to 80 years, with a diagnosis

of septic shock (diagnostic criteria of Rivers and collaborators [3]) and with a prescription for respiratory physiotherapy. The intervention performed consisted of the first respiratory physiotherapy after it had been prescribed.

Patients whose respiratory physiotherapy had been momentarily suspended, using vasopressors higher than 0.5 mcg/Kg/min and with associated heart diseases were excluded.

Physiotherapeutic Intervention

The patients included in this study received conventional respiratory physiotherapy, lasting approximately 15 minutes, which consisted of manual chest maneuvers, vibrations and manual hyperinflation associated with tracheal aspiration. The thoracic maneuvers consist of producing mechanical force transferred through the chest wall into the airways during the expiratory phase, for the purpose of increasing and redirecting air flow, for pulmonary reexpansion and airway clearance [9]. The vibrations were performed by isometric contraction of the forearm muscles, working in synergy with the palms of the hands perpendicular to the chest, in order to improve mucociliary depuration [10]. Manual hyperinflation was performed using a manual hyperinflation device (Ambu®) with inspiratory pressure less than 40 cmH_2O, inducing a tidal volume increase and generating subsequent improvement in the pulmonary compliance, inspiratory flow and bronchial secretions clearance [11]. Tracheal aspiration was performed using size 10 or 12 aspiration cannula (CPL®), which was introduced slowly and gently to remove secretions. The manual hyperinflation device was associated to keep up oxygenation [9].

Data collection

The evaluations and collections of materials were performed at two points in time. The first collection occurred before the physiotherapy session (control measure) including hemodynamic and clinical data: mean arterial pressure (MAP), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), peripheral oxygen saturation (SpO_2), heart rate (HR) and respiratory rate (RR).

Blood was also collected for arterial (arterial pH, arterial oxygen partial pressure (PaO_2), arterial carbon dioxide partial pressure ($PaCO_2$), bicarbonate (HCO_3) and arterial oxygen saturation (SaO_2)) and venous gasometry (venous pH, venous oxygen partial pressure PvO_2), venous carbon dioxide partial pressure ($PvCO_2$), bicarbonate (HCO_3) and venous oxygen saturation (SvO_2)). The plasma was separated to analyze lactate, thiobarbituric acid reactive substances (TBARS) and *transforming growth factor* (TGF-β). The second collection occurred 15 minutes after ending the physiotherapeutic intervention, when the same data were collected as at the first collection.

Clinical and hemodynamic evaluations

The clinical and hemodynamic analyses were evaluated according to the routine of the unit, using a heart monitor that supplies the data for HR, SpO_2, SAP, DAP and MAP. RR was evaluated through the data estimated on the invasive mechanical ventilator (Servo®).

Blood gas and biochemical evaluations

Blood gasometry (arterial and venous) was evaluated using an IL® analyzer. Plasma lactate was measured using a commercial kit for dry chemistry (VITROS® - Ortho-Clinical Diagnostics, Johnson & Johnson, Gateway, New Jersey, USA).

Plasma TGF-β measurement

The TGF-β plasma dosage was measured using the ELISA technique with a kit from *R&D Systems*®. The results were expressed in ng/mL.

Evaluations of oxidative stress parameters

Thiobarbituric acid reagent substances were evaluated through the reaction of cellular peroxidation products with the thiobarbituric acid, where 80%

of these substances are malondialdehyde NO was evaluated using the *Griess* reaction.

Statistical Analysis

The quantitative variables were described using mean and standard deviation (symmetrical distribution) or median and interquartile range (asymmetrical distribution). The qualitative variables were described by absolute and relative frequencies. The paired Student t test was used to compare the moments before and after. The results were considered significant when $p<0.05$. The *Graphpad Prism*® program, version 5.0 was used for data analysis.

Ethical aspects

The family of the participants in the study was informed of the study aim and invited to participate. After the study to be performed was appropriately explained to the individuals responsible for the participants, they received and signed the Free Informed Consent. The study was approved by the University Ethics and Research Committee (approval number 11/05550).

RESULTS

A total of 30 patients were included in the study. Table 1 shows the characteristics and clinical data of the patients. They were mainly male (67.7%) and the mean age was 61.8±15.9 years. Patients in septic shock with a pulmonary infection origin predominated and the SOFA (*Sequential Organ Failure Assessment)* index of these patients was 7.9±3.1. Sixteen patients (53.3%) died.

