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JOSÉ ROBERTO DE DEUS MACEDO

AVALIAÇÃO DA ACURÁCIA DO TESTE DE FORÇA-DURAÇÃO NA TRIAGEM ELETRODIAGNÓSTICA DA POLINEUROPATIA DA DOENÇA CRÍTICA

Brasília / DF
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Orientador:
Prof. Dr. Emerson Fachin Martins

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“Oh minha Alma, não aspire a vida imortal, mas esgote antes o campo do possível!”

Píndaro (517– 437 a.C)

RESUMO

Introdução: A polineuropatia da doença crítica (PNDC), frequentemente associada à miopatia da doença crítica (MDC), são as duas principais causas de fraqueza muscular adquirida na UTI, por isso chamada de polineuromiopatia da doença crítica (PNMDC). O diagnóstico e o manejo precoces dessa axonopatia são fundamentais para melhorar a funcionalidade e a qualidade de vida. A eletroneuromiografia (ENMG) é considerada o principal exame para identificar essa neuromiopatia, mas apresenta limitações intrínsecas e dificuldades operacionais. O Teste de Força-Duração (TFD) e o Teste Eletrodiagnóstico de Estímulo (TEDE) apresentam-se como alternativas de triagem eletrodiagnóstica não invasivas na UTI, com menor custo e maior viabilidade. No entanto, suas métricas e limiares diagnósticos ainda não foram adequadamente explorados na UTI. **Objetivo**: Analisar a acurácia e as métricas diagnósticas do TFD e do TEDE para triagem de PNMDC na UTI; avaliar a presença e a relevância clínica da assimetria eletrodiagnóstica na aplicação dos testes; e a possibilidade de automatizar essas ferramentas eletrodiagnósticas. **Método**: Foram realizados estudos transversais prospectivos envolvendo pacientes adultos em estado crítico, em ventilação mecânica por ≥72 horas na UTI. Os participantes foram submetidos bilateralmente ao Teste Eletrofisiológico Simplificado do Nervo Fibular (PENT) – o teste de referência, seguido pelos testes TFD e TEDE – testes índices. Os resultados foram analisados para uma descrição abrangente de suas métricas diagnósticas, e a relevância da assimetria eletrodiagnóstica foi verificada por meio de medidas bilaterais de PENT. O quarto manuscrito avaliou a automatização dos TFD e TEDE. **Resultados**: Foram estabelecidos limiares e métricas diagnósticas apropriadas para o TFD e o TEDE do nervo fibular em pacientes críticos com axonopatia, respectivamente: sensibilidade do SDT de 73% (62-85%), especificidade de 68% (53-81%), acurácia de 71% (62-81%) e área sob a curva ROC (AUC) de 0.8 (IC 95%: 0.7–0.8, $p<0.001$), com um ponto de corte ideal de 600 mC (teste de Youden); sensibilidade do SET de 89% (79-85%), especificidade de 42% (28-58%), acurácia de 71% (62-75%) e AUC de 0.7 (IC 95%: 0.59–0.81, $p=0.001$), com um ponto de corte ideal de cronaxia de 1.8 ms. Essas métricas diagnósticas foram ligeiramente mais favoráveis para o SDT. Ambos os testes podem ser automatizados com segurança. Assimetrias foram observadas em 12 (29%) participantes, mais importante para o grupo com PNMDC (risco atribuído de 17% (-30 a 64%)), com divergência diagnóstica em 5 (12%) pacientes, no qual a PNMDC poderia passar despercebida se a avaliação fosse unilateral, provavelmente associada à lateralidade e/ou lesões focais do sistema nervoso central (SNC). **Conclusão**: O SDT e o TEDE representam alternativas promissoras para o rastreio diagnóstico precoce de CIPNM na UTI, sendo a versão automatizada igualmente confiável. As avaliações eletrodiagnósticas devem ser realizadas bilateralmente, minimizando o risco de falsos negativos devido à relevância clínica da assimetria eletrodiagnóstica. Estudos de coorte prospectivos adicionais com amostras maiores e maior diversidade de pacientes devem ser conduzidos para reproduzir e validar melhor esses resultados.

Palavras chave: cronaxia; cuidados críticos; polineuropatia da doença crítica; fraqueza muscular; testes diagnósticos, rotina; assimetria.

ABSTRACT

Introduction: Critical illness polyneuropathy (CIPN), frequently associated with critical illness myopathy (CIM), are the two main causes of acquired muscle weakness in the ICU, hence the term critical illness polyneuromyopathy (CIPNM). Early diagnosis and management of this axonopathy are fundamental for improving functionality and quality of life. Electroneuromyography (ENMG) is considered the main examination to identify this neuromyopathy, but it has intrinsic limitations and operational difficulties. The Strength-Duration Test (SDT) and the Stimulus Electrodiagnostic Test (SET) present themselves as non-invasive electrodiagnostic screening alternatives in the ICU, with lower cost and greater feasibility. However, their diagnostic metrics and thresholds have not yet been properly explored in the ICU. **Objective**: To analyze the accuracy and diagnostic metrics of the SDT and SET for screening CIPNM in the ICU; to evaluate the presence and clinical relevance of electrodiagnostic asymmetry in the application of the tests; and the possibility of automating these electrodiagnostic tools. **Method**: Prospective cross-sectional studies were conducted involving critically ill adult patients on mechanical ventilation for ≥72 hours in the ICU. Participants underwent bilateral Simplified Electrophysiological Testing of the Peroneal Nerve (PENT) – the reference test, followed by SDT and SET – index tests. The results were analyzed for a comprehensive description of their diagnostic metrics, and the relevance of electrodiagnostic asymmetry was verified by bilateral PENT measurements. The fourth manuscript evaluated the automation of SDT and SET. **Results**: Appropriate thresholds and diagnostic metrics for SDT and SET of the peroneal nerve in critically ill patients with axonopathy were established, respectively: SDT's sensitivity of 73% (62-85%), specificity of 68% (53-81%), accuracy of 71% (62-81%), and area under Roc curve (AUC) of 0.8 (95% CI: 0.7–0.8, $p<0.001$), with an optimal cutoff point of 600 mC (Youden test); SET's sensitivity of 89% (79-85%), 42% (28-58%) specificity, 71% (62-75%) accuracy, and AUC of 0.7 (95% CI: 0.59–0.81, $p=0.001$), with an optimal chronaxie cutoff of 1.8 ms. These diagnostic metrics were slightly more favorable for SDT. Both tests can be safely automated. Asymmetries were observed in 12 (29%) participants, more significant for the group with PNMDC (attributed risk of 17% (-30 to 64%)), with diagnostic divergence in 5 (12%) patients, in whom PNMDC could go unnoticed if the assessment were unilateral, probably associated with laterality and/or focal lesions of the central nervous system (CNS). **Conclusion**: SDT and TEDE represent promising alternatives for the early diagnostic screening of CIPNM in the ICU, with the automated version being equally reliable. Electrodiagnostic assessments should be performed bilaterally, minimizing the risk of false negatives due to the clinical relevance of electrodiagnostic asymmetry. Further prospective cohort studies with larger samples and greater patient diversity should be conducted to reproduce and better validate these results.

Keywords: chronaxie; critical care; critical illness polyneuropathy; muscle weakness; diagnostic tests, routine; asymmetry.

RELAÇÃO DE FIGURAS

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RELAÇÃO DE SIGLAS E ABREVIATURAS

ACh - acetil colina

a-EMG – eletromiografia com eletrodo de agulha

Ca^{2+}-ATPase - bomba de cálcio do retículo sarcoplasmático

ECN – estudo de condução nervosa

ENMG - eletroneuromiografia

FA-UTI – síndrome de fraqueza muscular adquirida na UTI

ICUAW – intensive care unit acquired weakness

MDC – miopatia da doença crítica

MRC - Medical Research Council

PANS – potencial de ação nervoso sensitivo

PAMC – potencial de ação muscular composto

PENT – Teste Eletrofisiológico Simplificado do Nervo Peroneal

PICS – post intensive care syndrome

PICS-f - post intensive care syndrome - family

PNDC – polineuropatia da doença crítica

PNMDC- polineuromiopatia da doença crítica

RECARE® – equipamento neuromodulador para realização do TEDE

SDMO – síndrome de disfunção de múltiplos órgãos

SDRA – síndrome de desconforto respiratório agudo

SNC – sistema nervoso central

SPCI – síndrome de pós-cuidados intensivos

SPCI-F – síndrome de pós-cuidados intensivos - família

TEDE – Teste Eletrodiagnóstico de Estímulo

TFD – Teste de Força Duração de Estímulo

UTI – Unidade de Terapia Intensiva

VM – ventilação mecânica

SUMÁRIO

1. INTRODUÇÃO

Em função da melhora do acesso e dos avanços em medicina intensiva, a sobrevida de pacientes críticos internados em unidade de terapia intensiva (UTI) tem aumentado progressivamente nos últimos anos. Martin e cols. (2003) documentaram queda de 10% da mortalidade por Sepse no EUA no período de 1979 a 2000, devido melhorias em medicina intensiva, mesmo diante o incremento de idade e gravidade (1). Zimmerman e cols. (2013) aponta queda relativa de 35% da mortalidade hospitalar de pacientes admitidos em UTI de 1988 a 2012 nos EUA, em função dos avanços dessa especialidade e apesar do aumento da idade e severidade dos quadros clínicos (2).

Nos dias correntes, em geral cerca de 80% dos pacientes irão sobreviver à internação em UTI. Porém, no primeiro ano pós-alta da UTI, até metade desses sobreviventes (25 - 50%) irão permanecer com uma constelação de sequelas físicas, cognitivas e psiquiátricas - estabelecidas ainda durante a internação - com risco aumentado em duas a cinco vezes de óbito nesse intervalo de um ano (3) (4) (5). A relevância dessas sequelas funcionais tardias levou a Society of Critical Care Medicine à denominação de nova entidade sindrômica a partir de 2012: a Post Intensive Care Syndrome (PICS), em tradução direta para nosso idioma, Síndrome Pós-Cuidados Intensivos (SPCI) (6).

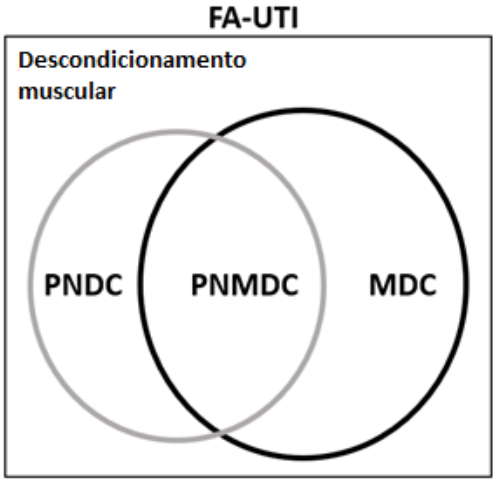
Esse novo ente nosológico aponta que os cuidados com os pacientes críticos não finalizam com a alta da UTI, mas ao contrário e com muita frequência estendem-se para além da sobrevida hospitalar. Os egressos de UTI, portadores da SPCI, necessitam de expressiva assistência e cuidados multidisciplinares por meses a anos pós-alta nosocomial, envolvendo recorrência de complicações, reinternações, alto custo de cuidados, aumento da mortalidade e falha de reconstrução social (5). A SPCI engloba uma miríade de sintomas, que refletem prejuízos distribuídos em três espectros: cognitivo (dificuldade de concentração, prejuízos na memória, na capacidade de decisão e no planejamento), mental (depressão, ansiedade, stress pós-traumático), e físico (dissonia, inapetência, fraqueza muscular, disfagia, polineuropatia periférica, disfunção respiratória, dor crônica, entre outros) - com frequência, combinados e em graus variados (4) (7) (8).

Embora os mecanismos fisiopatológicos envolvidos no desenvolvimento da SPCI durante internação em UTI não estejam absolutamente elucidados, há um consenso quanto à ação e interação da sepse e resposta inflamatória sistêmica - envolvendo isquemia por

microtrombose e vasoplegia, canalopatias, aumento de permeabilidade de membrana celular, produção de radicais livres e espécies reativas de oxigênio, e apoptose por disfunção mitocondrial; da hiperglicemia; de medicamentos de rotina em UTI (sedação venosa contínua, bloqueadores neuromusculares, carbapenêmicos e benzodiazepínicos) (9) (10). Esses mecanismos de agressão celular e tecidual sistêmicos nos quadros críticos, manifestos também no sistema nervoso central (SNC) e neuromuscular periférico, apontam para a SPCI como expressão da síndrome disfunção de múltiplos órgãos (SDMO) (11) (12) – conceito esse, que se refere a alterações fisiológicas em pacientes agudamente enfermos, que comprometem dois ou mais sistemas orgânicos, de forma que a homeostasia não possa ser mantida sem suporte avançado de vida (13) (14).

Nessa miríade de sequelas englobadas pela SPCI, associadas aos cuidados intensivos ao paciente crítico, dentre as manifestações físicas, destaca-se como principal complicação a ICU-Acquired Weakness (ICUAW) ou fraqueza muscular adquirida na UTI (FA-UTI) (15). Trata-se de transtorno neuromuscular periférico de alta prevalência entre pacientes críticos (100% nos pacientes sépticos com disfunção de múltiplos órgãos), que geralmente se manifesta como tetraparesia simétrica com distrofia muscular (sarcopenia), miopatia, e disfunção neural periférica por axonopatia (alteração eletrodiagnóstica); sensibilidade e reflexos músculo-tendíneos inicialmente preservados; e dificuldade de mobilidade (9). A FA-UTI tem duas etiologias principais: a polineuropatia da doença crítica (PNDC) e a miopatia da doença crítica (MDC); como também pode ser meramente resultado de descondicionamento muscular, pela imobilidade prolongada, catabolismo proteico e disfunção cardiopulmonar) – nesse caso, sem alterações eletrodiagnósticas do sistema neuromuscular (Figura 1) (4) (16).

Figura 1 - Classificação da Fraqueza Muscular Adquirida em UTI.
Na fraqueza muscular pelo descondicionamento, não há alteração eletrodiagnóstica aguda de nervos e fibras musculares.
PNDC: polineuropatia da doença crítica; *PNMDC*: polineuromiopatia da doença crítica; *MDC*: miopatia da doença crítica; *FA-UTI*: fraqueza muscular adquirida na UTI.

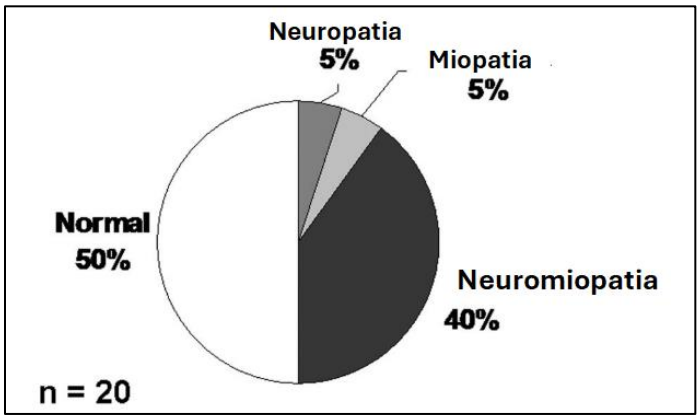


FONTE: in: *Inoue S, et.al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. Acute Med Surg. 2019;6(3):235.*

A importância da identificação dessas possibilidades reside principalmente na diferença prognóstica: o descondicionamento apresenta recuperação rápida, em poucas semanas de reabilitação; seguida da miopatia, que tende a apresentar expressiva melhora nos primeiros meses pós-alta nosocomial; enquanto quando há comprometimento neuronal (axonopatia), os sintomas melhoram modestamente no primeiro ano pós alta da UTI, podendo persistir déficits por anos (incluindo quadriplegia), com limitações associadas ao trabalho, redução da qualidade de vida do paciente e sua família, e aumento do risco de recorrência e de óbito (9) (15) (17) (18) (19). Com frequência, a neuropatia e miopatia manifestam-se simultaneamente (23) (24), por isso também chamada de polineuromiopatia da doença crítica (PNMDC) (Figura 2).

Figura 2 – Incidência de Neuropatia versus Miopatia

A disfunção neuromuscular acomete em geral, cerca de metade dos pacientes internados em UTI. Axonopatia e miopatia (neuromiopatia), quase sempre, manifestam-se conjuntamente.



Fonte: in: *Khan, J., Harrison, T. B., rich, M. M. & Moss, M. Early development of critical illness myopathy and neuropathy in patients with severe sepsis. Neurology. 2006; 67:1423.*

Além desses transtornos de médio/longo prazo descritos pela SPCI, o desenvolvimento de PNMDC no ambiente de UTI traz prejuízos durante a internação do paciente: disfagia, comprometimento diafragmático, desmame difícil da ventilação mecânica (VM), aumento do tempo de internação, imobilidade e piora da morbimortalidade em UTI (18) (20). Pesquisas sugerem que a abordagem terapêutica e preventiva precoce na PNMDC, ainda nos primeiros dias de internação em UTI, impactam favoravelmente no seguimento clínico desses pacientes (20) (21) (22) (23) (24) (26) (27) (28) (29).

Contudo, na contramão dessa relevância, aponta-se um sub-reconhecimento da PNMDC entre profissionais intensivistas (30), a despeito da alta prevalência, do impacto igualmente relevante nos custos, na função e na qualidade de vida dos pacientes e familiares, e dos benefícios do diagnóstico e abordagem precoces. Ao que se identifica, essa desconsideração deve-se a múltiplos fatores, sobretudo dificuldade diagnóstica, desconhecimento sobre medidas terapêuticas específicas, culminando em preterimento e postergação (16) (17) (18) (31) (32) (33) (34).

Nesse cenário frágil e de alto impacto para o paciente, justifica-se a importância dos esforços no diagnóstico dessa disfunção neuromuscular, ainda nos primeiros dias de internação em UTI, possibilitando o devido rastreio da PNMDC e a mobilização de estratégias terapêuticas para sua abordagem precoce, inseridas nas demais condutas voltadas à

manutenção da vida e reversão do quadro clínico (32).

Todavia, o diagnóstico precoce, por sua vez, defronta-se com outro desafio. O reconhecimento da FA-UTI é feito pelo registro da fraqueza muscular difusa, simétrica, acometendo membros e músculos respiratórios (poupa a face), que só pode ser explicada pela doença crítica, descartada outras possibilidades. Baseia-se no exame clínico, complementado pela avaliação de força muscular, por meio de ferramentas como a escala do Medical Research Council (MRC). Essa ferramenta de força muscular, além de outros vieses (cooperação, estado de humor e dor), depende do cooperação do paciente, sendo impraticável em pacientes críticos, inconscientes, em VM (17) (31) (33).

Em função disso, prioriza-se a investigação de alterações eletrofisiológicas da PNMDC pela eletroneuromiografia (ENMG), que engloba a eletroneurografia ou estudo de condução nervosa (ECN), e a eletromiografia com agulha (a-EMG). Entretanto, a ENMG também enfrenta grandes dificuldades operacionais dentro de UTI, sobretudo devido a logística, alto custo, interferências eletromagnéticas, necessidade do neurofisiologista, além de limitações intrínsecas que inviabilizam o exame: status não cooperativo do paciente (sedação ou coma) e coagulopatias/uso de anticoagulantes principalmente quanto a a-EMG. Em função disso, essa ferramenta comumente não está disponível em UTI (18) (31) (33).

Para contornar essa lacuna, alguns estudos têm proposto modelos simplificados para realização do ECN beira-leito em pacientes críticos (21), contudo compartilham das mesmas limitações da eletroneurografia. Nessa direção, tecnologias alternativas, mais facilmente exequíveis em ambiente de UTI - não invasivas, beira-leito, de baixo custo e de melhor logística e operabilidade - têm se despontado como opção para avaliação diagnóstica e seguimento de PNMDC em UTI: o Teste de Eletrodiagnóstico de Estímulo (TEDE) (32) (35) e o Teste de Força/Duração do Estímulo (TFD) (36). Objetos desse projeto de pesquisa, esses dois testes vêm sendo apresentados justamente com o propósito de suprir esse "*gap*" de desafio diagnóstico e avaliação seriada da disfunção neuromuscular desde os primeiros dias de internação em UTI, permitindo abordagem precoce, seguimento de seu comportamento e da resposta às estratégias terapêuticas. Entretanto, essas duas ferramentas – TFD e TEDE não foram submetidas, até a presente data, à devida avaliação de acurácia diagnóstica e descrição de suas métricas diagnósticas validadas para o cenário de UTI (sensibilidade, especificidade, acurácia, valores preditivos, taxas de verossimilhança e limiares).

Dessa forma, esse estudo procurou avaliar a acurácia do TFD e do TEDE no diagnóstico de PNMDC, tendo como teste de referência o Teste Eletrofisiológico Simplificado do Nervo Peroneal (PENT). Secundariamente, estudamos a presença e relevância de assimetria eletrodiagnóstica, e o possível impacto da lateralidade cerebral e lesões focais do SNC, para verificar se as avaliações unilaterais são adequadas e seguras para triagem diagnóstica da PNMDC no contexto de UTI. Ainda, a possibilidade de automação dessas ferramentas, corrigindo viés de reprodutibilidade de resultados e intersubjetividade de diferentes operadores.

1.1. Unidade de Terapia Intensiva

Unidade de Terapia Intensiva (UTI) constitui-se em ambiente hospitalar sistematizado e organizado para a prestação de cuidados a pacientes gravemente enfermos, que fornece cuidados médicos e multiprofissionais intensivos e especializados, com capacidade aprimorada de monitoramento e múltiplas modalidades de suporte fisiológico para sustentar a vida durante períodos de insuficiência ameaçadora de órgãos e sistemas (37).

De fato, como apontado anteriormente, com o acúmulo de avanços científico-tecnológicos e de recursos terapêuticos, a mortalidade de pacientes internados em UTI apresenta expressiva queda gradativa nos últimos anos, apesar do aumento gradativo da severidade e da idade, sobretudo nas últimas duas décadas. Pacientes que anos antes certamente iriam a óbito, passaram a sobreviver. Esse impacto observado na diminuição da mortalidade de pacientes graves levaram à expansão dos serviços de UTI em todo o mundo, voltados ao suporte intensivo necessário para a preservação de vidas de todas as faixas etárias ameaçadas pela sepse; queimaduras extensas; intoxicações; distúrbios metabólicos letais; politraumas; quadros críticos neurológicos, renais, cardiopulmonares, oncológicos e obstétricos; pós procedimentos cirúrgicos complexos (por sua vez, permitindo avanços em técnica operatória); entre outras inúmeras desordens orgânicas com risco de morte (1) (2) (37) (38).

Paralelamente, o envelhecimento progressivo da população tem corroborado com o aumento da necessidade de provisão global de cuidados em UTI, de forma que se observa aumento da idade média dos pacientes internados em UTI. Ademais, o aumento progressivo da longevidade das populações, culminam com a redução das reservas fisiológicas do idoso,

resultando no maior potencial de necessidade de internação em UTI em condições mais desafiadoras para os profissionais intensivistas. Mais da metade de todos os pacientes de UTI têm 65 anos ou mais, com a faixa etária de crescimento mais rápido entre aqueles com idade igual ou maior a 85 anos. À medida da progressão de idade, espera-se diminuição das reservas orgânicas, acúmulo de comorbidades e sequelas funcionais da sobrevivência a outros distúrbios e enfermidades. Os pacientes mais idosos egressos de UTI são, por consequência, muito mais propensos a apresentar piores sequelas cognitivas e funcionais, com condições mais limitantes de sobrevida pós-alta (4) (5) (7) (39) (40).

Esse aumento progressivo de demanda por leitos de UTI, junto aos altos custos desse setor (40), traduz-se em cenário de carência de leitos (41) (42), e conflitos bioéticos sobre decisão/seleção; eficiência de aplicação dos limitados orçamentos públicos par saúde; custo/benefício; entre outros (43) (44). Essa carência, dilemas e desafios médicos e ético-profissionais ficaram mais evidentes durante a última pandemia de COVID-19 - onde o mundo se deparou com a insuficiência de vagas de UTI, próteses respiratórias e fornecimento de oxigênio - causada pela rápida disseminação global do vírus SARS Cov-2 (45). Soma-se a essas reflexões, a qualidade de sobrevida pós-alta hospitalar, ponderadas possíveis sequelas psicofísicas dos sobreviventes de condições críticas (3) (4) (5).

O ambiente de UTI está imerso em questões bioéticas, envolvendo obstinação terapêutica *versus* medidas fúteis e sofrimento prolongado (distanásia); custo-benefício *versus* orçamento; direito à morte digna (ortotanásia); sobrevida *versus* autonomia e qualidade de vida (43) (44) (46) (47). Desde seus primórdios em meados dos anos 50, em meio a epidemia de poliomielite em Copenhagen / Dinamarca, quando os “pulmões de aço” demonstraram-se pouco eficazes para o suporte às vítimas com insuficiência respiratória grave (90% de óbito), sobretudo crianças; o médico anestesiologista Bjorn Ibsen inovou providenciando ventilação manual positiva via traqueostomia, em ambiente comum para os pacientes, onde revezavam dezenas de profissionais e estudantes, com queda substancial da mortalidade para 40%. Deixou assim, dois legados de absoluta relevância para a *práxis médica*: o ambiente de UTI e a ventilação mecânica por pressão positiva. Contudo, já se discutia nessa ocasião o custo aumentado com as equipes “beira-leito”, e o fato de o novo método de respiração artificial prolongar a vida dos pacientes infectados, ao mesmo tempo que “adiava a morte daqueles destinados a não sobreviver” (48) (49).

Dentro dessa perspectiva, estratégias capazes não só de aumentar a sobrevida e

diminuir o tempo de internação em UTI, mas que entreguem, pós-alta da UTI e do hospital, egressos com o mínimo possível de sequelas, com perspectiva de célere readaptação, de qualidade de vida, de independência de familiares e cuidadores, e de retorno a atividades laborais são absolutamente bem acolhidas.

A aplicação do TFD e do TEDE durante internação em UTI propõem agregar avanços no diagnóstico de desordens neuromusculares, de forma não-invasiva, célere e à beira-leito, otimizando a aplicação cada vez mais antecipada de medidas preventivas e terapêuticas (9) (28) (30) (50), como exemplo: eletroestimulação neuromuscular – recurso que possibilita mobilização muscular ativa mais precoce possível em pacientes sedados e/ou em coma, com acúmulo de resultados de favoráveis na diminuição do tempo de VM e de internação em UTI (21) (27) (32) (51).

1.2. Síndrome de Pós-Cuidados Intensivos

De fato, a saída com vida da internação em UTI é um avanço positivo para pacientes que, em passado recente, provavelmente não sobreviveriam à mesma injúria. Contudo, tal inegável progresso em suporte clínico e opções terapêuticas conflituam com as condições e qualidade de sobrevida entregues aos pacientes, como também a seus familiares pós-alta da UTI e do hospital. De forma que, cada vez mais se entende que o tratamento não se encerra pós-alta (3) (4) (5).

O período para além da sobrevida anuncia o início da trajetória de recuperação de significativas condições mórbidas adquiridas e/ou agravadas em um ou mais dos diversos aspectos do funcionamento físico, mental, cognitivo e/ou social dos pacientes (52) (53).

Devido crescente relevância dessas sequelas, o termo Síndrome Pós-Cuidados Intensivos (SPCI), desde 2012 (6), vem sendo cada vez mais utilizado para descrever a interação de uma gama de deficiências físicas, comportamentais e cognitivas que persistem após a alta da UTI, novos ou que representam agravamento de problemas preexistentes, não justificados por lesões cerebrais traumáticas ou vasculares (3) (4) (5).

Essas sequelas definidas pela SPCI podem limitar os pacientes por meses a anos, proporção alarmante, uma vez considerado que mais da metade dos pacientes adultos de UTI apresentam tais transtornos (54) (55). Marra et al. (2018) (58) observaram que 39% dos

egressos de UTI, ainda apresentavam após 3 meses ao menos um comprometimento relacionado à SPCI, com 35% deles continuando tais sintomas em 12 meses. A incidência de FA-UTI é de 40% entre os pacientes internados em UTI (4) (5), chegando a acometer 100% dos sobreviventes de sepse com disfunção múltipla de órgãos (59). Efeitos debilitantes semelhantes - particularmente sintomas psicológicos (stress, sensação de sobrecarga, melancolia), e psiquiátricos (ansiedade, depressão, stress pós-traumático) - têm sido documentados entre os membros da família que cuidam do paciente na UTI e após a alta, sendo denominados Post Intensive Care Syndrome-Family (PICS-F) ou Síndrome Pós-Cuidados Intensivos-Família (SPCI-F) (56) (57) (58).

A FA-UTI contribui para o aumento da mortalidade hospitalar, dos custos de hospitalização e maior mortalidade em seguimento de 1 ano pós-alta nosocomial (60). Menos de 15% daqueles que passaram por uma internação na UTI retornaram ao trabalho após a alta hospitalar (61) (62); e alguns participantes tornaram-se completamente dependentes de suas famílias, causando novos ou agravando problemas sociais e econômicos (55) (63).

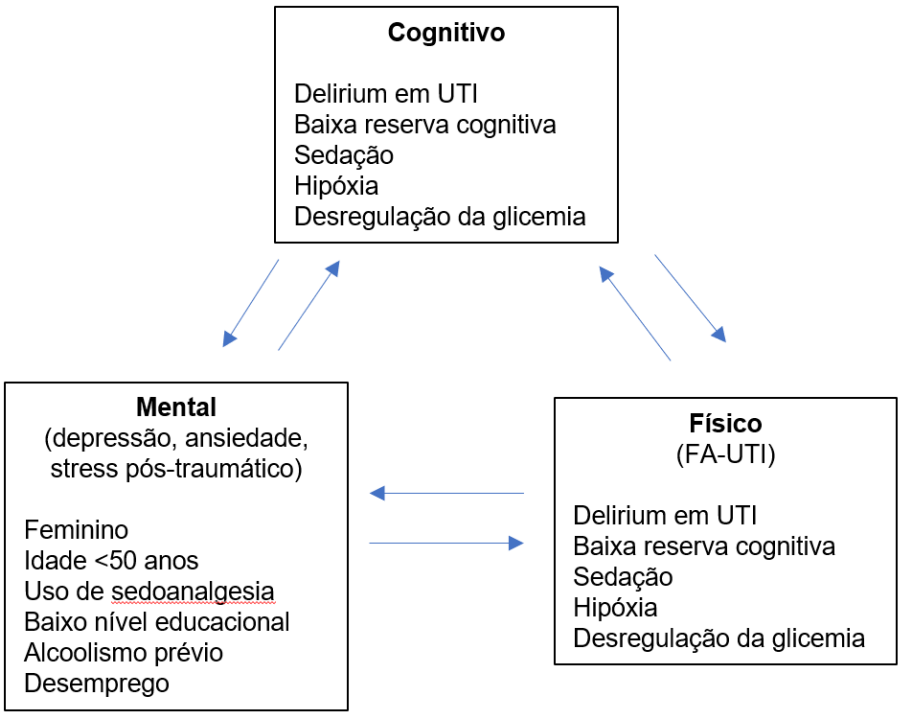
Esse contexto arrastado experimentado por sobreviventes de doenças críticas - envolvendo fraqueza muscular, capacidade reduzida de exercício, fadiga, comprometimento cognitivo, dor, dissonia, má qualidade de vida e dificuldades financeiras – está associado a maior incidência transtornos psiquiátricos. A prevalência de ansiedade, depressão e transtorno de stress pós-traumático nessa população variou de 13% (58), a 60% (52). Outro estudo documentou sentimento de sobrecarga com a experiência e relato de medo da morte devido internação em UTI (63). Fernando et al. (2021) (64) - comparando 423.060 sobreviventes de UTI, com 3.081.111 pacientes egressos de internação hospitalar sem passagem por UTI - mostrou que internação em UTI está associada ao aumento do risco de suicídio pós-alta nosocomial, sobretudo quando envolve procedimentos invasivos (ventilação mecânica e hemodiálise).

Sobretudo entre pacientes idosos, o conhecimento dessa condição torna-se de suma importância, posto o aumento progressivo dessa população com doenças graves (4) (65). Por exemplo, a incidência aumentada de delirium comparado aos pacientes mais jovens - fator de risco para a disfunção cognitiva em SPCI (65). Dentro dessa população, entre 50% e 70% de todos os sobreviventes da UTI têm pelo menos um comprometimento relacionado ao SPCI, que pode persistir por até 15 anos após alta nosocomial (66). Estudo com beneficiários do Medicare americano (idade média de 76.9 anos), constatou que 60% das 1.520 internações em

UTI com sepse foram associadas à piora do funcionamento cognitivo ou físico no primeiro ano de desospitalização, sendo 16.7% com prejuízos cognitivos moderado a grave (67) (68). Estudo de coorte retrospectiva com 21.520 pacientes beneficiários do Medicare americano demonstrou que permanência na UTI ≥3 dias, especialmente por sepse (81.8%), em pacientes com idade avançada em cuidados domiciliares, esteve associado a piora ou novos sintomas de incapacidade física (39). Outro estudo, também com beneficiários do Medicare americano, demonstrou aumento da incidência de demência nos idosos egressos de UTI em 3 anos, comparado com a população geral (aumento de 60% de risco relativo e 3% de risco absoluto) (69).

Os fatores de risco para SPCI dependem em parte de quais dos seguintes domínios são mais afetados: cognitivo, mental e físico. Esses três componentes estão inter-relacionados, de forma que o dano principal em um, está frequentemente associado à piora da função dos demais. Os fatores de risco para cada categoria estão resumidos na figura abaixo (Figura 3) (7):

Figura 3 - Fatores de risco associados à Síndrome Pós-Cuidados Intensivos.
FA-UTI: fraqueza muscular adquirida na UTI; *UTI*: Unidade de Terapia Intensiva.



Fonte: *Ahmad MH, Teo SP. Post-intensive Care Syndrome. Ann Geriatr Med Res [Internet]. 2021 Jun 30;25(2):73.*

O presente projeto concentra-se no espectro “físico” dessa síndrome, para o qual a eletroneuromiografia constitui ferramenta propedêutica de enorme relevância.

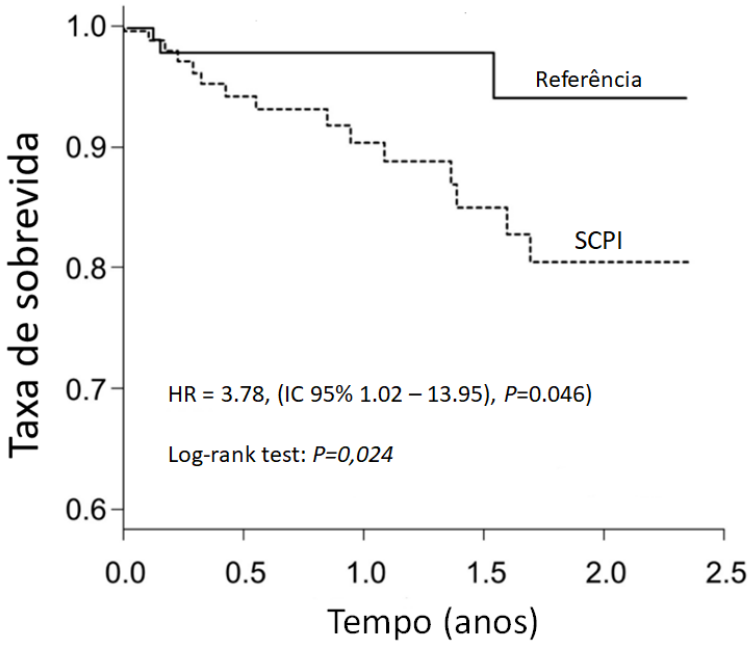
1.3. Fraqueza Muscular Adquirida na UTI

Em 1892, o médico canadense William Osler, considerado “pai da medicina moderna”, documentou as primeiras descrições do que chamou de "perda rápida de carne" após “septicemias”, com déficits neuromusculares (75). Avançou até meados do século XX com relatos de casos da ocorrência de fraquezas musculares após o acúmulo de doenças sistêmicas graves. A descrição dessa neuromusculopatia ocorreu no final da década de 60, após disseminação dos ambientes de UTI e da tecnologia de ventilação mecânica (76). Anos depois, Mertens (1961) demonstrou neuropatia disseminada relacionada ao coma, e sugeriu como mecanismo fisiopatológico lesões isquêmicas e metabólicas dos nervos (77). Somente em meados da década de 90, o termo PNDC foi introduzido por Bolton e col. (1984), que, a partir de estudos eletrofisiológicos, a caracterizaram como axonopatia de fibras neuronais sensitivas e motoras, devido “toxicidade da sepse”, preservando o sistema nervoso central (78). A MDC foi progressivamente reconhecida a partir dos anos 1990s (79). Acúmulo de evidências apontam, com muita frequência, a ocorrência concomitante das duas condições (80). Finalmente, o termo ICUAW (FA-UTI, em português) foi introduzido na língua anglo-americana para descrever a fraqueza muscular resultante da PNDC e/ou MDC - disfunção neuromuscular em pacientes críticos, que com frequência ocorrem combinados e de difícil distinção, por isso também chamada de PNMDC. Entretanto, o registro precoce dessa disfunção neuromuscular permanece incipiente em pacientes críticos, comatosos, sépticos, em VM, tratados em terapia intensiva (81).

Como visto, quanto à sua etiologia, classificada em PNDC, PNMDC e MDC, a síndrome de FA-UTI é a principal sequela do espectro físico da SPCI. Particularmente prejudicial ao retorno da autonomia, das atividades laborativas e da vida cotidiana. A prevalência média de FA-UTI é de 30-80%, a depender do coletivo da unidade de terapia intensiva. Não obstante o prognóstico potencialmente bom, mesmo nos casos mais graves, o problema reside na resolução frequentemente muito arrastada dos sintomas e nas sequelas residuais da FA-UTI (3) (4) (5).

A ocorrência de FA-UTI piora o prognóstico a médio e longo prazo dos pacientes de terapia intensiva e complica seu processo de reabilitação. Já a probabilidade de sobrevida hospitalar é reduzida em 30% em pacientes que desenvolvem FA-UTI durante internação. A mortalidade em 1 ano é 10-20% maior do que em pacientes não afetados. Pós-alta hospitalar, 20-30% dos pacientes ainda são afetados pelas consequências da FA-UTI após 3 meses; após 6-12 meses, ainda cerca de 10-15%; e após 2 anos, cerca de 10% (60) (84) (85). A incidência de "ansiedade/depressão" é cerca de duas vezes maior (51 vs 27%), entre pacientes que não recuperaram sua reserva fisiológica (síndrome de "fragilidade" / "vulnerabilidade") (86) (87). Hermans e cols. (2015) (88) trabalhando com estudo eletrofisiológico em 642 pacientes com síndrome do desconforto respiratório agudo (SDRA), com mais de 8 dias de internação em UTI, observou, nos pacientes com fraqueza muscular documentada, aumento de cerca de 20% (29,3% vs 48,2%), na mortalidade em 1 ano pós alta da UTI. Yanagi e cols. (2021) publicaram estudo observacional prospectivo com 555 pacientes críticos com >72h de internação em UTI. Desses, 53% tiveram diagnóstico de SCPI pós-alta. Essa síndrome foi associada a 4x maior risco de óbito entre os egressos, no intervalo de média de 1 ano pós-alta hospitalar. Deficiência física e cognitiva foram associadas com a mortalidade tardia, ao contrário da depressão (disfunção mental) (89) (Figura 4).

Figura 04. Mortalidade tardia de pacientes com e sem SCPI – curva de sobrevida.
Pacientes com sequelas pós-cuidados intensivos tem 4x mais chances de óbito em 2 anos. *SCPI*, síndrome de cuidados pós-intensivos; *HR*, hazard ratio.



Fonte: *Yanagi N, et al. Post-intensive care syndrome as a predictor of mortality in patients with critical illness: A cohort study. PLoS One. 2021 Mar 10;16(3):e0244564.*

A prevenção e abordagem precoce de fatores de risco para FA-UTI durante a permanência na UTI exigem prioridade equivalente às disfunções respiratórias, cardiovascular e renal. Ferramentas beira-leito e de fácil execução para diagnóstico e monitoramento de desordens neuromusculares (axonopatia e/ou miopatia), permitem antecipação dos prováveis quadros de FA-UTI, com o disparo precoce de opções terapêuticas específicas, ainda durante internação em UTI ou outra unidade hospitalar, mesmo sedado, em VM e em uso de drogas vasoativas: eletro-estimulação neuromuscular (mobilização precoce) (27) (29), controle glicêmico (40) e modulação nutricional (90) (91), uso de anabolizantes (92), e VM com endurance (93) (94).

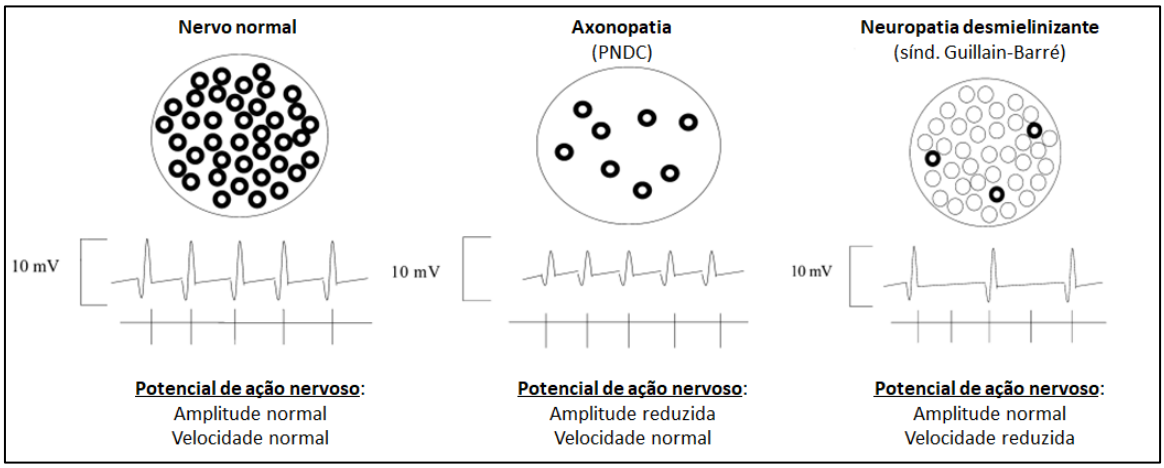
Importante reiterar que as alterações eletrofisiológicas (PNDC e/ou MDC), mesmo na ausência de manifestação de fraqueza muscular (FA-UTI) são fatores de piora do prognóstico (60), o que reforça a importância de sua identificação e intervenção precoces.

1.4. Polineuromiopatia da Doença Crítica

A injúria neural e muscular periféricas representam duas facetas etiológicas da FA-UTI, que se desenvolvem em conexão com doenças graves, requerem diagnóstico precoce, tratamento intensivo, com alto potencial de sequelas a longo prazo. Entretanto, não raro, durante internação em UTI, essa síndrome somente é evidenciada diante de dificuldades na progressão do desmame da VM, devido comprometimento do diafragma e demais músculos respiratórios.

A PNDC trata-se de uma axonopatia, não-desmielinizante, simétrica, que acomete os membros e musculatura respiratória, em pacientes internados em UTI, cuja causa não pode ser explicada além da doença crítica. É caracterizada por uma degeneração axonal primaria distal de ambas as fibras (motora e sensitiva), causada pelos efeitos citotóxicos da sepse, da restrição ao leito (imobilidade), e exposição medicamentos, tais como bloqueadores neuromusculares, corticosteroides e catecolaminas. Do ponto de vista eletrofisiológico, altera a excitabilidade neuromuscular, com redução do PAMC e preservação da condução nervosa (velocidade de propagação do estímulo) (96) (Figura 5).

Figura 5. Padrão eletrofisiológico da polineuropatia da doença crítica.
Na axonopatia ocorre diminuição do número de axônios, sem comprometimento da mielina – redução da amplitude do estímulo elétrico (somatório do estímulo de cada axônio), sem alteração relevante da velocidade de condução. Na mielinopatia, o número de axônios está preservado, porém com comprometimento da membrana de mielina – amplitude de estímulo elétrico normal, com lentidão da velocidade de propagação no nervo. *PNDC:* polineuropatia da doença crítica.



Fonte: *Latronico N, Peli E, Botteri M. Critical illness myopathy and neuropathy. Curr Opin Crit Care. 2005 Apr;11(2):127.*

Essas alterações neurofisiológicas da PNDC, manifestas como axonopatia primária, levam à redução da força (paresia) e massa (sarcopenia) muscular global, predominante de membros distais e músculos respiratórios, sem elevação de CK. Em 10% dos pacientes submetido a tratamentos críticos ocorre persistência de distúrbios musculares respiratórios, da marcha e dores neuropáticas para além do primeiro ano pós-alta (9) (15) (81).

Pode apresentar manifestações graves de comprometimento diafragmático, levando à dificuldade no desmame da prótese ventilatória, ao aumento do tempo de ventilação mecânica e ao maior tempo de internação em UTI. Entre os pacientes criticos, com 24h pós-intubação, até 64% apresentam “fraqueza diafragmática”; 63%, no desmame da VM; e em 80% dos pacientes com VM prolongada/desmame difícil (97).

Avaliação laringoscópica sistemática recentemente revelou disfagia em 90% dos pacientes do PNDC, que foi acompanhado de aspiração de líquidos em 75% dos afetados. Os sensores faríngeos também se mostraram comprometidos em 77% dos pacientes (98).

A prevalência de PNDC, considerada de cerca de 50% em todos os pacientes de terapia intensiva, depende do tipo, gravidade e duração do quadro, bem como da sensibilidade dos diagnósticos utilizados (puramente clínico *versus* neurofisiológico) (9) (15) (81). A maior, é encontrada na sepse - em torno de 70%, alcançando 100% nos pacientes com disfunção

orgânica adicional (disfunção múltiplas de órgãos) (11). Nos pacientes com duração de VM de 5-7 dias, a PNDC foi observada em 26-65% dos pacientes. Em pacientes em VM por > 10 dias foi diagnosticada em 2 terços. Sinais clínicos de PNDC foram encontrados em até 11% dos pacientes com um curto período de VM de 24 horas (99). Em pacientes com síndrome do desconforto respiratório agudo (SDRA), a prevalência de PNDC foi em torno de 60% após a interrupção da sedação, e 36% na alta hospitalar (84) (100) (101).