TABLE 1 – Characteristics and clinical data of the patients.

Variable	
Number of patients	30
Male sex	20 (67,7%)
Age (years)	61,8 ± 15,9
Weight (Kg)	78,3 ± 18,1
Days in ICU	17,5 ± 14,4
Septic Shock	
Pulmonary origin	19 (63,3%)
Abdominal origin	11 (36,7%)
Cause of admission	
Abdominal surgery	8 (26,7%)
Pneumonia	20 (66,7%)
Renal Failure	2 (6,7%)
Death	16 (53,3%)
SOFA	7,9 ± 3,1

ICU: Intensive Care Unit; SOFA: *Sequential Organic Failure Assessment*

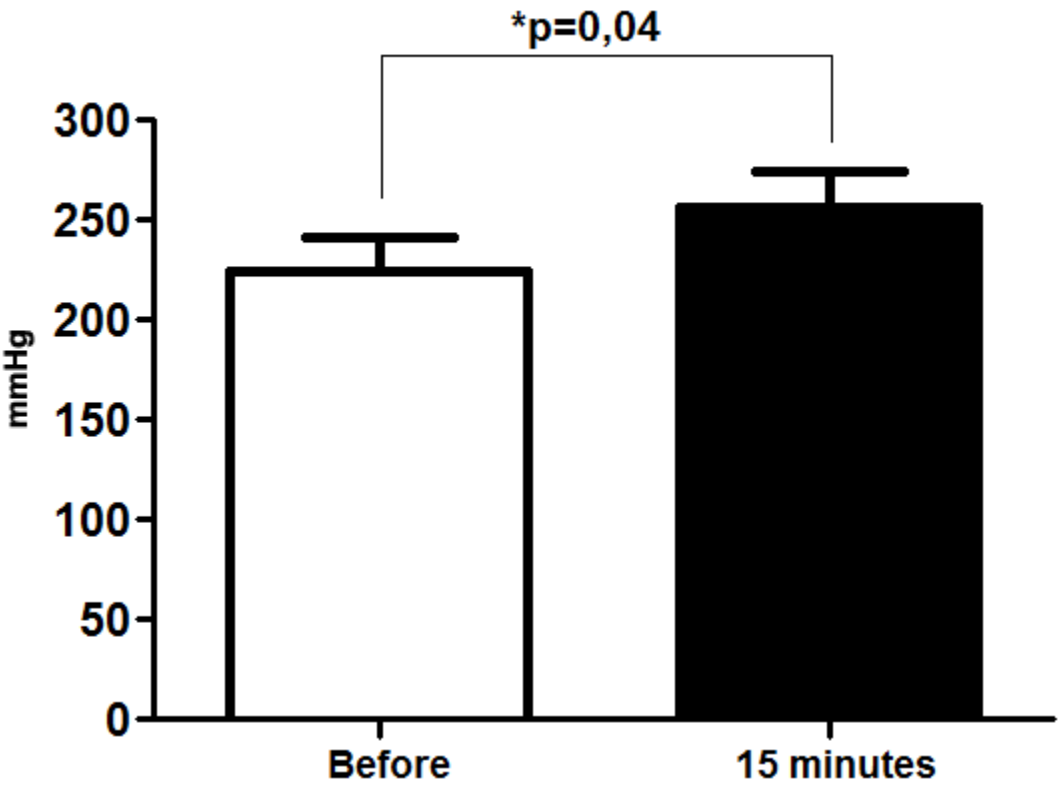
As to the arterial blood gasometry (Table 2), there was a significant increase in arterial pH, PaO_2 and in SaO_2 15 minutes after physiotherapeutic intervention. There was also a significant reduction in $PaCO_2$ 15 minutes after physiotherapy. When evaluating the PaO_2/FiO_2 (arterial pressure of oxygen/ inspired fraction of oxygen) ratio, a significant increase was obtained (Figure 1).

TABLE 2 – Arterial gasometry data before and after respiratory physiotherapy.