De fato, a inflamação e os distúrbios da microcirculação desempenham um papel fundamental no desenvolvimento da PNDC. Em modelos experimentais de sepse em animais, a PNDC é acompanhada pela superexpressão da E-selectina do endotélio vascular, particularmente dos nervos periféricos, o que induz a ativação endotelial e vasodilatação e, portanto, um aumento da permeabilidade vascular. A formação de edema endoneural e a hipoxemia e deficiência de energia resultantes resultam em danos no axônio do nervo secundário. Devido ao aumento da permeabilidade vascular, danos axonais diretos adicionais ocorrem através da penetração de metabólitos tóxicos (84) (102).

Danos aos músculos e axônios também podem ocorrer como resultado de danos aos canais iônicos (canalopatias) (103). Foi descrita uma alteração dos canais rápidos de sódio, que em experimentos com animais levou à subexcitabilidade da membrana da fibra muscular (104). Experimentos com animais também mostraram uma mudança na homeostase do cálcio intracelular com uma subsequente redução na contratilidade muscular (105) (106).

As alterações musculares funcionais e estruturais em particular ocorrem de maneira multifatorial e complexa. Por exemplo, devido à redução da síntese e aumento do consumo de proteínas musculares, especialmente miosina, gerando atrofia muscular precoce (107,108). Os processos inflamatórios, além da ação na axonopatia, também desempenham um papel importante no dano muscular. O fator de necrose tumoral alfa, bem como a interleucina 1, interleucina 2 (10), e também o "fator de crescimento e diferenciação (GDF-)15" (109) foram identificados como mediadores pró-inflamatórios promotores de atrofia de células musculares e, portanto, a uma agregação de componentes tóxicos com consequente dano à integridade da fibra muscular (110) (111).

A hiperglicemia foi identificada como um fator de risco adicional associado ao desenvolvimento de PNDC com uma razão de chances (OR) de 2,6 (IC 95% IC 95%: 1,6-4,2)

(20) (24) (88) (112) (113) (114). A hiperglicemia também induz disfunção mitocondrial neuronal e miogênica (115), e um esgotamento da adenosina-difostato (ADP) (116).

Também existem conexões confiáveis com hiperosmolaridade, nutrição parenteral e uso de vasopressores e aminoglicosídeos (99) (115). Outros fatores de risco, que não são independentes, também foram apontados - VM prolongada, permanência em leito de terapia intensiva e imobilidade (117). A diminuição prévia de massa magra, associada ao avanço da idade, também atua como fator de risco relevante (67) (88).

Os dados sobre uma promoção independente de PNDC por corticosteróides, a implementação de terapia renal substitutiva e o uso de relaxantes musculares são contraditórios ou ambíguos (16) (81) (117). Na correlação desses fatores com PNDC, não está clara a dose de exposição-resposta e questões sobre uma janela de tempo favorável versus vulnerável durante período terapêutico em UTI (24). As mulheres são afetadas quatro vezes mais frequentemente, embora não esteja claro se isso se deve apenas à menor massa muscular (117).

No geral, os fatores de risco potenciais pontuados para PNDC não são específicos ou independentes uns dos outros. Ao contrário, em seu conjunto, manifestam-se de forma gradativa e interdependente, sinalizando mais um parâmetro do status de gravidade da doença crítica no contexto de acúmulo de disfunções orgânicas. Em sua maioria, esses fatores de risco são identificáveis por análise de regressão e permitem tirar conclusões sobre os possíveis mecanismos patológicos subjacentes à PNDC, que devem ser considerados como multifatoriais e interativos (11) (12) (24) (50).

A ocorrência de PNDC piora o prognóstico a médio e longo prazo de pacientes de terapia intensiva e complicações seu processo de reabilitação. A probabilidade de sair do hospital com vida é 30% menor em pacientes do PNDC, firmando-se como critério de criticidade. A taxa de mortalidade em 1 ano é 10-20% maior do que em pacientes não afetados por essa disfunção neuromuscular. Alguns dos danos neuromusculares regridem apenas lentamente devido baixa velocidade de regeneração diária do dano axonal. Um platô é alcançado após um ano, mas pequenas melhorias ainda são possíveis no segundo ano após a doença. Isso também se reflete nos longos períodos de reabilitação de pacientes internados, que geralmente duram de 2 a 3 meses, podendo prolongar-se anos, com inúmeras necessidades e alto impacto econômico (55) (60) (118) (119).

Com o conhecimento dos fatores de risco descritos, dos mecanismos patológicos da PNDC, e da associação com piora do desfecho clínico; a prevenção, o diagnóstico precoce e a terapia apropriada antecipada são de grande valia para melhora do desfecho dos pacientes (22) (27) (28) (120).

As medidas terapêuticas recomendadas ainda são de natureza empírica ou plausíveis, com um nível geral de evidência insatisfatório, o que sinaliza necessidade premente de mais estudos da PNDC em ambiente de UTI (121). A combinação de ingestão adequada de nutrientes e exercícios pode melhorar o anabolismo proteico do tecido muscular, diminuir sua degradação e melhorar o desempenho físico em pacientes gravemente enfermos (122). Miranda Rocha e col. (123), publicaram revisão de diferentes protocolos de reabilitação utilizados durante a internação de pacientes em UTI, constatando que eles podem diminuir o tempo de VM e encurtar a permanência na UTI, além de melhorar o desempenho físico do paciente. A depender do perfil do paciente, sobretudo os mais grave, em sedação ou coma, somente a eletroestimulação neuromuscular permite mobilidade muscular ativa nos primeiros dias de internação em UTI.

Com frequência, até em função da contiguidade e "intimidade" fisiológica entre axônio e fibra muscular correspondente, a axonopatia e/ou miopatia confundem-se, compartilham as mesmas manifestações (exceto sensitivas, exclusivas da neuropatia), e ocorrem com frequência simultaneamente, o que torna um desafio a distinção neurofisiológica entre essas duas entidades, sobretudo na primeira semana (95). Alguns autores consideram que não há relevância na distinção dessas duas entidades em ambiente de UTI, restringindo-se à identificação de desordem neuromuscular como critério de abordagem precoce e disparos de estratégias terapêuticas específicas (39) (82).

1.5. Diagnóstico da Polineuromiopatia da Doença Crítica

O sintoma cardinal da PNDC é geralmente tetraparesia simétrica e flácida, com a parte neuropática manifestando-se mais distal, e a parte miopática mais proximal. Os reflexos musculares ainda podem ser desencadeados inicialmente, mas geralmente são enfraquecidos e, posteriormente ausentes. Manifestações sensitivas (parestesia, dor) são exclusivas da axonopatia (78) (79). O componente muscular está associado à progressão rápida de distrofia muscular (124). Em dois terços dos casos, os músculos respiratórios, incluindo o diafragma,

também estão envolvidos, com subsequente falha de desmame (125). A disfagia pode ser identificada por laringoscopia em cerca de 90% dos pacientes com PNDC (98).

A suspeição diagnóstica ocorre a partir do quadro clínico em meio a uma constelação de fatores de risco correspondentes, sendo confirmado por diagnóstico eletrofisiológico pela ENMG. No entanto, no contexto de sedação ou coma, ventilação mecânica ou uso de bloqueadores neuromusculares, propedêutica neurofisiológica clinicamente confiável nos primeiros dias de internação de quadros críticos em UTI se torna muito limitada ou até inviável. A ENMG fica prejudicada nesses casos devido dificuldade de acesso ao profissional e ao equipamento, artefatos de interferência, edema tecidual, hipotermia, limitações de contração muscular voluntária e de cooperação do paciente, e distúrbios de coagulação (impossibilita eletromiografia com estímulo por agulhas) (31).

Embora PNDC tenda a ser subdiagnosticada, atualmente, devido progressivo reconhecimento, aponta-se risco oposto: a desconsideração a outras possibilidades diagnósticas, particularmente quando envoltas a quadros sépticos com disfunção de múltiplos órgãos. Ainda que a PNDC represente a polineuropatia mais comum em ambiente de UTI, outras causas de tetraparesia podem ser descartadas ou requererem ação terapêutica específica, como hemorragias ou isquemias espinhais, mielites auto-imunes ou relacionadas a patógenos, abscessos medulares compressivos, mielinólise pontina central (síndrome de desmielinização osmótica), miastenia gravis, síndrome de Lambert-Eaton, botulismo, intoxicações, farmacotoxicidade (relaxantes ou bloqueadores neuromusculares, miopatia por esteróides), distúrbios hidroeletrolíticos (hipocalemia, hipofosfatemia e hipermagnesemia), polineuropatia diabética, neuropatias ou miopatias autoimunes, síndrome de Guillain-Barré, encefalite do tronco cerebral, vasculite, polineuropatia por HIV, porfiria, síndromes paraneoplásicas, rabdomiólise, distrofias musculares, miopatias mitocondriais e miopatias genéticas (81) (121) (125).

Na PNDC, a presença do componente neuropático agrava substancialmente o prognóstico e a velocidade de regeneração. A melhora da MDC, miopatia pura, é significativamente melhor (80-100%), do que nos casos associados a polineuropatia (50-70%). Assim, Guarneri e col. (2008) encontraram recuperação completa em 6 meses e normalização dos achados neurofisiológicos em 11 de 12 pacientes com miopatia exclusiva confirmada eletrofisiologicamente. Nos pacientes com componente neuropático, apenas 2 de 7 pacientes apresentaram uma recuperação completa após 6 meses (126).

A PNDC apresenta distúrbios pronunciados na sensibilidade da superfície, propriocepção e percepção de temperatura e dor. Não há distúrbios sensoriais na MDC (88). Na PNDC, os estudos neurofisiológicos espelham uma manifestação sensório-motora distalmente simétrica no ECN, como expressão do dano predominantemente axonal aos nervos, amplitudes reduzidas do PAMC, ou dos PANS, com velocidade de condução nervosa normal ou levemente reduzida. Essas alterações geralmente ocorrem dentro de 1-2 semanas do início clínico, mas às vezes podem ocorrer tão cedo quanto 72h após a admissão na UTI (127) (128).

As medidas de condução do nervo frênico e os registros de EMG dos músculos intercostais ou do diafragma têm valor diagnóstico na falha isolada do desmame sem outros déficits neuromusculares nas extremidades, mas requerem perícia neurofisiológica adequada (97).

O componente miopático pode ser diagnosticado por biópsia muscular. Os subtipos miopáticos possíveis são: MDC clássica - atrofia inespecífica de fibras tipo 1 e tipo 2, degeneração gordurosa, não necrótica (clínica sem aumento da enzima creatina-quinase (CK)); Miopatia Necrosante (clínica com aumento de CK); "Miopatia dos Filamentos Grossos" (perda da rede intermiofibrilar com aumento de CK). No entanto, isso não é recomendado na prática clínica, especialmente em pacientes sépticos com distúrbios de coagulação e risco aumentado de novos focos infecciosos, sendo reservado a interesse acadêmico (89). Outro detalhe limitante: as alterações eletrodiagnósticas de excitabilidade de membrana antecedem as alterações estruturais detectáveis pela biópsia, de forma que biópsia normal não implica necessariamente em ausência de disfunção neuromuscular (18).

Nos últimos anos, discute-se a possível importância da ultrassonografia muscular, cuja vantagem reside no fato de que, em comparação com a neurofisiologia, é facilmente acessível à beira do leito e não está vinculada à cooperação do paciente. Alterações musculares atróficas podem ser detectadas precocemente. Alterações na ecotextura do músculo, bem como a detecção de fasciculações, podem indicar danos (129). No entanto, um estudo atual com ultrassom em 71 pacientes não foi capaz de identificar FA-UTI com precisão suficientemente boa, de modo que a sensibilidade geral e a especificidade do método permanecem incertas (130).

1.5.1. Eletroneuromiografia

Trata-se de tecnologia eletrofisiológica que consiste em ferramenta bem estabelecida para o diagnóstico de nosologias neuromusculares periféricas, a partir da análise de comportamento da atividade elétrica e condução neuromuscular de nervos específicos (desde suas raízes nervosas), junção mioneural e fibras musculares que inervam (71).

I - História

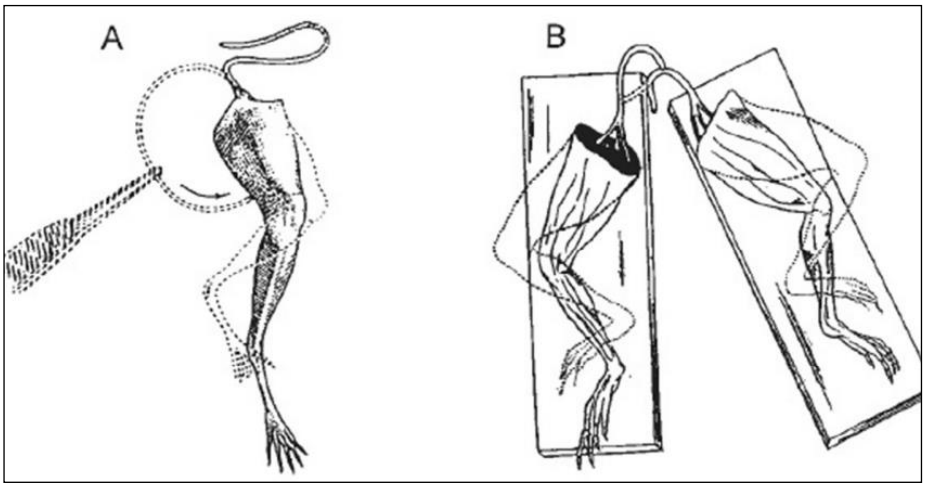
O desenvolvimento da eletroneuromiografia remonta os primórdios da descoberta da eletricidade moderna em meados do século XVIII, quando cientistas começaram a explorar os efeitos da atividade elétrica no corpo de animais e a observar que músculos e nervos poderiam gerar energia (72).

Luigi Galvani, professor de anatomia da Universidade de Bologna/Italia, em 1791, trabalhando com sapos, defendia que a eletricidade seria gerada pelo corpo e conduzida pelos nervos até os músculos, que podiam receber essa "eletricidade animal" (72) (Figura 6).

Figura 6 - Modelo experimental de Luigi Galvani, com membros inferiores de sapos amputados e seus respectivos nervos ciáticos dissecados.

A - O coto do nervo ciático em contato com o músculo gera contração, com o auxílio de pinça metálica (1794).

B– O coto de amputação do nervo ciático direito, toca o nervo ciático esquerdo íntegro, gerando contração nos dois membros, sem metal envolvido (1797).



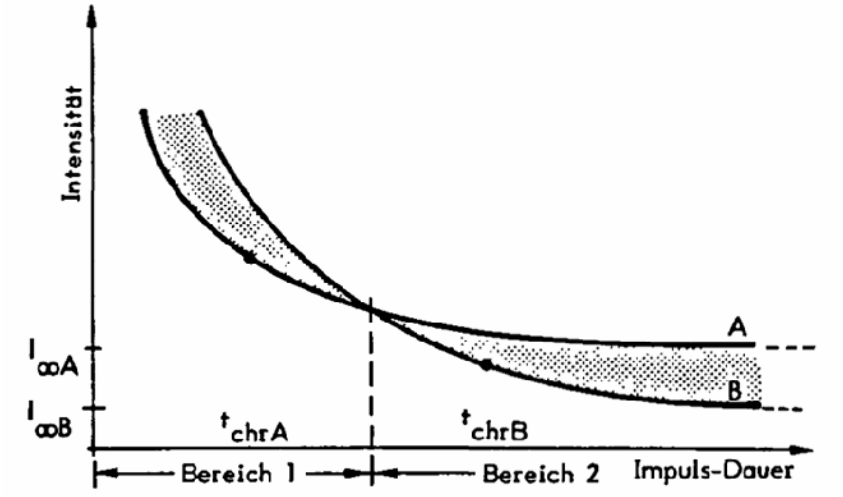
Fonte: *Kazamel M, Warren PP. History of electromyography and nerve conduction studies: A tribute to the founding fathers. J Clin Neurosci. 2017 Sep;43:56.*

Em 1849, o fisiologista alemão Emil du Bois-Reymond foi capaz de aumentar a sensibilidade de um galvanômetro (recém desenvolvido pelo alemão Oersted), e detectou o impulso elétrico propagado na superfície de uma contração muscular voluntária, demonstrando

que o tecido muscular gera correntes elétricas durante a contração. O médico francês Guillaume Benjamin Duchenne, em 1833, demonstrou que os nervos podem ser estimulados via percutânea. Nos anos seguinte, em contato com Pierre Paul Broca, Francois Aran e Jean Martin Charcot perceberam que os músculos responderiam mais rapidamente ao ser estimulados por corrente elétrica em certos pontos de sua superfície, desenvolvendo estimuladores e eletrodos para o que descreveram inicialmente como técnica de "Localized Electrization" (1855). Foram estabelecidas as bases para futuros estudos em eletrofisiologia (72).

O cenário do início do século XX estava preparado para o desenvolvimento da eletromiografia clínica por meio da invenção de registros mais sensíveis. Em 1909, Lapicque definiu reobase como a intensidade mínima contínua de corrente necessária para excitação muscular, e cronaxia, como a duração mínima de corrente necessária para excitar o tecido muscular usando uma intensidade dupla de reobase. Esses conceitos permitiram que o médico britânico Edgar Douglas Adrian relatasse as "curvas de duração da força muscular" em 1916. Suas curvas de intensidade/duração de estímulo eram consistentes em músculos saudáveis com mudanças previsíveis durante a degeneração ou recuperação muscular (72) (74) (Figura 07).

Figura 07 – Curvas de Intensidade-Duração de Estímulo, com a cronaximetria publicado por Lapicque (1915)



Fonte: *Lapicque L. Presentation d'un chronaximetre clinique. Compt Rend Soc Biol. 1915;78:695–8.*

Edgar Adrian, trabalhando com o fisiologista americano Detlef Bronk, utilizando eletrodo de agulha em modelo experimental em gatos, lograram gravar a atividade muscular suprida por uma única fibra nervosa - ''*motor unit potential*". Posteriormente, em 1932, Edgar

Adrian foi laureado com o prêmio Novel, e D. Bronk tornou-se o 6° presidente da Universidade de Johns Hopkins. Digno de nota, Edgar Adrian foi provavelmente o primeiro neurologista formalmente treinado, envolvido nos avanços em neurofisiologia (72).

Durante a Segunda Guerra Mundial (1939-45), houve um interesse crescente em estudar a fisiologia muscular, especialmente para melhorar a reabilitação de soldados feridos. O desenvolvimento de amplificadores eletrônicos e a miniaturização de equipamentos permitiram gravações mais precisas da atividade elétrica dos músculos. Em 1948, a equipe de Herbert Jasper, James Golseth e James A. Fizzel, com o apoio do Departamento Médico do Exército Americano, foi capaz de projetar e construir o protótipo da primeira máquina de EMG comercialmente disponível para uso clínico (72) (Figura 8).

Figura 8 - Imagem do primeiro protótipo de eletromiógrafo comercialmente disponível em 1948

Fonte: *Kazamel M, Warren PP. History of electromyography and nerve conduction studies: A tribute to the founding fathers. J Clin Neurosci. 2017 Sep;43:58*.

Em 1949, o neurofisiologista britânico Sir Thomas Lewis e outros pesquisadores aprimoraram a técnica de eletromiografia, introduzindo eletrodos de agulha que possibilitaram uma avaliação mais detalhada da atividade elétrica em músculos profundos (72).

A década de 1960 ficou marcada pelo início da integração da eletromiografia com a eletroneurografia. O desenvolvimento de equipamentos que permitiam simultaneamente a estimulação e a gravação dos potenciais de ação nervosos resultaram em uma avaliação mais abrangente das funções neuromusculares. Pesquisadores como Sir Alan Hodgkin e Andrew Huxley contribuíram significativamente para a compreensão dos mecanismos de condução nervosa, utilizando modelos de laboratório que serviram como referência (71). Em setembro de 1961, na Universidade de Pavia (Itália), ocorreu o Primeiro Congresso Internacional de Eletromiografia (EMG) – "pedra fundamental" para os avanços em neurofisiologia como um campo organizado (73) (Figura 9).

Figura 9. Participantes do 1° Congresso Internacional de Eletromiografia
Universidade de Pavia / Itália, 1961.

Fonte: *Mazzarello P. Pavia, September, 1961: a window on muscles and nerves. Funct Neurol. 2012 Jan-Mar;27(1):64.*

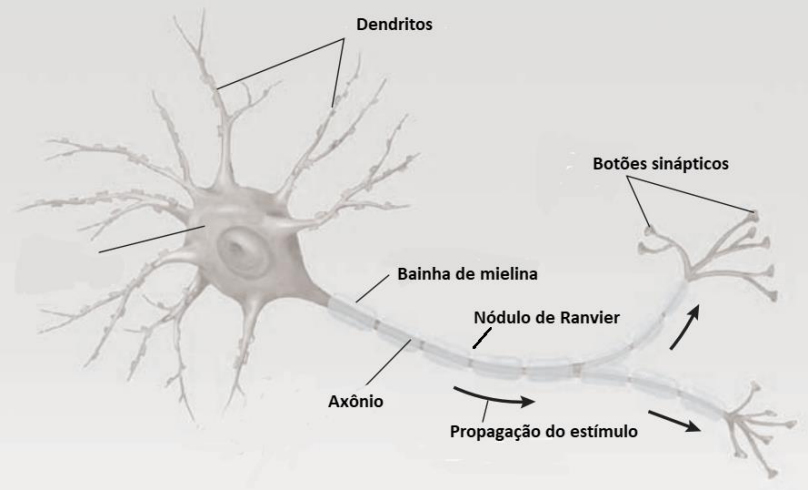
Finalmente, a partir dos anos 80, com o avanço da tecnologia de microprocessadores e computação, a eletroneuromiografia experimentou uma revolução. Equipamentos digitais e softwares avançados possibilitaram a análise em tempo real dos dados coletados, tornando os resultados mais precisos e acessíveis. Houve miniaturização dos dispositivos de gravação como também refinamento das doses de estimulo elétrico, tornando o exame mais confortável para os pacientes (72).

II – Neurofisiologia: conceitos básicos

Em esforço de síntese, o sistema nervoso periférico é constituído predominantemente por fibras nervosas (conjunto de axônios), cuja função primordial é a conexão entre o sistema nervoso central (encéfalo, tronco cerebral, cerebelo e medula espinhal), e outras estruturas corporais, incluindo o sistema musculoesquelético. Integra o sistema nervoso a todos os demais sistemas orgânicos e ao meio exterior, possibilitando, em conjunto com outros sistemas (p.ex. imuno-endócrino), o controle de órgãos e tecidos - a homeostase, e o desenvolvimento de comportamentos (70) (71).

A unidade celular fundamental do sistema nervoso é o neurônio, composto por dendritos, corpo celular, axônio (envolto por seguimentos de membrana de mielina, intercalados pelos nódulos de Ranvier), e terminais axonais ou botões sinápticos. Os axônios são prolongamentos dos neurônios, que podem alcançar metros de comprimento e transmitem sinais elétricos para outros neurônios, músculos ou glândulas (70) (Figura 10).