	Before	15 min after	p
pH	7,385 (7,298-7,443)	7,405 (7,330-7,453)	0,003*
$PaCO_2$	39,93±12,52	36,13±10,60	0,009*
PaO_2	103,8±41,15	118,8±49,61	0,026*
HCO_3	21,28±4,85	21,80±5,51	0,490
SaO_2	97,50 (94,75-98,80)	98,00 (95,95-99,00)	0,018*

Values are presented as mean and standard deviation (symmetric variables) and median and interquartile range (asymmetric variables). *Indicate significant differences by the paired student t test.

FIGURE 1 – PaO_2/FiO_2 ratio before and 15 minutes after respiratory physiotherapy



In the venous blood gasometry data, there was no significant difference in $PvCO_2$, PvO_2 and SvO_2 15 minutes after these patients had physiotherapy. However, a significant increase in venous pH was seen 15 minutes after the intervention (Table 2).

The clinical and hemodynamic results collected at the bedside before and 15 minutes after the physiotherapeutic intervention are shown in table 3. A significant increase in SpO_2 was observed, but there were no significant alterations in HR, RR and in the arterial pressure values.

As to the effect of physiotherapy on lactate, a significant reduction was shown 15 minutes after physiotherapy (Figure 2). In the oxidative stress data evaluation, respiratory physiotherapy provoked a significant reduction in the TBARS plasma concentration (Figure 3), but there was no significant difference in NO and TGF-β (Table 3).

FIGURE 2 – Serum lactate values before and 15 minutes after respiratory physiotherapy.

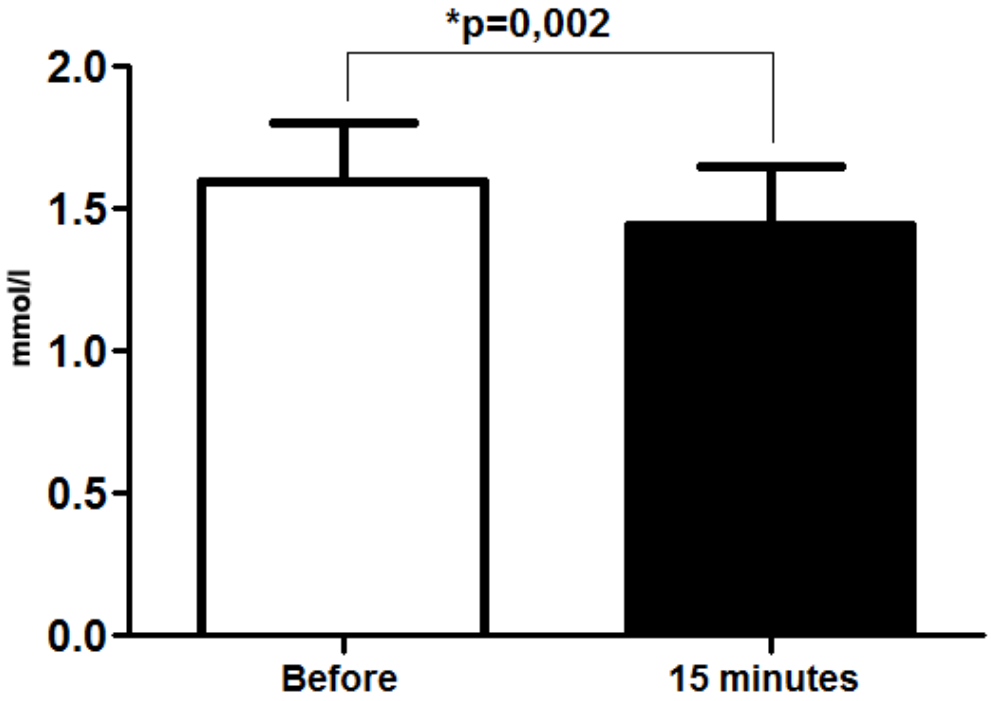
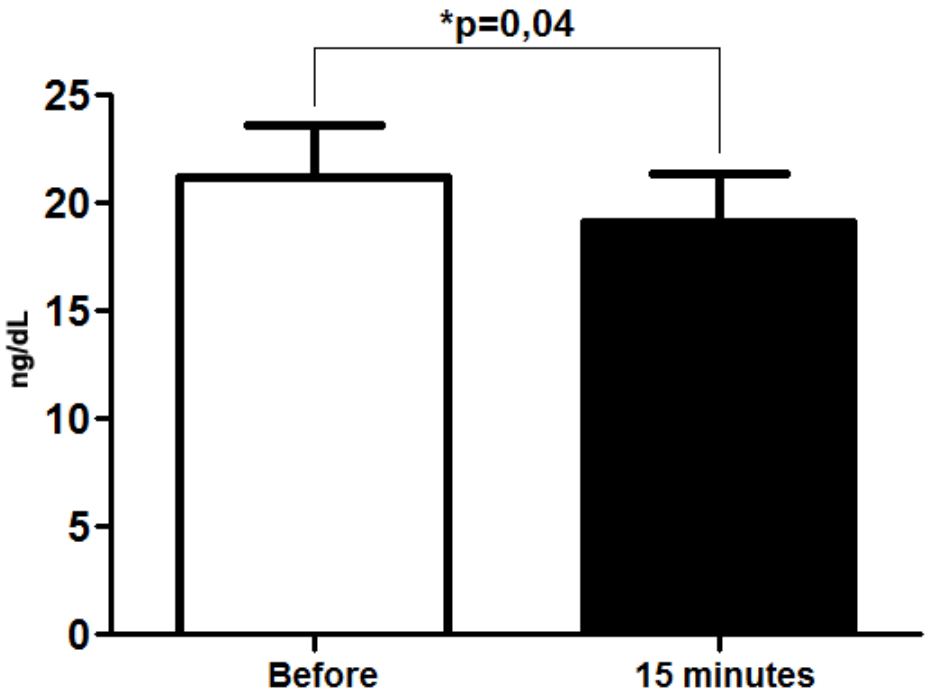