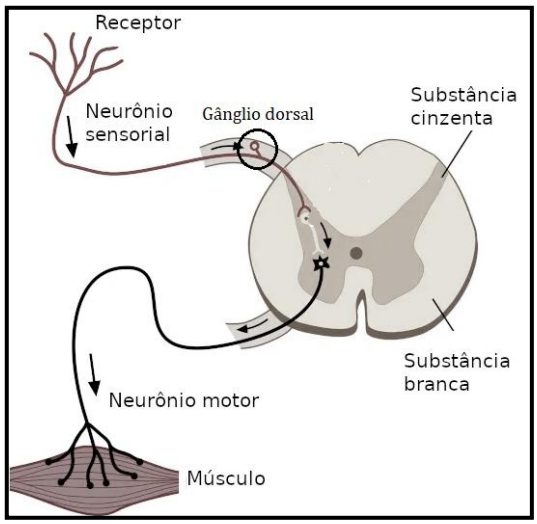
Figura 10 - Estrutura celular básica de um neurônio.



Fonte: *Carlson NR. Structure and Functions of Cells of the Nervous System. In: Physiology of Behavior. 8.ed. San Francisco / NY: Pearson Education, Inc, 2013. p.29.*

Os corpos celulares das fibras sensitivas aferentes estão localizados no gânglio dorsal, no ramo dorsal da raiz nervosa, próximo à sua junção com o ramo ventral, em sua emergência na medula espinhal. Quanto às fibras nervosas motoras eferentes, seus corpos celulares encontram-se no corno anterior da medula espinhal (70) (71) (Figura 11).

Figura 11 – Disposição anatômica dos neurônios sensitivos e motoneurônio.



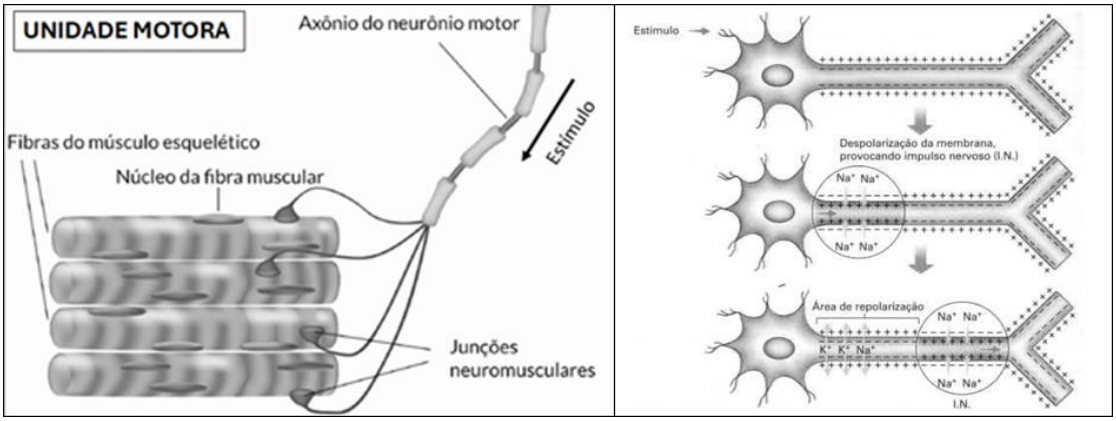
Fonte: in: *https://brasilescola.uol.com.br/biologia/medula-espinhal.htm* .

Nos animais complexos, os axônios são envoltos, em sua maioria, por uma bainha de mielina, composta de camadas de membrana celular de composição lipoproteica, funcionando como um isolante elétrico. Esta mielina é produzida pelas células de Schwann (derivadas dos oligodendrócitos) no sistema nervoso periférico, e por oligodendrócitos no sistema nervoso central. É seguimentada e separada em intervalos regulares ao longo do axônio, chamados nódulos de Ranvier, onde a bainha de mielina é interrompida e há alta concentração de canais de sódio voltagem-dependentes, essenciais para a geração e propagação do potencial de ação (Figura 3). A alternância entre regiões mielinizadas e não mielinizadas permite que o impulso elétrico "salte" de um nódulo a outro, caracterizando a chamada “condução saltatória”, permitindo processo de condução mais rápido e eficiente (cerca de 50x mais rápido que axônios não-mielinizados de mesmo diâmetro), posto que contorna a necessidade de despolarização de toda a extensão do axônio para propagação do estímulo até a fenda sináptica, onde ocorre a quimiotransmissão do estímulo. Trata-se de uma vantagem evolutiva, visto que respostas rápidas a estímulos internos e ambientais, permitem comunicação entre diferentes partes do corpo e com o meio ambiente com alta eficiência energética do sistema nervoso, o que garantiu o desenvolvimento de estruturas orgânicas mais complexas, em aprendizado, memória e coordenação muscular (71).

O neurônio em estado de repouso apresenta uma carga negativa no interior em relação ao exterior, com diferença de voltagem em torno de -70 mV, mantida por diferenças de cargas positivas (cátions) – gradientes de concentração de K^+ e Na^+ conferidos ativamente por “bombas” de Na/K ao longo da membrana plasmática: sódio para fora, potássio para dentro,

mantendo maior concentração de cátions no meio externo. O impulso elétrico, em resposta a um estímulo (p.ex. neurotransmissor na membrana dendrítica), é gerado pela despolarização inicial de um neurônio em estado de repouso, normalmente na região de conexão do corpo celular com o axônio (cone axonal), em direção distal. Implica na abertura de canais de sódio na membrana, de forma que os íons Na^+, que estão em maior concentração no exterior da célula, entram rapidamente no neurônio, movendo-se a favor do gradiente de concentração. Esse influxo de cargas positivas faz com que o potencial da membrana se torne menos negativo, até um limiar específico em torno de -55 mV. A partir desse ponto, ocorre a despolarização completa, onde os canais de sódio se abrem de forma massiva (canais voltagem-dependentes), com influxo rápido de íons Na^+ impulsionado pelas forças de difusão e pressão eletrostática, resultando em um aumento rápido do potencial da membrana até picos de valores positivos de potencial de membrana, entre +30 a +40 mV (inversão de carga elétrica da membrana). Esse pico marca o final da fase de despolarização e o início da repolarização, onde o neurônio retornará ao seu estado de repouso. Os canais de sódio voltagem-dependentes se inativam, interrompendo a entrada de mais Na^+, e os canais de potássio (K^+) voltagem-dependentes começam a abrir, permitindo a saída de cátion K, promovendo a diminuição da carga positiva interna, ultrapassando levemente a voltagem inicial de -70 mV, normalizando com o fechamento dos canais voltagem-dependentes de K^+. Na sequência, os canais de Na/K normalizam as concentrações iniciais de Na/K, restabelecendo o estado de repouso. Todo esse processo de despolarização leva cerca de 1 milissegundo e permite a geração de um potencial de ação - sinal elétrico de baixa voltagem que se propaga ao longo do axônio até as terminações sinápticas. A propagação desse sinal leva à liberação de neurotransmissores na fenda sináptica, viabilizando a comunicação entre neurônios, glândulas e músculos, e, em última análise, a resposta do organismo a estímulos (70) (71) (Figura 12).

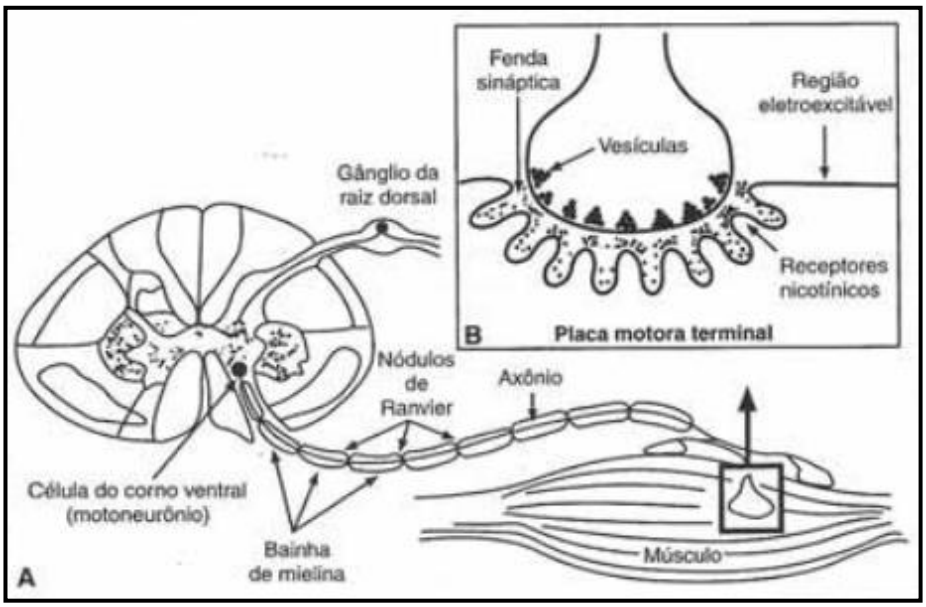
Figura 12 – Despolarização do neurônio: comportamento dos cátions de Na e K na membrana.



Fonte: in: *https://www.alamy.de/stockfoto-innervation-der-skelettmuskulatur-49341588.html*; in: *https://www.sobiologia.com.br/conteudos/FisiologiaAnimal/nervoso3.php* .

Na placa motora (junção neuromuscular), quando o potencial de ação atinge o terminal axonal, ocorre a abertura dos canais de cálcio voltagem-dependentes, permitindo que íons de cálcio entrem no terminal axonal. Esse influxo de cálcio promove a fusão de vesículas sinápticas com a membrana do terminal axonal, liberando o neurotransmissor acetilcolina (ACh) na fenda sináptica por exocitose. A ACh difunde-se pela fenda sináptica e se liga aos receptores nicotínicos localizados na membrana da fibra muscular. Esses receptores são canais iônicos que se abrem ao se ligarem à acetilcolina, permitindo o influxo de íons Na^+ na fibra muscular e a saída de uma quantidade menor de íons de K^+. Semelhante ao processo no neurônio, essa entrada de sódio gera despolarização da membrana da fibra muscular, criando um potencial de placa motora, que, quando atinge seu limiar, desencadeia um potencial de ação de membrana, que se propaga por toda a fibra, promovendo a liberação de íons Ca^{2+} do retículo sarcoplasmático, para o citoplasma da célula muscular (sarcoplasma), onde se ligam à troponina e alteram sua conformação para tropomiosina, expondo os sítios de ligação à actina. Dessa forma, a miosina pode então se ligar à actina e realizar o ciclo de pontes cruzadas, promovendo a contração muscular. Na fenda sináptica, a acetilcolina é rapidamente degradada pela enzima acetilcolinesterase, impedindo a continuação da estimulação da fibra muscular. O cálcio é recolhido pelo retículo sarcoplasmático por bombas de cálcio (Ca^{2+}-ATPase), permitindo que a fibra muscular relaxe. Esses processos asseguram que a contração muscular ocorra apenas quando o neurônio motor envie o sinal apropriado e que a sinalização termine rapidamente, preparando a fibra muscular para um novo ciclo de contração (70) (71) (Figura 13).

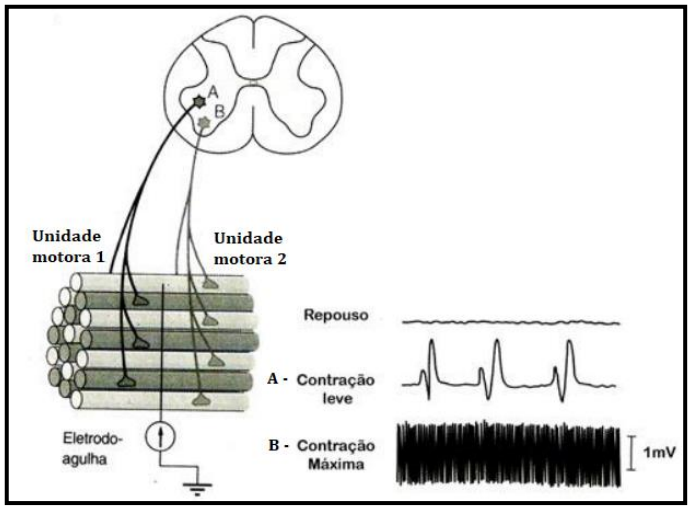
Figura 13 – Condução do estímulo nervoso



Fonte: *Gallaci M; Oliveira AC. Farmacologia da Junção Neuromuscular. In:Farmacologia Integrada. 3.ed. Rio de Janeiro: Revinter, 2007. p. 175-183.*

Cada axônio despolariza as fibras musculares alcançadas pelos botões sinápticos de seus "brotos", constituindo uma unidade motora. À medida da intensidade de contração muscular, mais unidades motoras vão sendo recrutadas permitindo a contração de maior quantidade de fibras musculares de um músculo somático específico. Na EMG, à medida desse recrutamento, em condições normais, registra-se o imbricamento dos potenciais de ação muscular, intensificando o registro (71) (Figura 14).

Figura 14 – Despolarização de unidades motoras / registros de a-EMG
A – Despolarização de uma unidade motora (contração mínima). Traçado rarefeito na a-EMG;
B – Recrutamento de várias unidades motoras à medida da intensidade da contração muscular. Traçados dos potenciais de ação muscular vão se sobrepondo na a-EMG.
a-EMG: eletromiografia com eletrodo de agulha.



Fonte:*in:https://www1.ibb.unesp.br/Home/Departamentos/Fisiologia/Neuro/aula20_fisiologia-muscular_controle-da-forca.pdf* .

Ainda sobre conceitos básico, quanto à fisiopatologia, as neuropatias periféricas são classificadas em mielínicas (mielinopatias), e não-mielínicas (axonopatias). Nas primeiras, espera-se alteração na condução nervosa; e nas segundas, queda da amplitude do estímulo, a princípio, sem alteração da condução nervosa. São encontradas as duas alterações nas lesões mistas, como também tais alterações não são absolutamente especificas. Dessa forma, pode se observar leve queda na velocidade de condução nas axonopatias, como também diminuições de amplitude nas mielinopatias (71).

III - Técnica: princípios básicos

A ENMG consiste em ferramenta propedêutica minimamente invasiva (eletrodos de agulha), que se utiliza de estímulos elétricos de baixa voltagem (risco desprezível de lesões teciduais, queimaduras ou arritmias), fundamental para a investigação eletrodiagnóstica de disfunções neuromusculares (nervos periféricos e músculos), composta basicamente em duas etapas: estudo de condução nervosa (ENC) ou eletroneurografia – avaliação axonal, e eletromiografia (EMG) - junção neuromuscular e fibras musculares correspondentes (71).

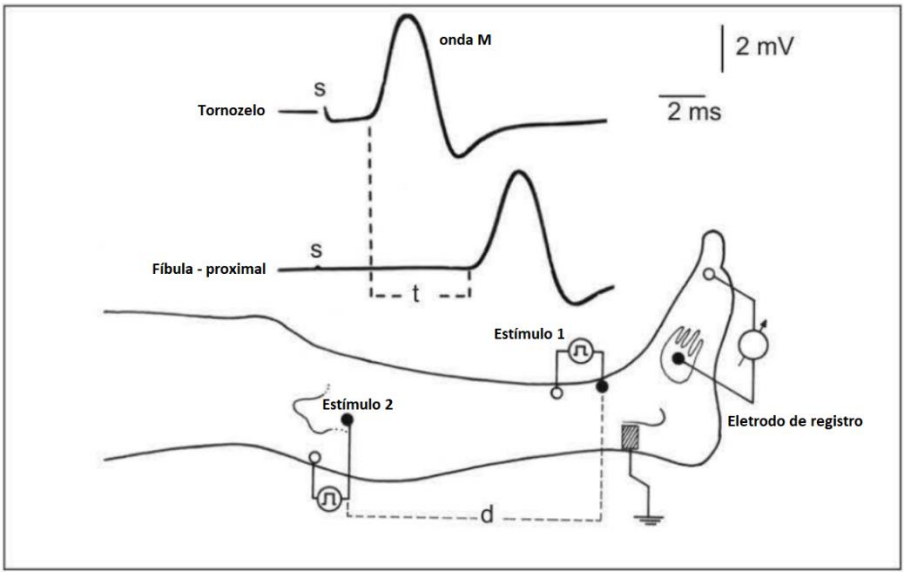
O ECN avalia a condução elétrica ao longo dos nervos, medindo a velocidade de condução nervosa (velocidade e latência de propagação do estímulo), e a amplitude do potencial de ação muscular composto (PAMC) – para motoneurônio, ou potencial de ação nervoso

sensitivo (PANS) – para nervos sensitivos, auxiliando no diagnóstico de lesões neuroperiféricas. O teste é realizado estimulando um nervo em um ponto e registrando a resposta em outro ponto, onde se verifica a despolarização do conjunto de fibras musculares inervados por cada axônio que compõem esse mesmo nervo (unidade motora) (71).

A amplitude da energia elétrica de propagação nervosa do estímulo corresponde ao somatório da energia (voltagem) gerada pela despolarização (reposta ao estímulo elétrico no nervo), de cada axônio e sua unidade motora correspondente. Por isso, a medida de amplitude da energia elétrica gerada pela condução nervosa em um nervo periférico é chamada de PAMC, vez que correspondem ao somatório da voltagem gerada por cada axônio do nervo despolarizado pelo estímulo elétrico do aparelho. Espera-se amplitude diminuída, sem alteração da condução nervosa (velocidade de propagação do estímulo), quando há lesão do axônio e/ou lesão de fibra muscular da unidade motora, em função da perda do quantitativo de voltagens gerados devido à queda do número de axônios ativos ou fibras musculares excitáveis na unidade motora. Ou seja, o PAMC pode estar diminuído tanto pela lesão do axônio (motoneurônio), entre os pontos de estímulo e captação da resposta elétrica, como pela lesão estrutural ou funcional (excitabilidade de membrana) da fibra muscular correspondente (unidade motora) (71). Portanto, diminuição da PAMC pode corresponder tanto a axonopatia, quanto a miopatia, ou ambos, visto que se altera, seja pela perda de axônios (lesão axonal), quanto pela perda ou alteração de excitabilidade das fibras musculares correspondentes (lesão muscular). No caso de nervos sensitivos (p.ex. nervo sural), somente na axonopatia se espera alteração sensitiva – detectado pela queda do PANS, o que reforça a PNDC, mas não descarta a presença de MDC .

A condução nervosa é avaliada pelas medidas de latência e cálculo de velocidade da condução do estímulo elétrico ao longo do nervo – respectivamente, o tempo de disparo, e a relação tempo e distância da condução do estímulo elétrico entre dois pontos nervosos distintos, e sua contração muscular correspondente (nervo motor ou misto), ou despolarização de ponto terminal sensitivo (nervo sensitivo). Novamente, as alterações de aumento na latência e queda da velocidade de propagação do estímulo elétrico (marcadores de condução nervosa), apontam para mielinopatias (71) (Figura 15).

Figura 15. Imagem de Eletroneurografia do nervo fibular (nervo motor)
Eletrodo de registro posicionado na topografia do músculo extensor curto dos dedos.
Etapa 1: eletrodo de estimulação posicionado antero-lateralmente no tornozelo – mede a amplitude do estímulo; Etapa 2: eletrodo de estimulação posicionado na cabeça do fêmur (emergência do nervo fibular) – cálculo de velocidade de condução.



Fonte: *Nobrega JA, Manzano GM. Manual de Eletroneuromiografia e Potenciais Evocados Cerebrais para a Prática Clínica. São Paulo: Atheneu; 2007. p. 12.*

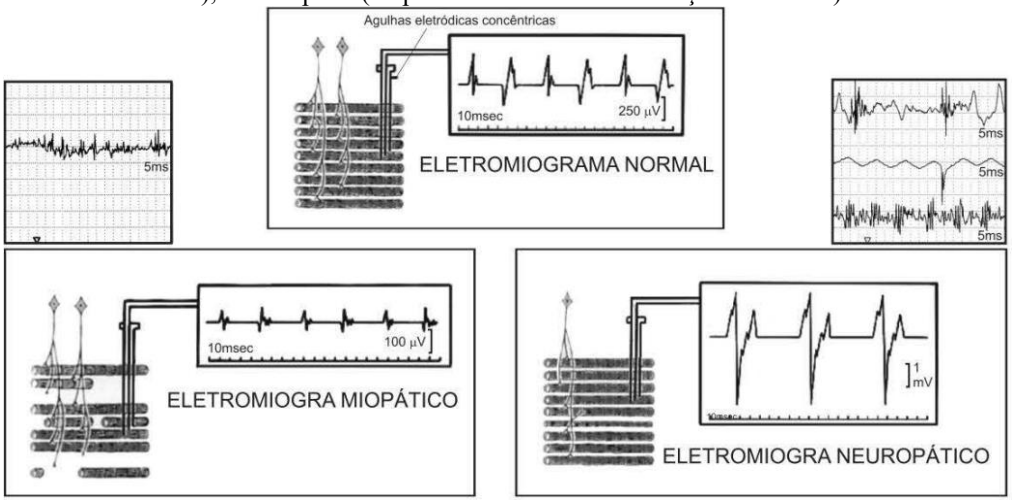
Igualmente importante, após um dano nervoso (fase aguda), o exame ao longo da extensão distal à lesão, de imediato, permanece normal. As alterações eletrodiagnósticas demoram cerca de 7 dias (fibras motoras) e 14 dias (fibras sensitivas) para atingirem o nadir (valores mais baixos de condução e/ou amplitude) (71). Dessa forma, na primeira semana de agressão neuromuscular, ausência de alteração na PANS, na presença de queda da PAMC, não descarta neuropatia. Consequência disso em PNMDC: nos primeiros dias de internação em UTI, a ausência de queda de amplitude do PANS não descarta neuropatia. Aliás, mesmo após a primeira semana, outros fatores podem interferir no registro de PANS – edema, obesidade, lesões teciduais, etc. Nesse contexto, podemos afirmar que, em UTI, a presença de PAMC baixa significa disfunção neuromuscular. Quanto à etiologia dessa desordem, queda da PANS confirma axonopatia, mas não descarta miopatia; enquanto a PANS normal, não descarta axonopatia ou confirma miopatia. Ambas as situações necessitam da complementação do ECN com a a-EMG (17) (19) (23) (71).

A a-EMG analisa a atividade elétrica especificamente dos músculos em três fases: repouso, contração muscular leve e máxima. São utilizados eletrodos de agulha para estímulo

elétrico diretamente nas fibras musculares, que geram potenciais de ação captados por eletrodos de superfície. Os resultados são fundamentais para diferenciar dano neural e/ou muscular (71).

Contudo, essa capacidade de distinção entre neuro e/ou miopatia pela a-EMG depende do fenômeno do "brotamento" ou ramificação de terminação nervosa. Ao longo de cerca de três meses, no caso da axonopatia, observa-se a reinervação das fibras musculares saudáveis correspondentes à unidade motora do axônio lesado (inicialmente denervadas), por ramificações de axônios saudáveis vizinhos. Como também, no caso das miopatias, regeneração de fibras musculares, com recuperação da unidade motora. Na neuropatia, devido diminuição do número de unidades motoras com aumento simultâneo do número de fibras musculares pelas unidades motoras restantes (reinervação por ramificações axonais), observa-se, na fase de contração muscular da a-EMG, traçado mais rarefeito com amplitudes aumentadas. Na miopatia, ao contrário da "rarefação" do traçado de recrutamento de unidades motoras, observa-se apenas a diminuição da amplitude do traçado devido queda do número de fibras musculares ativas nas unidades motoras (71) (Figura 16).

Figura 16. Eletromiografia
Distinção de anormalidades elétrico-musculares pela miopatia (queda de amplitude com recrutamento normal), e neuropatia (amplitude aumentada com traçado rarefeito).



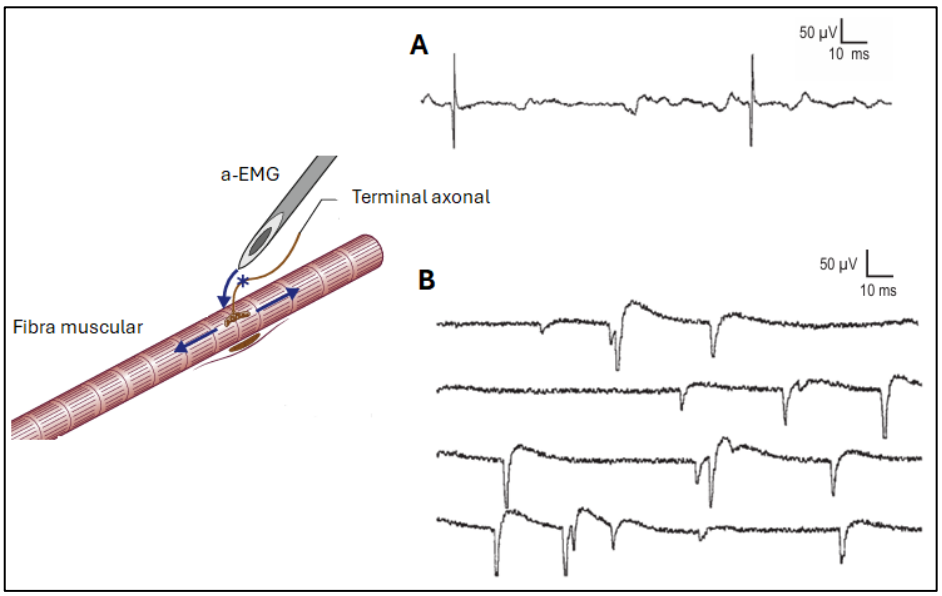
Fonte: *Nobrega JA, Manzano GM. Manual de Eletroneuromiografia e Potenciais Evocados Cerebrais para a Prática Clínica. São Paulo: Atheneu; 2007. p. 21.*

Entretanto, como já pontuado, a condição de inconsciência (sedação ou coma) inviabiliza a fase de análise de contração muscular da a-EMG, de sorte que as alterações da fase de repouso do exame, são comuns tanto à neuro, como à miopatia. Logo, nos primeiros dias de internação em UTI, na fase inicial do dano não se espera essa distinção de resultados na

eletromiografia. Ao exame, ondas patológicas de fase de repouso podem estar presente nas duas situações: tanto na axonopatia – por despolarização muscular espontânea, como na miopatia - devido aumento da excitabilidade de membrana muscular pelo processo inflamatório (71) (Figura 17).

Figura 17. Eletromiografia – ondas patológicas de fase de repouso

A – Fibrilação: despolarização espontânea de única fibra muscular, de curta duração e deflexão inicialmente positiva. B – Axonopatia: despolarização espontânea de fibras musculares, de deflexão inicialmente positiva e fase negativa lenta. Ambas têm o mesmo significado e podem estar presentes tanto na axonopatia, como na miopatia. *a-EMG:* eletromiografia com eletrodo de agulha.



Fonte: *Preston DC, Shapiro BE. Electromyography and Neuromuscular Disorders. Elsevier; 2005. p. 234.*

Na tabela abaixo, segue a síntese das alterações esperadas entre PNDC versus MDC (Tabela 1):

Tabela 1. Características comparativas da ENMG de polineuro e miopatia da doença crítica.

No ECN o padrão de axonopatia é o mesmo para ambas as disfunções – CMAP reduzido com velocidade de condução normal, exceto pela diminuição do SNAP na neuropatia, cuja presença confirma neuropatia, mas não descarta miopatia. As diferenças detectadas pela a-EMG, depende do voluntarismo do paciente para contrair o músculo e da reinervação de fibras musculares ao longo de 3 meses. PANS = potencial de ação nervoso sensitivo; PAMC = potencial de ação muscular composto; PAUM = potencial de ação de unidade motora; a-EMG = eletromiografia com agulha; PNDC = polineuropatia da doença crítica; MDC = miopatia da doença crítica.

Características	PNDC	MDC
PANS	reduzido ou ausente	normal
PAMC (motor)	reduzido ou ausente	reduzido ou ausente
Velocidade de Condução	Normal	normal
a-EMG	PAUMs aumentados com rarefação; recrutamento lentificado.	PAUMs de baixa amplitude, curtos e polifásicos; recrutamento precoce.

Fonte: *Preston DC, Shapiro BE. Electromyography and Neuromuscular Disorders. Elsevier; 2005.*

Enfim, importante reforçar as limitações da ENMG – seja o ECN, seja a a-EMG - na fase inicial de internação dos pacientes críticos, devido coma e/ou uso de sedoanalgesia (impossibilidade de contrações musculares voluntárias); restrições no uso de eletrodos de agulha (uso de anticoagulantes e formação de solução de continuidade da pele, com potencial aumento do risco de infecções); ruído eletromagnético dos demais dispositivos eletrônicos; edema de membros/anasarca; lesões superficiais; uso de outros dispositivos (fixadores ortopédicos, tala gessada e catéteres); dificuldades de aterramento dos equipamentos e de acesso a neurofisiologistas; custos (12) (19) (35).

1.5.2. Teste Eletrofisiológico Simplificado do Nervo Peroneal

A ECN ou eletroneurografia, é capaz de identificar a axonopatia (PAMC anormal), e mesmo confirmar polineuropatia pela alteração sensorial (queda do PANS), ainda que isso não descarte a miopatia. A presença dessa alteração nos 4 seguimentos é altamente indicativa de PNMDC.

Contudo, devido às dificuldades logísticas para realização da ECN em UTI - custo, deslocamento do eletroneuromiógrafo e do neurofisiologista, interferências eletromagnéticas – alguns autores propuseram modelos simplificados.

Mark Moss (2014) (21) fez o seguimento de pacientes críticos em UTI com ECN e a-EMG, concluindo que a alteração de melhor acurácia para PNMDC foi a do nervo peroneal profundo (AUC = 0.89, $p<0.05$, curva Roc), ao que aponta, por se tratar de terminação nervosa distal, extensa, de baixo diâmetro proporcional; por essas características, mais sensível à isquemia e hipóxia citopática. Esse modelo de ECN simplificado, de nervo único (nervo peroneal profundo), passou a ser chamado do Teste Eletrofisiológico Simplificado do Nervo Peroneal (PENT), e vem sendo utilizado por outros pesquisadores (14) (15).

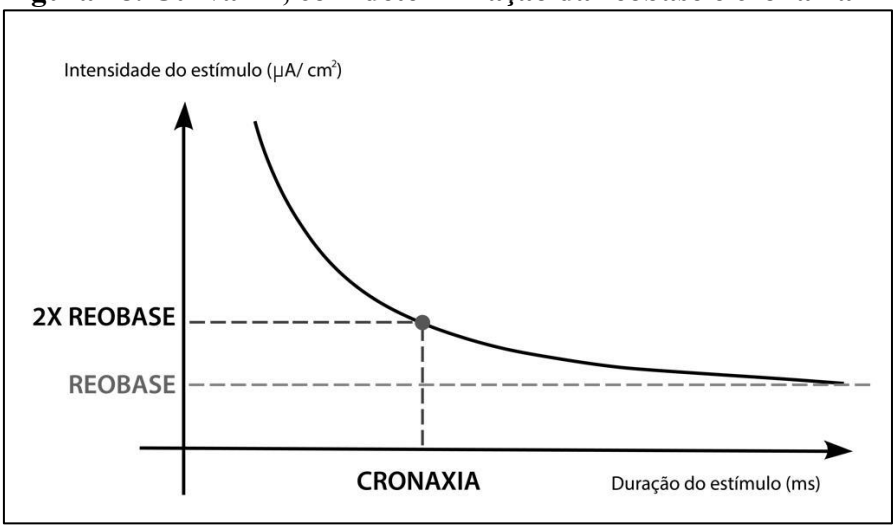
1.5.3. Teste de Força/Duração e Teste de Eletrodiagnóstico de Estímulo

Como exposto, as avaliações precoces de provável PNMDC em UTI vem sendo realizadas a partir de estudos eletrofisiológicos para a detecção de alterações na excitabilidade neuromuscular (19), posto que a inviabilidade de avaliação de força, a relevância da disfunção eletrofisiológica independente da manifestação posterior de fraqueza muscular (59), e as limitações da biópsia neuro/muscular (18). Entretanto, sendo considerada a principal ferramenta para avaliar as alterações eletrofisiológicas em UTI, a realização da ENMG não raro é inviável, seja pelo custo operacional, dificuldades logísticas, necessidade de equipe médica especializada, inconsciência (coma/sedação) (19) (131).

No entanto, o ECN não é o único método capaz de detectar as alterações eletrofisiológicas neuromusculares provocadas pela PNMDC. Estas alterações podem ser também detectadas por meio de testes eletrodiagnósticos alternativos, não invasivos, beira-leito, de melhor logística e custo-benefício: o TEDE (32) e o TFD (36).

O TEDE é um exame não invasivo, com baixo custo e validado para diagnosticar alterações da excitabilidade neuromuscular em neuropatias a nível ambulatorial (35). Através de estímulos transcutâneos, o TEDE mensura os valores de reobase e cronaxia. Essa ferramenta, por meio de gradações de impulsos elétricos, excita neurônio adjacente até o limite de evocar contração muscular detectável. O estímulo mínimo com forma de pulso retangular e largura de pulso considerada infinita (1 ms) para alcançar este limiar de excitabilidade é chamado de reobase – variável de intensidade de estímulo, mensurada em miliampere. Já a cronaxia - variável de duração de estímulo (tempo), mensurada em milisegundos - é a menor largura de pulso para provocar contração visível com o dobro da reobase, utilizando um pulso retangular (24) (35) (88) (Figura18).

Figura 18. Curva ID, com determinação da reobase e cronaxia



Fonte: *próprio autor*.

À medida da disfunção neuropática, os valores de cronaxia (duração do estímulo elétrico), suficientes para provocar contração muscular visível, tornam-se gradativamente maiores, a extremo da resposta ao estímulo elétrico não mais ser adquirida a partir da condução nervosa de nervo adjacente comprometido, mas sim, diretamente pelo músculo desnervado (não excitabilidade) (117).

Nos músculos saudáveis, suas respectivas fibras nervosas disparam em reposta à estimulação elétrica, enquanto nos músculos desnervados, são as fibras musculares que respondem ao estímulo. Os nervos, como melhores condutores, apresentam menores valores de cronaxia do que as fibras musculares, de sorte que músculos inervados têm menores cronaxias (78). O valor médio de cronaxia de um músculo inervado é cerca de 400 µs (35).

O índice de acomodação corresponde à relação entre a acomodação e a reobase. Acomodação é a propriedade que o músculo sadio tem de não responder, ou de responder apenas com altas intensidades, aos pulsos de crescimento lento (exponencial). É a menor intensidade necessária para produzir uma contração muscular, evocada por um pulso exponencial de largura infinita (1 ms) (19) (78). A acomodação expõe as diferentes respostas de nervos e músculos aos pulsos elétricos em formato exponencial. Nas fibras nervosas, um pulso elétrico com formato exponencial, de até duas vezes o valor da reobase, inativa temporariamente os canais de sódio antes da despolarização ocorrer, assim, não é evocada qualquer contração. No caso das fibras musculares, a condutância de sódio é menos alterada por pulsos exponenciais. Desta forma, é possível evocar contrações

musculares com pulsos exponenciais de intensidade menor do que o dobro da reobase (78).

Paternostro-Sluga e cols. (2002) (35), demonstraram correspondência diagnóstica do TEDE com eletromiografia de agulha, em pacientes com denervação neuropática completa, com valores de cronaxia >1000 µs e índice de acomodação <2, com sensibilidade de 100%, na fase aguda. Considerando que PNDC é caracterizada pela disfunção da excitabilidade elétrica neuromuscular (117) (132), o TEDE apresenta-se como ferramenta alternativa para o rastreamento de disfunção neuromuscular em pacientes críticos (24) (78).

Entretanto, Paternostro-Sluga e col. (2002) (35) aplicaram o TEDE em pacientes com neuropatias diversas (sem incluir miopatias), a nível ambulatorial. Basearam-se em limiar pré-definido de cronaxia, sem análise metodológica adequada de acurácia diagnóstica, descrevendo apenas a sensibilidade do método. A presente tese pretende suprir essa lacuna. Os próprios autores sugeriram a utilização da curva completa de intensidade/duração de estímulo (curva ID), posto que a cronaxia (medida de tempo/duração de estímulo) corresponde a único ponto dessa curva, como forma de observar mais fibras musculares e melhorar a performance do teste, evitando falsos negativos. A curva ID é construída pelo TFD, a partir da identificação das intensidades de corrente para gerarem contrações visíveis com diferentes durações de pulso (p.ex. 50 µs a 1000 µs), que não só a correspondente à cronaxia.

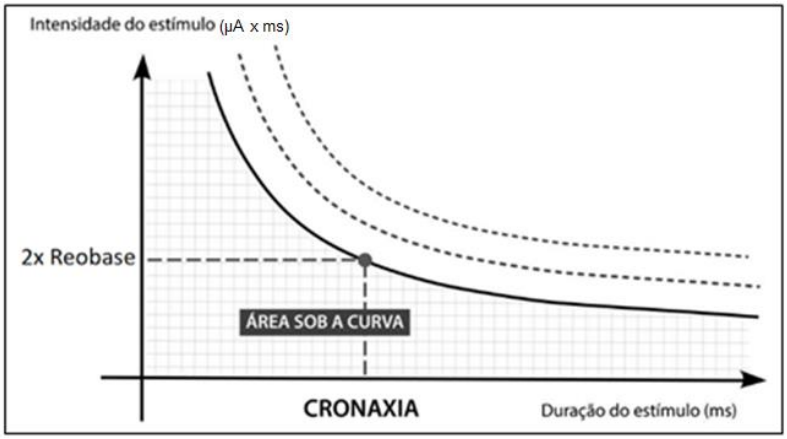
Fagoni e cols. (2021) (36) reavaliaram a aplicação do TFD para identificação de pacientes críticos com deficiência neuromuscular. Basicamente compararam as curvas ID entre voluntários normais e pacientes críticos internados em UTI submetidos ao TFD do músculo *rectus femoris*. Arbitraram como "anormal" padrão de curva ID acima de 2x o padrão dos pacientes voluntários, incluindo média aritmética das diferentes intensidades de estímulos elétricos registrados na curva ID de cada participante. Categorizaram os pacientes em 4 graus (0 a 3, sendo 0 = normal), à medida da piora dos registros de intensidade de estímulo para as diferentes durações de impulso elétrico (50 a 450 µs). Por fim, correlacionaram com resultados e estabeleceram forte correlação entre os resultados do PENT (avaliação da unidade nervo fibular profundo / musculo *extensor digitorum brevis*), e a categorização baseada no TFD de músculo reto femoral ($R^2 = 0.946$, $p=0.027$). Embora os resultados reforcem a forte correlação inversa entre o TFD e os registros de CPAM (pelo PENT) em pacientes críticos com desordem neuromuscular, trata-se de estudo metodologicamente frágil: comparou resultados de testes de unidades neuromusculares

distintas (músculo *rectus femoris* versus *extensor digitorum brevis*); não aplicou adequada metodologia de estudo de acurácia diagnóstica; não definiu a métricas diagnósticas do teste (sensibilidade, especificidade, acurácia, etc.); definiu arbitrariamente o limiar de normalidade. A presente tese pretende suprir também essa lacuna e estabelecer o TFD com alternativa viável e acurada para triagem diagnóstica de PNMDC.

Nossa hipótese considerada que, à medida da progressão da disfunção neuromuscular, o paciente necessitaria de intensidade/duração estímulos progressivamente maiores para disparo de mínima contração muscular, de forma que a Curva ID apresente tendência de desvio superior-direito (35), espera-se, dessa forma, aumento correspondente da área sob a curva ID. Propomos como metodologia mais efetiva, a análise da curva ID como um todo, incluindo todos seus pontos de intensidade/duração de estímulo, inclusive a cronaxia (ponto único de duração de estímulo). Faremos a estimativa de energia (μC) a partir do cálculo de área sob a curva ID – critério que propomos ser mais acurado que a cronaxia isoladamente para detecção de desordem neuromuscular (Figura 19).

Figura 19. Gráfico intensidade x duração de estímulo elétrico, com representação da área sob a curva ID

As curvas pontilhadas representam o comportamento esperado da curva ID: à medida da progressão da disfunção neuromuscular em pacientes críticos, há o aumento da área sob a curva, com seu deslocamento superior direito.



Fonte: *próprio autor*.

A proposta não é apresentar os referidos testes como substitutos da ENMG.

Finalmente, outra vantagem importante dos testes eletrodiagnósticos alternativos (TFD e TEDE) - além de serem portáteis, não invasivos, de menor custo, de melhor

operabilidade e custo-benefício - reside no fato de serem capazes de detectar com considerável precisão o ponto neuromotor de superfície ideal para estímulo elétrico e estabelecer o limiar de excitabilidade adequado e necessário para guiar o tratamento de eletroestimulação neuromuscular (29).

1.6. Objetivos

1.5.1. Objetivo Geral

I. Análise de acurácia diagnóstica de TFD e TEDE (testes eletrodiagnósticos alternativos à ENMG), para triagem diagnóstica não invasiva, beira-leito e precoce de PNMDC em pacientes críticos, mecanicamente ventilados, em UTI.

1.5.2. Objetivos Específicos

I. Definir os pontos de corte ótimos do TFD e do TEDE do nervo peroneal profundo para o diagnóstico de PNMDC;
II. Comparar a acurácia, sensibilidade, especificidade, valor preditivo positivo (VPP), valor preditivo negativo (VPN), taxa de verossimilhança positivo (LR+) e negativo (LR-) dos pontos de cortes estabelecidos no estudo para o TFD e o TEDE do nervo fibular profundo no diagnóstico da PNMDC, tendo o PENT como padrão de referência;
III. Comparar a acurácia, sensibilidade, especificidade, VPP, VPN, LR+ e LR- do ponto de corte estabelecido no estudo para o TEDE do nervo fibular no diagnóstico da PNMDC, comparado ao ponto de corte previamente estabelecido na literatura para pacientes ambulatoriais (cronaxia = 1 ms);
IV. Avaliar a factibilidade e a segurança do TFD e do TEDE do nervo fibular no diagnóstico da PNMDC;
V. Investigar a presença de assimetria eletrodiagnóstica no desenvolvimento da PNMDC, avaliando a relevância e segurança da realização de protocolos de avaliações eletrofisiológicas unilaterais versus bilaterais para triagem diagnóstica da PNMDC em UTI;
VI. Explorar a associação entre assimetria e fatores centrais, incluindo lateralidade cerebral e lesões focais do SNC, quando presentes;
VII. Comparar o TFD e TEDE do nervo fibular profundo avaliados por método manual e automatizado.

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TITLE

Diagnostic Performance of the Strength-Duration Test for Bedside Screening of Critical Illness Polyneuromyopathy: A Prospective, Cross-Sectional Study

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ABSTRACT

Introduction/Aims

Critical illness polyneuromyopathy (CIPNM) is a major cause of muscle weakness in intensive care unit (ICU) patients. However, the availability of comprehensive ICU diagnostic tests, such as electroneuromyography, is limited. Alternative electrophysiological methods, such as the Stimulus Electrodiagnosis Test (SET) and the Strength-Duration Test (SDT), emerge as promising candidates for early CIPNM screening. Therefore, this study aimed to evaluate the diagnostic metrics, including sensitivity, specificity, and accuracy, of the SDT for the screening of CIPNM.

Methods

This prospective, cross-sectional study included adult, mechanically ventilated ICU patients. A single assessment per patient comprised the Peroneal Simplified Electrophysiological Test (PENT), SDT, and SET. Using PENT as the reference standard, we calculated the accuracy, sensitivity, specificity, predictive values, and likelihood ratios of the SDT. Receiver Operating Characteristic (ROC) curves were constructed to assess the discriminative capacity of the tests for CIPNM and to define the optimal cutoff point (Youden test).

Results

Sixty participants were enrolled, yielding 101 assessments (including bilateral evaluations where feasible). The SDT demonstrated an Area Under the Curve (AUC) of 0.8 (95% CI: 0.7–0.8, $p<0.001$), with an optimal cutoff point of 600 mC. At this cutoff, SDT exhibited a sensitivity of 73% (62-85%), specificity of 68% (53-81%), and an accuracy of 71% (62-81%) for CIPNM screening. The SET yielded an AUC of 0.7 (95% CI: 0.6–0.8, $p=0.001$).

Discussion

This study provides crucial insights into the utility of the SDT as a diagnostic screening tool for CIPNM. With considerable accuracy, the SDT emerges as a useful adjunct in early CIPNM screening.

Keywords: Chronaxie; Critical Illness Polyneuropathy; Sensitivity; Specificity; Strength-duration Test.

INTRODUCTION

Significant advancements in critical care medicine have dramatically improved survival rates for patients admitted to the Intensive Care Unit (ICU), reaching an impressive 70–80% [1]. However, a substantial proportion of these survivors experience severe and debilitating long-term sequelae, collectively known as Post-Intensive Care Syndrome (PICS) [2,3]. A predominant physical manifestation of PICS is Intensive Care Unit Acquired Weakness (ICUAW) [4], a complex neuromuscular disorder primarily caused by Critical Illness Polyneuropathy (CIP) and/or Critical Illness Myopathy (CIM) [5]. CIP, characterized as a sensory-motor axonopathy, affects 30–50% of critically ill patients, with incidence soaring to nearly 100% in cases of sepsis [6,7].

Given that CIP and CIM frequently co-occur and present with similar clinical features, their clinical differentiation is inherently challenging [8]. Consequently, the overarching term Critical Illness Polyneuromyopathy (CIPNM) is widely adopted to describe these conditions, as is the case in the present study. CIPNM carries substantial clinical relevance, significantly impacting long-term outcomes and recovery trajectories [9], leading to complications such as difficulties in ventilator weaning [10], persistent limb weakness, and, in severe instances, quadriplegia [11], with sequelae lasting up to five years [12]. Specifically, the peroneal nerve is reported to be an early site of electrophysiological dysfunction in CIPNM.

Early and accurate diagnosis of CIPNM is paramount for initiating timely rehabilitation interventions and ultimately improving patient outcomes; however, it remains a formidable challenge within the demanding ICU environment [13]. Conventional clinical muscle strength tests, such as the Medical Research Council (MRC) score, are often impractical for uncooperative or sedated patients due to their inherent subjective nature and reliance on patient participation. Moreover, the Peroneal Simplified Electrophysiological Test (PENT), while a validated reference standard in diagnostic studies for CIPNM screening [14,15], can present significant practical limitations. Its execution relies on specialized neurophysiological devices that are frequently unavailable in many ICU settings, alongside the necessity for highly specialized physician expertise. These constraints highlight an urgent and critical need for accessible, cost-effective, and feasible bedside diagnostic tools capable of early screening for CIPNM.