FIGURE 3 – TBARS values before and 15 minutes after respiratory physiotherapy.



DISCUSSION

This study was conducted to find out whether physiotherapy can have major and immediate beneficial effects (15 minutes) on parameters that can influence the survival of the patient in septic shock. The results indicate that respiratory physiotherapy is conducive to better tissue oxygenation with important metabolic effects.

Fifteen minutes after the intervention, it was possible to detect important beneficial effects in these patients. We obtained an elevation of the PaO_2 and this can be considered an important result, considering that improved oxygenation in patients with septic shock makes it possible to have greater tissue oxygenation, reducing ischemia that result from vascular complications and a possible delay in the organic dysfunction process [1,3]. The elevation of PaO_2 levels appears to be directly related to improvement in the gas exchange capacity and consequent hyperoxygenation, which may be provided by the physiotherapeutic intervention. In a previous study [12] on patients during the immediately postoperative period of heart surgery, this same elevation could be seen, using the manual hyperinflation technique with positive end expiratory pressure (PEEP). Also, some studies show that manual hyperinflation can improve pre and post tracheal aspiration arterial oxygenation, as well as the SpO_2, which was also demonstrated in our study [13-15].

The PaO_2/FiO_2 ratio significantly increased 15 minutes after intervention in our study. This is the contrary of what is shown by two previous studies [8,13] which did not find any effects on this parameter. This increase in the PaO_2/FiO_2 ratio was due to the increase in PaO_2, since the FiO_2 values were not modified during the period of the study.

The significant reduction in $PaCO_2$, shown in our study, may be related to the improved alveolar ventilation, with possible recruitment of new pathways and consequent improvement of the gas exchange. These results agree with the study by Barker and collaborators [17] that performed respiratory physiotherapy with manual hyperinflation and tracheal aspiration. Also, there is a relationship between the reduction of $PaCO_2$ and the subsequent increase of

venous pH. Although no study evaluating the proposed procedure has demonstrated this effect, we believe that the increase in venous pH occurs due to a better distribution of oxygen and reduction of $_{CO2,}$ resulting in a less acidotic venous pH.

The venous blood gasometry data in the present study were in accordance with the literature, in which no alterations were observed in different techniques studied [8,17]. As to the clinical parameters (Table 3), only a significant SpO_2 increase was observed, although this alteration (98% vs. 98,5%) is not relevant from the clinical perspective.