In this context, alternative electrophysiological methods, such as the Stimulus Electrodiagnosis Test (SET) [16] and the Strength-Duration Test (SDT) [17], emerge as promising candidates for early CIPNM screening. These techniques assess the electrical excitability of nerves and muscles, building upon established principles like chronaxie [18] and the comprehensive strength-

duration curve [19]. The chronaxie measured by SET represents a single point within the broader strength-duration curve [20]. A compelling hypothesis, advanced by Paternostro-Sluga et al. (2002) [20], suggested that evaluating multiple points along the strength-duration curve as done by the SDT could offer superior detection of muscle denervation and mitigate the risk of false-negative records compared to assessing chronaxie alone. This approach aims to provide a more nuanced understanding of neuromuscular excitability. However, despite this theoretically appealing rationale, comprehensive advancements in defining and validating the full diagnostic metrics of the SDT for routine CIPNM screening have been notably constrained in the literature [17].

Therefore, the present study aimed to rigorously evaluate the diagnostic metrics, including sensitivity, specificity, and accuracy, of the SDT for the diagnostic screening of probable CIPNM, specifically assessing the peroneal nerve. This evaluation utilized the PENT as the reference standard. Furthermore, the study sought to compare the diagnostic metrics of SDT against those of SET. We hypothesized that the SDT would be a safe and feasible bedside tool in the ICU setting, yielding accurate results that could serve as a valuable surrogate for screening CIPNM.

METHODS

Study design

This prospective, cross-sectional study was conducted with critically ill patients admitted in ICU.

Participants

The study population comprised critically ill adult patients (aged ≥18 years, of both sexes) who were sedated for at least 3 days and receiving mechanical ventilation and had no history of orthopedic deformities or pre-existing neuromuscular diseases. Patients were excluded if they presented with bilateral lower limb disorders precluding nerve conduction study (e.g., edema, fractures, amputation, plaster casts, and/or local skin injuries), a Body Mass Index (BMI) >35 kg/m², brain death, current use of neuromuscular blockers, or pregnancy.

The study was conducted at the critical care units of a tertiary public reference hospital in the Federal District, Brazil. The study adhered to the Declaration of Helsinki. Ethical approval for the project was obtained from the local ethics committee (HB/IGESDF, Brasília/DF, Brazil; Approval Number 5.731.715). Written informed consent was obtained from the legally authorized representative (e.g., closest responsible family member), as all participants were

intubated and sedated at the time of enrollment. Participants were consecutively recruited upon meeting the inclusion criteria, until the pre-established sample size was achieved.

Test methods

Each participant underwent a single evaluation during their ICU stay. This evaluation included the randomized application of PENT, SET, and SDT to the lower limbs, performed bilaterally whenever possible. The Peroneal Simplified Electrophysiological Test (PENT) [14,21], a nerve conduction study, was designated as the reference standard test for screening for probable CIPNM. The Strength-Duration Test (SDT) [17], serving as the index test, was then evaluated against PENT. The reporting of this diagnostic accuracy study adhered to the Standards for Reporting Diagnostic Accuracy (STARD) 2015 guidelines [22].

Primary outcomes

The primary outcomes of the present study were to evaluate the power and diagnostic accuracy, and to define the optimal cutoff point of the SDT of peroneal nerve for the diagnostic screening of CIPNM.

Secondary outcomes

The secondary outcomes included comparing the diagnostic metrics of SDT versus SET for screening for CIPNM, using PENT as the reference standard. Additionally, the safety and feasibility of SET and SDT were evaluated. Safety was assessed by monitoring the incidence of skin burns. Feasibility was determined by the time required to complete the SET and SDT assessments.

Variables

After enrollment, baseline information was collected to characterize the study patients. This included: comorbidities, hospitalization diagnosis, Body Mass Index (BMI), Simplified Acute Physiology Score (SAPS 3), Sequential Organ Failure Assessment (SOFA) score, Richmond Agitation-Sedation Scale (RASS), presence of sepsis or septic shock, PaO2/FiO2 ratio (P/F), and renal failure (defined as the necessity of hemodialysis).

All participants underwent assessment, with a 30-minute interval between tests. These assessments were performed by two independent examiners: Examiner 1 (JRDM) conducted the PENT, while Examiner 2 (PES) performed the SET and SDT. To ensure blinding, examiners did not share results or diagnostic impressions with each other.

A purely electrophysiological diagnostic approach for CIPNM was employed via the PENT. This method's sensitivity has been previously reported to range from 92% to 100% [14,15]. PENT was performed using a portable electroneurograph (Neuro-MEP-Micro®, Neurosoft, Russia).

The low-pass filter was set at 3 Hz and the high-pass filter at 10 kHz. The device sensitivity and sweep speed were set at 3 mV and 2 ms, respectively.

Stimulation was performed at two sites to record distal motor latencies, amplitudes, and to calculate the conduction velocity for each nerve (right and left). Amplitudes were measured from baseline to the negative peak. For testing, surface recording electrodes (Ambu®, WhiteSensor 0315M, Ambu, Denmark) were placed over the belly and tendon of the *extensor digitorum brevis*. The peroneal nerve was stimulated over the anterior region of the ankle, slightly lateral to the tendon of the *tibialis anterior* muscle, 6 to 8 cm from the recording electrodes, and below the head of the fibula for motor conduction velocity recording[14]. Incremental electrical stimulation of the peroneal nerve was applied until optimal Compound Muscle Action Potential (CMAP) amplitudes were obtained, with motor conduction velocity and latency duly recorded. All participants were in a supine position with a 30° head-of-bed elevation and lower limbs fully extended.

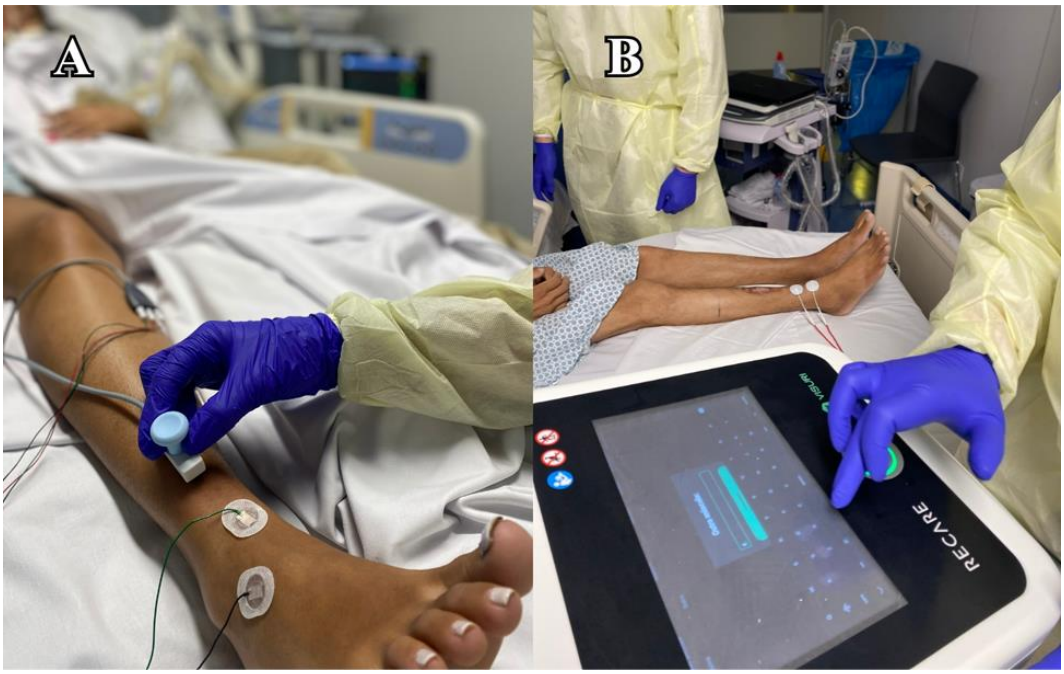
Diagnostic Criteria for CIPNM

CMAP amplitudes falling 80% [15,21] below Katirj's[23] normative values (i.e., ≥3 mV for ages 20-50 years; ≥2.5 mV for ages 51-90 years) were considered abnormal. Axonopathy pattern in motor conduction velocity were assessed using Tan's [24] criteria: 80% above the lower limit of normal if CMAP was <50% of normal, or 90% above if CMAP was >50% of normal. The diagnostic pattern indicative of CIPNM was defined as axonopathy, characterized by a reduction in CMAP amplitude with normal or mildly reduced nerve conduction velocity [8].

Stimulus Electrodiagnosis Test and Strength-Duration Test

Both the SET and SDT were performed using a bedside peripheral electrical neuromodulator (Recare®, Visuri, Brazil). These tests aimed to assess the neuromuscular excitability of the *extensor digitorum brevis* muscle in response to electrical stimuli, applied to elicit a minimal visible contraction. Two circular electrodes, 3 cm in diameter (ValuTrode®, Axelgaard, Denmark), were positioned over the dorsum of the foot, near the ankle, with the objective of exciting the peroneal nerve (Figure 1).

Figure 1. Electrode positioning for peroneal nerve excitation



Legend.
Peroneal nerve stimulation was performed at the anterior ankle, slightly lateral to the tibialis anterior muscle tendon, 6 to 8 cm from the recording electrodes. (A) Peroneal Simplified Electrophysiological Test assessment; (B) Stimulation site for Stimulus Electrodiagnosis Test and Strength Duration Test.

This electrode positioning adhered to the recommendations by Latronico et al. (2007) [25]. All participants were in a supine position with a 30° head-of-bed elevation and their lower limbs fully extended.

SET

During the SET, neuromuscular excitability was quantified through the measurement of rheobase and chronaxie. Rheobase is defined as the minimal current intensity required to elicit a muscle excitation threshold when delivered as a rectangular pulse of long duration (e.g., > 200 ms) [16]. Chronaxie is the shortest pulse duration necessary to reach this muscle excitation threshold using a current amplitude that is twice the rheobase. Rheobase and chronaxie measurements were performed using a single, rectangular, biphasic, and symmetric electrical pulse [16]. For rheobase assessment, the current amplitude was progressively increased from 1 to 240 milliampere peak-to-peak (mAp-p), in 1 mAp-p increments, until a minimal visible muscle contraction was elicited. During this assessment, a pulse duration of 500 milliseconds (ms) and an inter-pulse interval of 2 seconds were utilized. For chronaxie assessment, the current amplitude was set to twice the rheobase value. Subsequently, the pulse duration was increased from 0.1 ms to 500 ms in 0.1 ms increments, until a minimal visible muscle contraction was

observed [16]. Based on previous publications, the SET's positive cutoff value was pre-defined at 1 ms (i.e.: 1000 μs) [20].

SDT

The SDT employed a single, rectangular, biphasic, and symmetric electrical pulse with varying durations: 0.1 ms, 0.2 ms, 0.5 ms, 1 ms, 2 ms, 5 ms, 10 ms, 20 ms, and 50 ms. The pulse duration, for this specific pulse type, is defined as the summation of the pulse widths of its positive and negative phases. For each tested pulse duration, the examiner adjusted the current intensity within a range of 1 to 240 mAp-p to elicit a minimal visible muscle contraction. The electrical charge applied during the SDT was quantified from the product of pulse amplitude (mAp-p) and pulse duration (ms). This calculation was performed automatically by the Recare® software. The electrical charge unit was expressed in millicoulombs (mC). It is anticipated that as neuromuscular dysfunction progresses, a greater electrical charge will be necessary to elicit a detectable muscle contraction[17]. An exploratory rationale was used to define the SDT's positivity cutoff points and the resulting categories.

Study size

The sample size was determined using the Power Analysis and Sample Size (PASS) software, adhering to the recommendations by Flahault et al. (2005) [26]. This calculation incorporated several parameters: disease prevalence, the null hypothesis, statistical power (1-β), an alpha (α) level, the maximal distance from sensitivity (δ), and the expected sensitivity and specificity.

The prevalence of neurophysiological abnormalities was estimated at 55%, based on a previous study [16]. Statistical power and the α level were set at 80% and 5%, respectively, and δ was defined as 25%. The expected sensitivity was established at 80% based on the study by Paternostro et al. (2002) [20], while specificity was arbitrarily set at 70%, given the absence of corresponding data in the available literature. Accounting for an anticipated dropout rate of 5%, a minimum of 100 tests was required.

Statistical methods

Data normality was assessed using the Shapiro-Wilk test. Non-parametric data were described as medians with interquartile ranges [IQR], while nominal variables were presented as absolute frequencies and percentages.

To characterize the diagnostic utility of the tests, Receiver Operating Characteristic (ROC) curves were constructed [27]. This methodology graphically depicts the trade-off between the true positive rate (sensitivity) and the false positive rate (1-specificity) across all potential classification thresholds, thereby elucidating the test's capacity to discriminate individuals with and without the target condition (CIPNM).

ROC curves were constructed for both SET and SDT, with the Area Under the Curve (AUC) serving as an aggregate measure of diagnostic accuracy. An AUC of 0.5 indicates discriminatory ability no better than random chance. For interpretative purposes, AUC values were categorized as follows: ≥ 0.9 as Excellent; 0.8 to < 0.9 as Considerable; 0.7 to < 0.8 as Fair; 0.6 to < 0.7 as Poor; and 0.5 to < 0.6 as Fail [28].

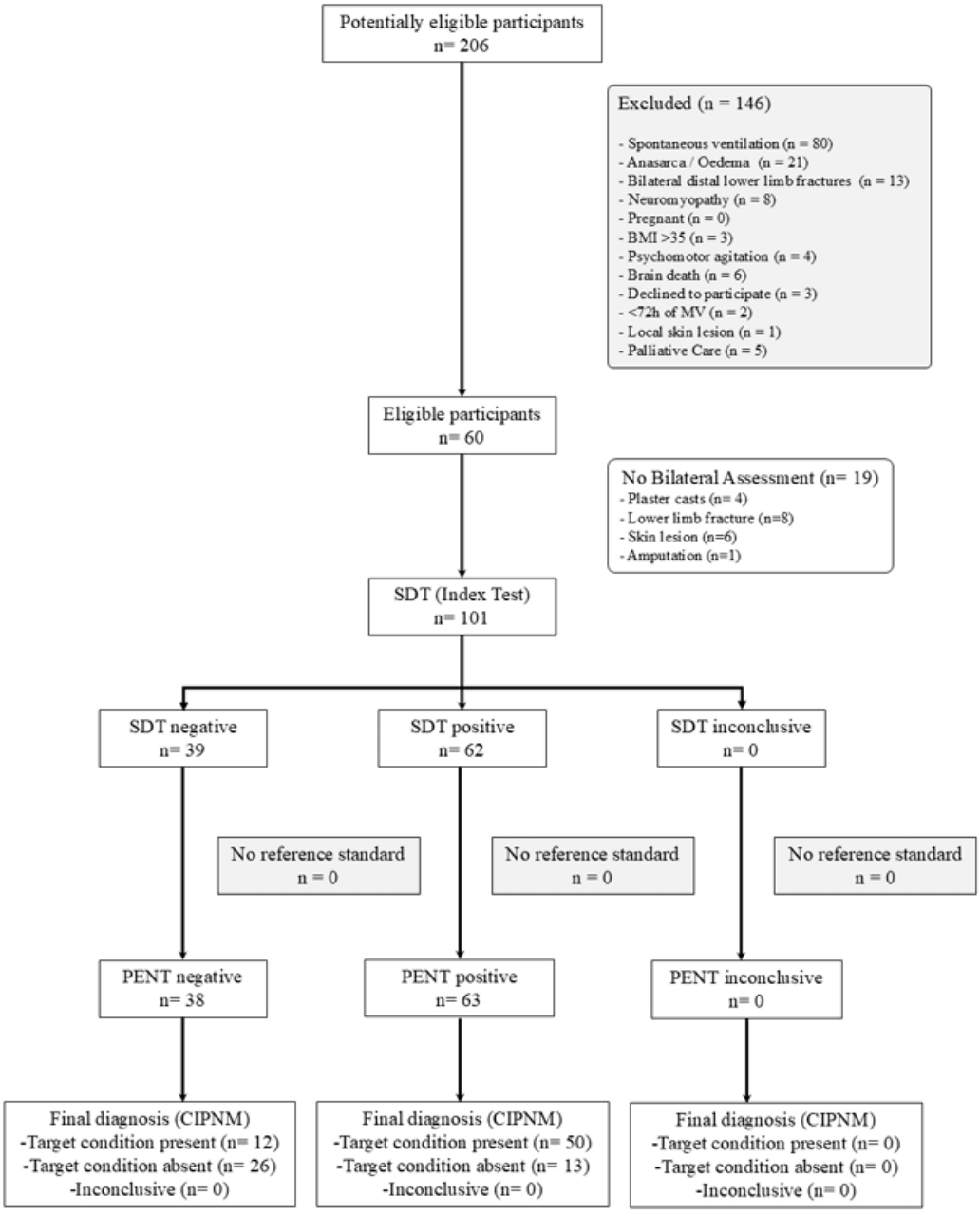
The SDT's optimal cutoff point was determined using Youden's J index. The test diagnostic metrics (sensitivity, specificity, predictive values, accuracy, and likelihood ratios) for the selected optimal cutoff point were calculated with their respective 95% confidence intervals, using Wilson's method for interval estimation. The ROC curves (SET versus SDT) were statistically compared using the DeLong test.

A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics (Version 29, IBM Corp., Armonk, NY) and R Statistical Software (Version 4.2.2; R Core Team, 2022).

RESULTS

Between April 2024 and June 2025, 206 participants were screened for eligibility, and 60 were subsequently enrolled. Among these, a total of 101 assessments were conducted using PENT, SET, and SDT methodologies. Further details regarding participant flow are provided in the study flow diagram (Figure 2).

Figure 2. Flow diagram.



Legend.
The flow diagram was developed according to the Standards for Reporting of Diagnostic Accuracy (STARD). Assessments were performed bilaterally when feasible. The Strength-Duration Test (SDT) was employed as the index test, with the Peroneal Simplified Electrophysiological Test (PENT) serving as the reference standard for diagnosing critical illness polyneuropathy and myopathy (CIPNM), which was defined as the target condition.

Enrolled participants were predominantly adult males (41, 68%), with a median age of 47 [34.3–57.8] years. The primary cause of ICU admission was central nervous system injury (42, 70%). On the day of assessment, participants had a median of 6 [4–10] days on mechanical

ventilation. Their median SAPS III score at admission was 58 [49–67]. Detailed baseline characteristics are presented in Table 1.

Table 1. Baseline demographic and clinical characteristics

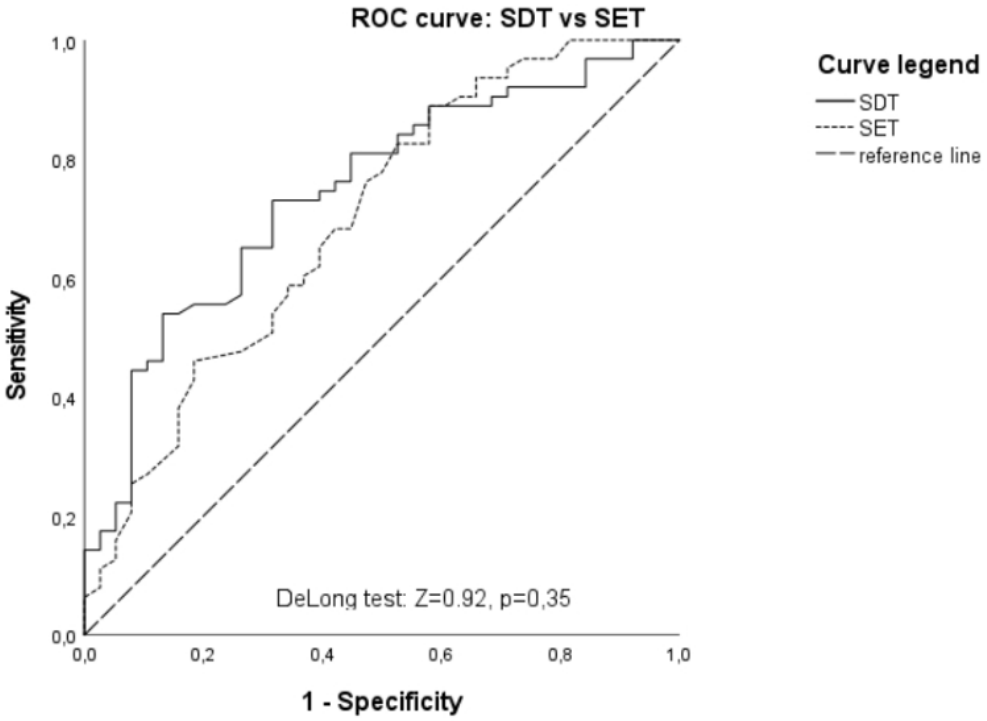
Variables	Participants (n=60)	Positive PENT (n=17)	Negative PENT (n=43)
Age, years	47 [34.3 – 57.8]	40 [28.5 – 50.5]	49 [35 – 59]
Sex, n (%) male	41 (68.3%)	12 (70.6%)	29 (67.4%)
BMI, Kg/m^2	24.2 [21.5 – 28]	24.7 [22 – 29.6]	24 [21 – 27]
SAPS 3, on admission	58 [49 – 67]	50 [48 – 67]	58 [51 – 67]
SOFA, on assessment	7 [6 – 9]	9 [6 – 10]	7 [6 – 9]
Reason for ICU admission, n (%)			
Traumatic brain injury	24 (40%)	8 (47%)	16 (37.2%)
Hemorrhagic stroke	9 (15%)	2 (11.8%)	7 (16.3%)
Ischemic stroke	4 (6.8%)	1 (5.9%)	3 (7%)
Subarachnoid hemorrhage	2 (3.3%)	0 (0%)	2 (4.7%)
CNS Infection	3 (5%)	2 (11.8%)	1 (2.3%)
Abdominal trauma	3 (5%)	1 (5.9%)	2 (4.7%)
Thoracic trauma	3 (5%)	2 (11.8%)	1 (2.3%)
Heart surgery	2 (3.3%)	0 (0%)	2 (4.7%)
Myocardial infarction	2 (3.3%)	0 (0%)	2 (4.7%)
Cancer	3 (5%)	1 (5.9%)	2 (4.7%)
Others	5 (8.3%)	0 (0%)	5 (11.6%)
Comorbidities			
Type 2 diabetes, n (%)	3 (5%)	1 (6%)	2 (4.7%)
SAH, n (%)	11 (18.3%)	2 (12%)	9 (20.9%)
Heart disease, n (%)	5 (8.3%)	3 (18%)	2 (4.7%)
Epilepsy	2 (3.3%)	1 (6%)	1 (2.3%)
HIV, n (%)	2 (3.3%)	1 (6%)	1 (2.3%)
Ventilation days, on assessment	6 [4 – 10]	4 [3.5 – 8]	7 [5 – 12]
ICU length of stay, on assessment	4 [2 -8.8]	3 [2 – 6.5]	5 [2 – 10]
Hospital length of stay, on assessment	6,5 [4 – 12]	5 [4 – 9]	8 [5 – 14]
Sepsis, n (%)	50 (83.3%)	14 (82.4%)	36 (83.7%)
Lung	43 (71.7%)	11 (64.7%)	32 (74.4%)
Abdomen	3 (5%)	1 (5.9%)	2 (4.7%)
CNS	3 (5%)	2 (11.8%)	1 (2.3%)
Mediastinum	1 (1.7%)	0 (0%)	1 (2.3%)
Septic Schock, n (%)	24 (40%)	8 (47.5%)	16 (37.2%)
GCS, on admission, n (%)			

10 - 14	13 (21.7%)	2 (11.8%)	11 (25.6%)
6 - 9	43 (77.7%)	13 (76.5%)	30 (69.8%)
3 - 5	4 (0.7%)	2 (11.8%)	2 (4.7%)
RASS score, on assessment	-5 [-5 – -5]	-5 [-5 – -5]	-5 [-5 – -5]
Norepinephrine n (%)	24 (40%)	8 (47.5%)	16 (37.2%)
dosage (mcg/kg/min)	0.13 [0.1 – 0.36]	0.13 [0.1 – 0.45]	0.12 [0.1 – 0.3]
Lactate, dosage (mg/dl)	1.4 [1.2 – 1.8]	1.4 [1.2 – 1.8]	1.5 [1.1 – 1.8]
P/F rate, on assessment	297 [237 – 336]	292 [240 – 342]	302 [236 – 337]
Hemodialysis n (%) on assessment	4 (6.7%)	0 (0%)	4 (9.3%)

Legend.
Data are presented as count (percentage, %) or median (interquartile range, IQR). The subpopulation of neurological participants is n=42 (70%).
BMI: body mass index; **CNS**: central nervous system; **GCS**: glasgow Coma scale; **HIV**: human immunodeficiency virus; **ICU**: intensive Care unit; **P/F ratio**: ratio between the partial pressure of arterial oxygen (PaO_2) and the fraction of inspired oxygen (FiO_2); **RASS**: Richmond Agitation-Sedation Scale; **SAH**: systemic arterial hypertension; **SAPS3**: simplified acute physiology score 3; **SOFA**: sequential organ failure assessment.

ROC curve analysis for SDT indicated considerable diagnostic performance for screening probable CIPNM via peroneal nerve assessment (AUC = 0.8, 95% CI: 0.7–0.8, $p < 0.001$). Similarly, ROC curve analysis for SET revealed fair performance for screening probable CIPNM (AUC = 0.7, 95% CI: 0.6–0.8, $p = 0.001$). The difference between the two ROC curves was not statistically significant ($Z = 0.92$, $p = 0.35$, DeLong test) (Figure 3).

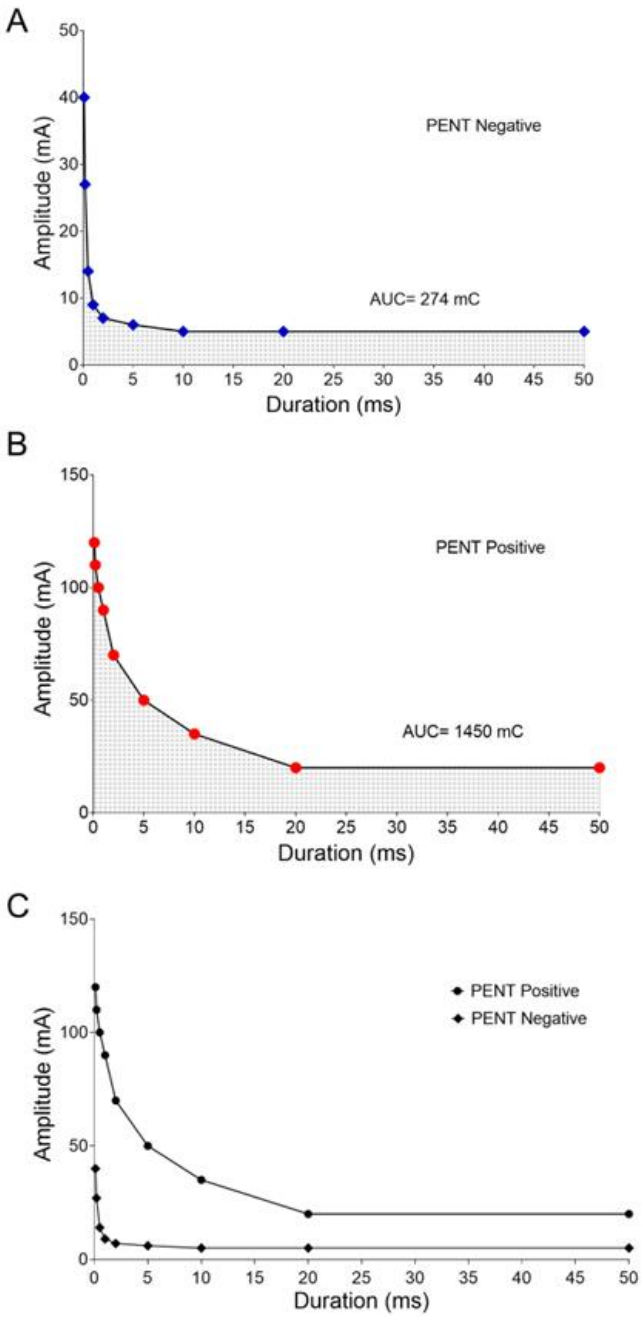
Figure 3. Receiver Operating Characteristic Curves Illustrating the Discriminative Power of SET and SDT for Detecting CIPNM.



Legend.
For the SDT, the optimal cutoff point was identified at 600 mC (indicated by the black line representing its ROC curve), demonstrating an AUC of 0.8 (95% CI: 0.7–0.8, $p < 0.001$). The SET's ROC curve (traced line) yielded an AUC of 0.7 (95% CI: 0.6–0.8, $p = 0.001$).
ROC: receiver operating characteristic; **SET**: stimulus electrodiagnosis test; **SDT**: strength-duration test.

The exploratory analysis identified an optimal cutoff point for the SDT at 600 mC, as determined by Youden's J index ($J = 0.414$). This threshold maximizes the difference between the true positive rate and the false positive rate, thereby representing the point of optimal balance between sensitivity and specificity. The diagnostic metrics from the identified cutoff for diagnostic screening of CIPNM are presented in Table 2. Representative examples are presented in Figure 4, where participants with a negative PENT demonstrated a lower electrical charge compared to those with a positive PENT.

Figure 4. Representative examples of SDT electrical charges in PENT-negative and PENT-positive participants



Legend.
This figure displays representative Strength-Duration Test (SDT) curves, plotting pulse amplitude (mA) against pulse duration (ms), from individual participants. The shaded region beneath each curve represents the electrical charge, which is calculated as the area under the curve (AUC) derived from the product of pulse amplitude and pulse duration.
Panel A: SDT curve from a participant with a negative PENT result, indicating no CIPNM. **Panel B**: SDT curve from a participant with a positive PENT result, indicating the CIPNM **Panel C**: Overlaid SDT curves from Panels A and B, illustrating the magnitude of the difference in electrical charge between participants with negative and positive PENT results.
mC: millicoulomb; **ms**: milliseconds; **mA**: milliampere; **PENT**: peroneal simplified electrophysiological test; **SDT**: strength-duration test.

The diagnostic metrics for the SET, using the pre-defined chronaxie cutoff of 1 ms, are presented in Table 2.

Table 2. Diagnostic metrics from SET and SDT with PENT as refence test.

Diagnostic Metrics	**SET** value (IC 95%)	**SDT** value (IC 95%)
Cutoff point	Chronaxie >1 ms (Pre-defined)	EC > 600 mC (Exploratory)
Sensitivity	95% (87-98%)	73% (61-82%)
Specificity	29% (17-45%)	68% (53-81%)
Accuracy	70% (61-79%)	71% (62-79%)
PPV	69% (59-78%)	79% (67-88%)
NPV	79% (52-92%)	60% (46-74%)
PLR	1.3 (1.09-1.65)	2.3 (1.4-3.8)
NLR	0.2 (0.05-0.55)	0.4 (0.2-0.6)

Legend.

SET: stimulus electrodiagnosis test; **SDT**: strength-duration test; **PENT**: peroneal simplified electrophysiological test; **PPV**: positive predictive value; **NPV**: negative predictive value; **PLR**: positive likelihood ratio; **NLR**: negative likelihood ratio.

Safety and Feasibility

Sixty participants were recruited, providing for a maximum of 120 SET and SDT assessments. Of these, 101 assessments were successfully completed. Only 19 (16%) of the planned PENT, SET and SDT assessments were not performed due to clinical contraindications or practical limitations, as outlined in the study flow diagram (Figure 1). No adverse events, including skin burns, were observed. The mean preparation and execution times were 8.1 (± 0.9) minutes for SET and 10.6 (± 1.4) minutes for SDT, respectively. All initiated assessments have been completed.

DISCUSSION

Our study provides crucial insights into the utility of the SDT as a diagnostic screening tool for probable CIPNM, particularly when assessed at the peroneal nerve. While both SDT and SET demonstrated acceptable diagnostic performance, with SDT exhibiting a numerically superior AUC, this difference was not statistically significant. Nevertheless, SDT emerged as a more

balanced test, characterized by higher specificity and accuracy, positioning it as a valuable adjunct in early CIPNM detection.

A key methodological strength of our approach is the precise focus on the peroneal nerve and the *extensor digitorum brevis* muscle, coupled with the identification of a specific positive cutoff. The peroneal nerve is particularly relevant as it is frequently an early site of CIPNM axonopathy due to its anatomical and physiological characteristics [15,21]. This targeted assessment offers greater precision than broad applications of a single muscle excitability threshold, which, as highlighted by Paternostro-Sluga et al. [20], may lack the necessary sensitivity for reliable detection in the heterogeneous critical care environment. Our nerve-specific cutoff point, grounded in neurophysiological principles, aims to overcome this limitation, offering a more accurate and contextually relevant diagnostic threshold [29,30].

Paternostro-Sluga et al. (2002) [20] posited that SDT, by evaluating the entire strength-duration curve beyond the isolated chronaxie point, would be more robust in identifying neuromuscular excitability dysfunctions than SET. This hypothesis stems from the potential for chronaxie to yield falsely normal results in partial denervation, where rapid responses from intact nerve fibers could mask underlying denervated muscle damage. Although our study found no statistically significant difference in diagnostic power (AUC) between SDT and SET, SDT's improved balance between sensitivity and specificity is clinically significant. It is important to recognize that SET effectively represents a single point on the broader SDT curve. Therefore, SDT does not merely serve as a surrogate but rather encompasses and complements SET, offering a more comprehensive assessment. However, SET remains critical for both screening and guiding neuromuscular electrical stimulation (NMES) prescription [31,32].

The feasibility and safety of SDT in the ICU have gained traction in recent literature [33,34]. Our findings further corroborate that SDT and SET are safe and feasible, even demonstrating that these tests can be performed effectively by individuals with short training time, as demonstrated by Amaro et al. (2019) [35]. This broadens the potential for widespread adoption in resource-limited settings or for routine monitoring by various healthcare professionals. However, a crucial aspect requiring standardization for inter-study comparability is the range of pulse duration markers utilized in SDT construction. Our study used pulse durations up to 50 ms, contrasting with Fagoni et al. (2021) [34] who extended to 0.45 ms, and Silva et al. (2023) [33] up to 500 ms. Harmonizing these methodological parameters is essential for facilitating robust comparisons and meta-analyses.

Our research also advances a novel quantitative approach: using the SDT curve to objectively quantify changes in neuromuscular excitability through the calculation of electrical charge. A higher calculated electrical charge directly correlates with worsening neuromuscular excitability [17]. Like SET, this method functions as a screening tool and is not intended for definitive confirmation of critical illness polyneuropathy (CIP) or critical illness myopathy (CIM) [16]. However, this distinction is often challenging even with conventional electroneuromyography (ENMG) in the ICU. ENMG itself has limitations in early ICU assessment [21]: CMAPs occur in both axonopathy and myopathy; sensory nerve action potentials (SNAPs), while useful for CIP, do not rule out myopathy and can be obscured in critically ill patients [15,21]. Furthermore, motor changes often precede sensory deficits [36], and needle electromyography is frequently unfeasible for uncooperative patients [37]. Given the frequent co-occurrence of CIM and CIP [4] and the difficulty of their early differentiation [38], detecting any peripheral neuromuscular disorder is sufficient for initial screening in the early phase of CIPNM [39]. The portability, cost-effectiveness, and ease of operation inherent to SDT and SET make them ideal for both initial screening and serial monitoring of CIPNM's dynamic behavior and response to therapy. Moreover, the charge-dependence of neuromuscular excitability reinforces SDT's potential to guide precise, individualized NMES dosing in the ICU [17], moving beyond generic treatment regimens.

These findings carry significant clinical implications. The dynamic nature of critical illness profoundly alters drug pharmacokinetics and pharmacodynamics, leading to marked inter-individual variability. Similarly, the altered neuromuscular excitability highlighted by SDT underscores the inadequacy of a 'one-size-fits-all' approach. For instance, early aggressive NMES could be beneficial for patients with rapidly declining excitability, while de-escalation might be necessary for others. This reinforces the imperative for precision medicine in critical care, advocating for individualized strategies to optimize outcomes.

Our study acknowledges several limitations. We did not confirm CIPNM through nerve and muscle biopsy, which was unavailable, nor via needle electromyography, often unfeasible in non-cooperative patients [13]. However, the PENT served as our validated reference standard with high sensitivity for CIPNM [15,40]. Being a cross-sectional study, it inherently precludes the assessment of CIPNM incidence or the longitudinal behavior of these tests over time. It is crucial to acknowledge that the post-hoc determination of a test's positivity cutoff to maximize its observed performance carries a significant risk of yielding over-optimistic accuracy estimates, a concern particularly pronounced in studies with limited sample sizes [22].

Future multicenter prospective studies with larger cohorts are essential to validate the found cutoff point and refine the applicability and precision of SDT for CIPNM screening. Such research should incorporate serial assessments to monitor disease progression and therapeutic responses longitudinally. Ultimately, correlating these kinetic profiles and diagnostic metrics with hard clinical endpoints, such as mortality, organ support-free days, or duration of mechanical ventilation, will be crucial to firmly establish their ultimate clinical relevance and impact on patient care.

Our study confirmed the SDT as a potential tool for the diagnostic screening of probable CIPNM. Compared to the SET, SDT demonstrates a more balanced diagnostic profile with superior specificity and accuracy. These findings underscore the potential of SDT to guide individualized therapeutic strategies in the ICU. Future research should focus on its longitudinal monitoring capabilities and clinical outcome correlations to further enhance critical care management.

Abbreviations

AUC	Area under curve
CMAP	Compound muscle action potential
ENMG	Electroneuromyography
SNAP	Sensory nerve action potential
PENT	Peroneal simplified electrophysiological test
SET	Stimulus electrodiagnosis Test
SDT	Strength-duration Test
NCS	Nerve conduction study
nEMG	Needle-electromyography
CIP	Critical illness polyneuropathy
CIM	Critical illness myopathy
CIPNM	Critical illness polyneuromyopathy
ICUAW	Intensive care unit-acquired weakness
PICS	Post-intensive care syndrome
CNS	Central nervous system
ICU	Intensive care unit
SAPS 3	Simplified acute physiology Score 3
SOFA	Sequential organ failure assessment

BMI	Body mass index
GCS	Glasgow coma scale
RASS	Richmond agitation-sedation scale
MV	Mechanical ventilation
ROC	Receiver operating characteristic

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Author contributions

Concept and Design: JRDM and PES. Acquisition, analysis, and interpretation of the data: all authors. Drafting the manuscript: JRDM, PES, and EFM. Graphics: JRDM, PES, and EFM. Critical revision of the manuscript for important intellectual content: all authors. Supervision: RNMF and EFM. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of HB/IGESDF, under protocol number 5.731.715. Written informed consent was obtained from the closest responsible family member for each included participant.

Consent for publication

Written informed consent for publication was obtained.

Competing interests

Author PES holds patents in neuromuscular electrical stimulation, has equity in Visuri SA, and serves as a scientific advisor for the company. The remaining authors declare no relevant conflicts of interest.

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INTRODUCTION

Critical illness polyneuropathy (CIP) is the most prevalent peripheral polyneuropathy encountered in the intensive care unit (ICU).1 Characterized by distal, symmetrical sensory-motor axonopathy, CIP affects both limbs and respiratory muscles.2 It frequently manifests simultaneously with critical illness myopathy (CIM)2 and has been collectively termed critical illness polyneuromyopathy (CIPNM).3 CIPNM constitutes the main cause of ICU-acquired weakness (ICUAW).4 With a high incidence, ICUAW leads to significant long-term consequences and increased mortality.4 Timely diagnosis of CIPNM is therefore crucial, as emerging evidence highlights the benefits of early ICU rehabilitation.4

However, definitive diagnosis of CIP and/or CIM remains challenging within the ICU setting.5 For this reason, the comprehensive term CIPNM is employed in this study to describe these conditions.

--Manuscript Draft--

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Abstract:	Objective: This study aimed to analyze the diagnostic metrics of the Stimulus Electrodiagnosis Test (SET), including the optimal chronaxie cutoff point for the common peroneal nerve, as an early bedside screening tool for critical illness polyneuromyopathy (CIPNM). Design: A prospective, cross-sectional study was conducted with adult mechanically ventilated intensive care unit (ICU) participants. A single bilateral assessment per participant included the peroneal simplified electrophysiological test (PENT) as the reference, and SET as the index test. A receiver operating characteristic (ROC) curve was constructed to determine the optimal chronaxie cutoff point, and SET's accuracy, sensitivity, specificity, predictive values, and likelihood ratios were determined. Results: From sixty participants, 101 assessments were performed. SET's AUC was 0.7 (95% CI: 0.59–0.81, p=0.001), with an optimal chronaxie cutoff of 1.8 ms. At this cutoff, SET showed 71% accuracy, 90% sensitivity, and 42% specificity for CIPNM screening. Conclusions: Analysis of common peroneal nerve chronaxie using SET presents a promising alternative for accurate early diagnostic screening of CIPNM.

Title

Diagnostic accuracy of common peroneal nerve chronaxie for early screening of critical illness polyneuromyopathy: a prospective, cross-sectional study

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Running title: Diagnostic test for Critical Illness Polyneuromyopathy

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Competing interests

Author PES holds patents in neuromuscular electrical stimulation, has equity in Visuri SA, and serves as a scientific advisor for the company. The remaining authors declare no relevant conflicts of interest.

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Abstract

Objective: This study aimed to analyze the diagnostic metrics of the Stimulus Electrodiagnosis Test (SET), including the optimal chronaxie cutoff point for the common pe
oneal nerve, as an early bedside screening tool for critical illness polyneuromyopathy (CIPNM).

Design: A prospective, cross-sectional study was conducted with adult mechanically ventilated intensive care unit (ICU) participants. A single bilateral assessment per participant included the peroneal simplified electrophysiological test (PENT) as the reference, and SET as the index test. A receiver operating characteristic (ROC) curve was constructed to determine the optimal chronaxie cutoff point (Youden test), and SET's accuracy, sensitivity, specificity, predictive values, and likelihood ratios were determined.

Results: From sixty participants, 101 assessments were performed. SET's AUC was 0.7 (95% CI: 0.59–0.81, p=0.001), with an optimal chronaxie cutoff of 1.8 ms. At this cutoff, SET showed 71% (62-75%) accuracy, 89% (79-85%) sensitivity, and 42% (28-58%) specificity for CIPNM screening.

Conclusions: Analysis of common peroneal nerve chronaxie using SET presents a promising alternative for accurate early diagnostic screening of CIPNM.

Keywords: Chronaxie; Critical Illness Polyneuropathy; ROC curve; Critical Care.

What is Known

Early diagnosis of critical illness polyneuromyopathy (CIPNM) is vital for rehabilitation but remains challenging. The Stimulus Electrodiagnosis Test (SET) has been used for early screening, yet its diagnostic metrics and previously established cutoff points for CIPNM screening have not been adequately studied.

What is New

This study provides insights into SET's utility as a CIPNM screening tool. It offers a new, more balanced cutoff point (1.8ms) and comprehensive diagnostic metrics (accuracy, sensitivity, specificity), establishing a basis for its clinical application.

INTRODUCTION

Critical illness polyneuropathy (CIP) is the most prevalent peripheral polyneuropathy encountered in the intensive care unit (ICU).[1] Characterized by distal, symmetrical sensory-motor axonopathy, CIP affects both limbs and respiratory muscles.[2] It frequently manifests simultaneously with critical illness myopathy (CIM)[2] and has been collectively termed critical illness polyneuromyopathy (CIPNM).[3] CIPNM constitutes the main cause of ICU-acquired weakness (ICUAW).[4] With a high incidence, ICUAW leads to significant long-term consequences and increased mortality.[4] Timely diagnosis of CIPNM is therefore crucial, as emerging evidence highlights the benefits of early ICU rehabilitation.[4]

However, definitive diagnosis of CIP and/or CIM remains challenging within the ICU setting.[5] For this reason, the comprehensive term CIPNM is employed in this study to describe these conditions. While electroneuromyography (ENMG), particularly needle electromyography, can differentiate CIP and/or CIM in cooperative, clinically stable patients, its utility in ICU patients is limited or even infeasible.[5] Furthermore, ENMG is time-consuming, requires specialized equipment, and necessitates physicians with a high level of neurophysiology expertise.[6] Routine muscle and nerve biopsy is often unfeasible, as electrophysiological disturbances frequently precede detectable structural alterations.[1] As a result, early diagnosis of CIPNM in sedated or non-cooperative patients is often impractical, leading to delays in diagnosis and interventions.[7]

To address these diagnostic limitations, simplified bedside screening tests have been actively explored for use in the ICU. The peroneal simplified electrophysiological test (PENT), a nerve conduction study (NCS) of the common peroneal nerve, demonstrates high sensitivity for screening CIPNM.[6,8] However, PENT presents some practical barriers: devices to perform PENT are commonly unavailable in ICU settings and the procedure also necessitates specialized physician expertise. Thus, researchers have long sought solutions to diagnose neuromuscular electrophysiological dysfunction.[9–11] In this context, the stimulus

electrodiagnosis test (SET) has emerged as a cost-effective and feasible alternative for early screening of CIPNM.[9,10] The aim of SET is to assess neuromuscular electrophysiological dysfunction from responses evoked by pre-defined electrical stimuli. Two sequential points on the strength-duration curve need to be detected during SET: the rheobase and chronaxie, where chronaxie values can indicate neuromuscular electrophysiological dysfunction.[12] . First defined by Lapicque in 1909, chronaxie consists of the minimum pulse duration required to excite neuromuscular tissue using a pulse amplitude twice that of the rheobase[13]. Innervated muscles exhibit very short chronaxies compared to denervated muscles (neuropathy).[12] Similarly, lesions directly affecting muscle fibers (myopathy) alter sarcolemma excitability, resulting in a decreasing in muscle excitability.[5] With SET, similar to PENT, it is not possible to differentiate CIP from CIM, only to detect the presence of neuromuscular electrophysiological dysfunction.[12]

Paternostro-Sluga et al.[12] demonstrated the high sensitivity of chronaxie for diagnosing muscle denervation in outpatients using ENMG as the reference test. However, their study was not designed to assess diagnostic accuracy in CIPNM and assumed a pre-specified positive cutoff point for chronaxie in neuropathies of 1 ms (i.e., 1000 μs). Despite this gap in proper SET validation for early CIPNM assessment, researchers and clinicians have applied this test in critically ill patients.[9,14] Consequently, the screening of CIPNM using SET may have been underestimated or overestimated.[15]

Therefore, the primary aim of the present study is to evaluate the SET's diagnostic metrics and determine its optimal cutoff point for screening CIPNM. The study hypothesized that SET can serve as an accurate, safe, and feasible point-of-care tool for screening CIPNM.