We have also demonstrated an increased PaO_2, which we believe that there could be an improvement in tissue perfusion. For this reason we measured the plasma lactate concentration. We found that physiotherapy immediately reduces this concentration, showing that the procedure had a significant therapeutic effect. We can associate this reduction with an increase in PaO_2, which may have provoked a longer use of the aerobic route, resulting in a lower lactate production [18]. In clinical practice the reductions of at least 10% in lactate production may be a good indication of resuscitation.

In septic shock, when the tissue perfusion is reduced, it causes an increase of the anaerobic metabolism and may cause direct tissue injury because of the exhaustion of Adenosine Triphosphate (ATP) needed to maintain the structural integrity of the cells. Cellular lesions may be intensified by free radicals when the offer of O_2 follows a period of dysoxia. In our study, we evaluated the plasma concentration of TBARS, which results from the deleterious action of free radicals on the cells. Our results show a significant drop in the plasma TBARS, showing a beneficial protective action against the cell deterioration caused by septic shock. This rapid and important effect is probably due to increased PaO_2 provoked by the therapeutic procedure. Considering these results we decided to evaluate the formation of NO, which besides being a free radical is a major inflammatory parameter. Our results did not show significant differences of this parameter 15 minutes after physiotherapy. We believe that this result is due to the time used in our study,

since the NO needs a metabolic route for synthesis, i.e., more time may be needed to evaluate this effect.

Among the cytokines induced by septic shock, IL-1 and TNFα are the keys to the development of severity of the disease. However, therapies that neutralize these cytokines have not been able to improve patient survival. During the course of the disease, the LPS, a product of gram negative bacteria, provoke apoptosis of the lymphocytes, thus diminishing the defenses against infection and worsening the clinical picture of the patient. The reduction of the apoptosis of immunocompetent cells may raise the organism defenses, with consequent increase of antiinflammatory cytokines, mainly IL-10 and TGF-β which also has a strong immunosuppressive property. Based on these premises, we decided to evaluate the plasma concentration of TGF-β, since we did not obtain a significant reduction of NO, an important metabolic inflammatory agent. However, our results did not show differences 15 minutes after treatment, once again showing that the treatment does not alter the inflammatory picture of the patient in the short time (15 minutes).

CONCLUSION

The results indicate that respiratory physiotherapy provokes immediate effects improving oxygenation and diminishing lactate and oxidative damage in patients with septic shock, but it does not provoke alterations in the inflammatory and hemodynamic parameters.

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8. CONCLUSÕES:

A) Manobras torácicas associadas à HM e uso de PEEP, em pacientes com choque séptico internados em uma UTI foi técnica de fisioterapia segura e benéfica, não apresentando efeitos deletérios e deteriorização hemodinâmica com descompensação clínica durante os atendimentos.

B) O uso das técnicas avaliadas foi bem tolerado, não propiciando efeitos deletérios.

C) As alterações encontradas foram semelhantes, independente da técnica utilizada.

D) No aspecto de oxigenação, há um efeito isolado do tempo na variável SAO_2 que tende a aumentar ao longo do tempo em ambos os grupos, bem como no VO_2, que apresentou benefício significativo do tempo.

E) A fisioterapia respiratória provoca efeitos imediatos, melhorando a oxigenação, diminuindo o lactato e o dano oxidativo em pacientes com choque séptico, porém sem provocar alterações nos parâmetros inflamatórios e hemodinâmicos.

9. ANEXOS:

Submissão Artigo I:

From: **Judy Waters** <Judy.Waters@physiotherapy.asn.au> Date: 2013/3/26

Subject: RE: JoP MS1331

Dear Evelyn/Clarissa:

Thank you for responding so quickly. I am pleased to advise that now that the submission meets Editorial Board requirements in all respects, I have sent the paper to the journal editor this morning for initial inspection.I wish you well through the review.

Judy Waters

Co-ordinator, Journal of Physiotherapy

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9. ANEXOS:

Submissão Artigo III:

Submission Confirmation

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Editorial Office [anitha.selvarajan@springer.com]

Dear Dr. Jarbas de Oliveira,

Thank you for submitting your manuscript,

"Immediate effects of chest physiotherapy on the hemodynamic, metabolic and

inflammatory parameters and oxidative stress in patients with septic shock", to

Intensive Care Medicine

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