MATERIALS AND METHODS

Study design

This prospective, cross-sectional study was conducted with critically ill participants in the ICU. The current data constitutes part of a larger ongoing project designed to comprehensively examine CIPNM in mechanically ventilated participants.

Participants

The study population comprised critically ill adult participants (aged ≥18 years, of both sexes) who were sedated for at least 3 days and receiving mechanical ventilation, and who had no history of orthopedic deformities or pre-existing neuromuscular diseases. Patients were excluded if they presented with bilateral lower limb disorders precluding nerve conduction studies (e.g., edema, fractures, amputation, plaster casts, and/or local skin injuries), a Body Mass Index (BMI) >35 kg/m², brain death, current use of neuromuscular blockers, or pregnancy.

The study was conducted at the ICU of a tertiary public reference hospital in the Federal District, Brazil. The study adhered to the Declaration of Helsinki. Ethical approval for the project was obtained from the local ethics committee (HBDF/IGESDF, Brasília/DF, Brazil; Approval Number 5.731.715). Written informed consent was obtained from the legally authorized representative (e.g., closest responsible family member), as all participants were intubated and sedated at the time of enrollment. Participants were consecutively recruited upon meeting the inclusion criteria until the pre-established sample size was achieved.

Test methods

Each participant underwent a single evaluation during an ICU stay. This evaluation included the randomized application of PENT and SET to the lower limbs, performed bilaterally whenever possible. The PENT was designated as the reference test for CIPNM. The SET, serving as the index test, was then evaluated against PENT. The reporting of this diagnostic

accuracy study adhered to the Standards for Reporting Diagnostic Accuracy (STARD) 2015 guidelines.[15]

Primary outcomes

The primary outcomes of the present study were the determination of SET's power and diagnostic accuracy, and the definition of the optimal cutoff for the common peroneal nerve in the diagnostic screening of CIPNM.

Secondary outcomes

Secondary outcomes included the determination and comparison of SET's diagnostic metrics (sensitivity, specificity, predictive values, and likelihood ratios) based on a pre-specified cutoff (1 ms) versus an exploratory (optimal) cutoff point for screening CIPNM in the ICU. Additionally, the safety and feasibility of SET were evaluated. Safety was assessed by monitoring the incidence of skin burns. Feasibility was determined by the time required to complete the SET assessments in the ICU.

Variables

After enrollment, baseline information was collected to characterize the study participants. This included hospitalization diagnosis, Body Mass Index (BMI), Sequential Organ Failure Assessment (SOFA) score, Richmond Agitation-Sedation Scale (RASS), and the presence of sepsis or septic shock.

A purely electrophysiological diagnostic approach for CIPNM was employed via PENT. Its sensitivity for axonopathy has been previously reported to range from 92% to 100%.[6,16]

All participants underwent assessment, with a 30-minute interval between tests. These assessments were performed by two independent examiners: Examiner 1 (JRDM) conducted the PENT, while Examiner 2 (PES) performed the SET. To ensure blinding, examiners did not share results or diagnostic impressions with each other. Each record was analyzed independently.

Peroneal Simplified Electrophysiological Test

Participants underwent bilateral PENT performed by a single trained intensivist physician using a portable electroneuromyograph, ENMG (Neuro-MEP-Micro®, Neurosoft, Russia). The low-pass filter was set at 3 Hz and the high-pass filter at 10 kHz. The device sensitivity and sweep speed were set at 3 mV and 2 ms, respectively. Stimulation was performed at two sites to record distal motor latencies, amplitudes, and to calculate the conduction velocity for each nerve (right and left). Amplitudes were measured from baseline to the negative peak. For testing, surface recording electrodes (Ambu®, WhiteSensor 0315M, Ambu, Denmark) were placed over the belly and tendon of the extensor digitorum brevis. The common peroneal nerve was stimulated over the anterior region of the ankle, slightly lateral to the tendon of the tibialis anterior muscle, 6 to 8 cm from the recording electrodes, and below the head of the fibula for motor conduction velocity recording (Figure 1).

Figure 1. Electrode positioning for common peroneal nerve stimulation and assessment

Legend.
Common peroneal nerve stimulation was performed at the anterior ankle, slightly lateral to the tibialis anterior muscle tendon, 6 to 8 cm from the recording electrodes. **(A)**: Stimulation site for the Stimulus Electrodiagnosis Test (SET). **(B):** Stimulation site for the Peroneal Simplified Electrophysiological Test (PENT) assessment.

Incremental electrical stimulation of the common peroneal nerve was applied until optimal compound muscle action potential (CMAP) amplitudes were obtained, with motor conduction velocity and latency duly recorded. All participants were in a supine position with a 30° head-of-bed elevation and lower limbs fully extended.

Diagnostic Criteria for CIPNM

The electrodiagnostic criteria for CIPNM were predefined based on the following parameters: CMAP amplitudes falling 80% below Katirji's normative values[17] (i.e., ≥3 mV for ages 20-50 years; ≥2.5 mV for ages 51-90 years) were considered abnormal.[8,16] The pattern of axonopathy of motor conduction velocity was assessed using Tan's[18] criteria (80% above the lower limit of normal if CMAP was <50% of normal, or 90% above if CMAP was >50% of normal). The electrodiagnostic findings for CIPNM are characterized by a decrease in CMAP amplitude with nerve conduction velocities that were either normal or subtly impaired.[19]

Stimulus Electrodiagnosis Test

SET was performed using a bedside neuromuscular electrical stimulator (Recare®, Visuri, Brazil). These tests aimed to assess the neuromuscular excitability of the common peroneal nerve and extensor digitorum brevis muscle in response to electrical stimuli. SET was conducted by applying incremental electrical stimuli to elicit a minimal visible contraction. Two circular electrodes, 3 cm in diameter (ValuTrode®, Axelgaard, Denmark), were positioned over the dorsum of the foot, near the ankle, with the objective of exciting the common peroneal nerve. This electrode positioning adhered to the recommendations by Latronico et al.[6] (Figure 1). All participants were in a supine position with a 30° head-of-bed elevation and their lower limbs fully extended. During SET, neuromuscular electrophysiological dysfunction was quantified through the measurement of rheobase and chronaxie. Rheobase is defined as the minimal current intensity required to elicit a neuromuscular excitation threshold when delivered as a rectangular pulse of long duration (e.g., > 200 ms). Chronaxie is the shortest pulse duration

necessary to reach this neuromuscular excitation threshold using a current amplitude that is twice the rheobase.[9] Rheobase and chronaxie measurements were performed using a single, rectangular, biphasic, and symmetric electrical pulse. For rheobase assessment, the current amplitude was progressively increased from 1 to 240 milliampere peak-to-peak (mAp-p) in 1 mAp-p increments until a minimal visible muscle contraction was elicited. During this assessment, a pulse duration of 500 milliseconds (ms) and an inter-pulse interval of 2 seconds were utilized. For chronaxie assessment, the current amplitude was set to twice the rheobase value. Subsequently, the pulse duration was increased from 0.1 ms to 500 ms in 0.1 ms increments until a minimal visible muscle contraction was observed.[20] The pre-specified chronaxie cutoff was at 1 ms, based on Paternostro et al.[12] An exploratory rationale was used to define the optimal SET cutoff for CIPNM screening in the ICU.

Study size

The sample size calculation was conducted using Power Analysis and Sample Size (PASS) software. This approach rigorously adhered to the established recommendations outlined by Flahault et al.[21] ensuring methodological soundness. This method integrates a variety of crucial statistical parameters: statistical power (1-β), an alpha (α) level, disease prevalence, the null hypothesis, expected sensitivity and specificity, and the maximal distance from sensitivity (δ). The estimated prevalence of neurophysiological abnormalities was benchmarked at 55%.[9] For the statistical framework, a statistical power of 80% was selected, while the alpha level was set at 5% and δ was defined as 25%. The expected sensitivity was established at 80%[12], while specificity was arbitrarily set at 70%, given the absence of corroborative data within the existing academic literature. Accounting for an anticipated dropout rate of 5%, a minimum of 100 tests was required.

Statistical methods

Data normality was assessed using the Shapiro-Wilk test. Non-parametric data were described as medians with interquartile ranges [IQR], while nominal variables were presented as absolute frequencies and percentages.

The diagnostic utility of the tests was characterized using receiver operating characteristic (ROC) curves. This methodology graphically depicts the trade-off between the true positive rate (sensitivity) and the false positive rate (1-specificity) across all potential classification thresholds, thereby elucidating the test's capacity to discriminate individuals with and without the target condition (CIPNM).[22]

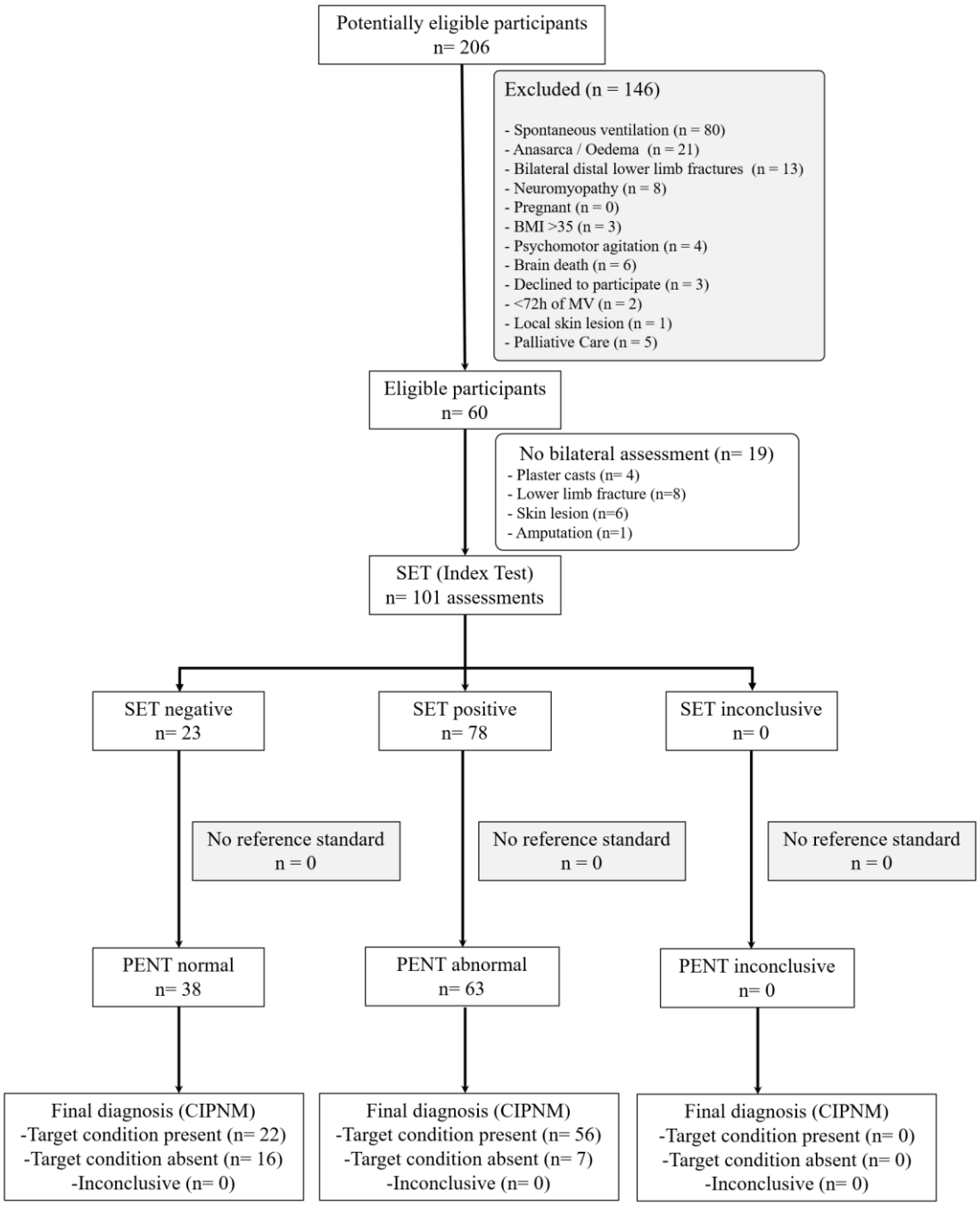
The ROC curve was constructed with the area under the curve (AUC) serving as an aggregate measure of diagnostic accuracy. An AUC of 0.5 indicates discriminatory ability no better than random chance. For interpretative purposes, AUC values were categorized as follows: ≥ 0.9 (Excellent); 0.8 to < 0.9 (Considerable); 0.7 to < 0.8 (Fair); 0.6 to < 0.7 (Poor); and 0.5 to < 0.6 (Fail).[22]

The SET's optimal cutoff point was determined using Youden's J index. The test diagnostic metrics (sensitivity, specificity, predictive values, accuracy, and likelihood ratios) for the optimal cutoff point were calculated with their respective 95% confidence intervals, using Wilson's method for interval estimation. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics (Version 29, IBM Corp., Armonk, NY) and epiR1 package (version 2.0.88) in the R2 software (version 4.5.0).

RESULTS

From April 2024 to June 2025, 206 participants were assessed for eligibility, and 60 were enrolled, resulting in 101 assessments by PENT and SET. Further details are available in the flow diagram (Figure 2).

Figure 2. Standards for Reporting of Diagnostic Accuracy (STARD) flowchart



Legend.
The assessment was performed bilaterally whenever feasible. The SET served as the index test for CIPNM, with the PENT as the reference test.
CIPNM: Critical Illness Polyneuromyopathy; **PENT**: Peroneal Simplified Electrophysiological Test; **SET**: Stimulus Electrodiagnosis Test.

Participants were predominantly adult males, 41 (68%), with a median age of 47 [34 – 58] years. The major cause of ICU admission was central nervous system injury, observed in 47 (70%) of the participants. On the day of assessment, participants had a median of 6 [4-10] days on mechanical ventilation, with a SOFA score of 7 [6 – 9]. More details are presented in Table 1.

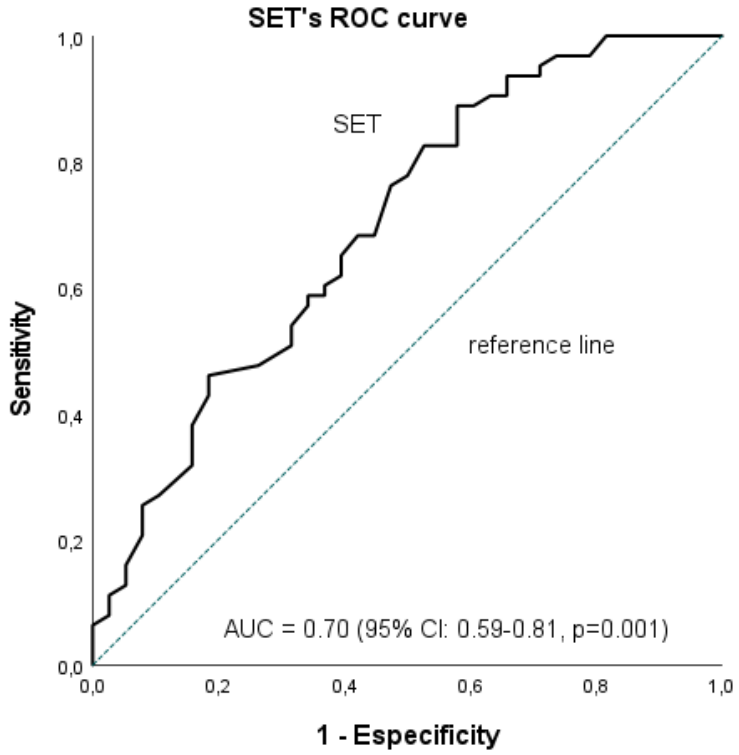
Table 1. Baseline clinical characteristics

Variables	Participants (n=60)	Positive PENT (n=17)	Negative PENT (n=43)
Age, years	47 [34 – 58]	40 [29 – 51]	49 [35 – 59]
Sex, n (%) male	41 (68%)	12 (71%)	29 (67%)
BMI, Kg/m^2	24 [22 – 28]	25 [22 – 30]	24 [21 – 27]
SOFA, on assessment	7 [6 – 9]	9 [6 – 10]	7 [6 – 9]
Reason for ICU admission, n (%)			
Traumatic brain injury	24 (40%)	8 (47%)	16 (37%)
Hemorrhagic stroke	9 (15%)	2 (12%)	7 (16%)
Ischemic stroke	4 (7%)	1 (6%)	3 (7%)
Subarachnoid hemorrhage	2 (3%)	0 (0%)	2 (5%)
CNS Infection	3 (5%)	2 (12%)	1 (2%)
Abdominal trauma	3 (5%)	1 (6%)	2 (5%)
Thoracic trauma	3 (5%)	2 (12%)	1 (2%)
Heart surgery	2 (3%)	0 (0%)	2 (5%)
Myocardial infarction	2 (3%)	0 (0%)	2 (5%)
Cancer	3 (5%)	1 (6%)	2 (5%)
Others	5 (8%)	0 (0%)	5 (12%)
Ventilation days, on assessment	6 [4 – 10]	4 [3.5 – 8]	7 [5 – 12]
ICU length of stay, on assessment	4 [2 -9]	3 [2 – 7]	5 [2 – 10]
Hospital length of stay, on assessment	7 [4 – 12]	5 [4 – 9]	8 [5 – 14]
Sepsis, n (%)	50 (83%)	14 (82%)	36 (84%)
Septic Schock, n (%)	24 (40%)	8 (48%)	16 (37%)
RASS score, on assessment	-5 [-5 – -5]	-5 [-5 – -5]	-5 [-5 – -5]
Norepinephrine n (%)	24 (40%)	8 (48%)	16 (37%)
• dosage (mcg/kg/min	0.13 [0.1 – 0.4]	0.13 [0.1 – 0.5]	0.12 [0.1 – 0.3]

Legend.
Data are presented as count (percentage) or median [interquartile range]. **BMI**: Body Mass Index; **SOFA**: Sequential Organ Failure Assessment; **ICU**: Intensive Care Unit; **CNS**: Central Nervous System; **RASS**: Richmond Agitation-Sedation Scale.

ROC curve analysis for SET revealed a fair performance for screening CIPNM via common peroneal nerve assessment (AUC = 0.7, 95% CI: 0.59–0.81, p = 0.001) (Figure 3).

Figure 3. Receiver operating characteristic curve of the stimulus electrodiagnosis test



Legend.
The ROC curve depicts the trade-off between the true positive rate (sensitivity) and the false positive rate (1-specificity) across all potential classification thresholds, elucidating the test's capacity to discriminate individuals with and without the target condition, CIPNM. The PENT served as the reference test.
CIPNM: Critical Illness Polyneuromyopathy; **PENT**: Peroneal Simplified Electrophysiological Test; **SET**: Stimulus Electrodiagnosis Test; **ROC**: Receiver Operating Characteristic; **AUC**: Area Under the Curve.

The optimal cutoff point defined for the AUC generated by the SET was 1.8 ms (J= 0.31, Youden's J index). This optimal cutoff equalizes the difference between the true positive rate and the false positive rate, corresponding to the point of best balance between sensitivity and specificity. The diagnostic metrics from the SET's identified optimal cutoff, compared to the pre-specified cutoff (1 ms), are presented in Table 2.

Table 2. Diagnostic Metrics of the Stimulus Electrodiagnosis Test for Critical Illness Polyneuromyopathy Screening

Diagnostic metrics	**SET** value (IC 95%)	
	Chronaxie >1 ms (Pre-defined)	Chronaxie >1.8 ms (exploratory)
Sensitivity	95% (87-98%)	89% (79-85%)
Specificity	29% (17-45%)	42% (28-58%)
Accuracy	70% (61-79%)	71% (62-79%)
PPV	69% (59-78%)	72% (61-81%)
NPV	79% (52-92%)	70% (49-84%)
PLR	1.3 (1.09-1.65)	1.5 (1.15-2.04)
NLR	0.2 (0.05-0.55)	0.3 (0.12-0.58)

Legend.
PENT was the reference test, and SET was the index test. For the calculation of diagnostic metrics, two SET cutoff points were established: a pre-specified one (≥1 ms) and an exploratory optimal cutoff point, determined post-hoc (≥1.8 ms).
CIPNM: Critical Illness Polyneuromyopathy; **SET**: Stimulus Electrodiagnosis Test; **PENT**: Peroneal Simplified Electrophysiological Test; **PPV**: Positive Predictive Value; **NPV**: Negative Predictive Value; **PLR**: Positive Likelihood Ratio; **NLR**: Negative Likelihood Ratio.

Safety and Feasibility

A total of 60 participants were recruited, allowing for a potential of 120 SET assessments. Of these, 101 assessments were successfully performed. Only 19 (16%) of the planned SET assessments were not conducted due to clinical contraindications or practical limitations, as previously detailed in the flow diagram (Figure 1). No skin burns or other adverse events were observed. The mean time required for participant preparation and execution of SET was 8.1 (± 0.9) minutes. All initiated assessments have been completed.

DISCUSSION

The present study provides insights into the usefulness of the SET as a diagnostic screening tool for CIPNM, precisely assessed at the common peroneal nerve. It was demonstrated that SET presents an adequate diagnostic performance with high sensitivity and fair accuracy. Compared to a predefined cutoff, the new optimal cutoff point emerged as more balanced and specific.

Although the diagnostic accuracies were nearly coincident, marginally favoring the 1.8 ms threshold (71% vs. 70%), the 1 ms threshold demonstrated significantly diminished specificity (29% vs. 42%). This reduction in specificity invariably leads to a higher incidence of false positives, which subsequently necessitates additional, potentially superfluous, confirmatory tests (such as ENMG). Such a situation not only increases healthcare costs but can also inflict undue distress upon patients and their families.[23] While maximizing sensitivity is a paramount objective for any screening diagnostic tool to avoid false negatives, 89% (79-85%) sensitivity of the 1.8 ms threshold represents a robust indicator for an effective screening test,

adept at identifying most affected individuals in the screened cohort via a non-invasive and inexpensive approach.[23] Therefore, the 1.8 ms optimal cutoff for the common peroneal nerve emerges as a more balanced cutoff between sensitivity and specificity, providing a more effective screening for CIPNM than 1 ms.[22]

The landmark study on SET diagnostic metrics published by Paternostro-Sluga et al.[12] presents some external validity barriers for its use in the ICU. These authors did not comprehensively study SET diagnostic metrics, focusing only on sensitivity; moreover, no participant was critically ill, and they assessed several nerves. The present study, however, focused on the common peroneal nerve, a well-known nerve susceptible to neuropathy in the ICU, and aimed to determine all diagnostic metric outputs. This focus increases the external validity of the present results, facilitating the incorporation of this test into clinical practice.

A significant methodological strength of the present study lies in its decision to focus on the common peroneal nerve and extensor digitorum brevis muscle, thereby establishing a specific cutoff. The common peroneal nerve is a prominent motor nerve in the lower limbs and, due to its characteristics (length, thickness, and low tolerance to hypoxia), is often affected early by axonopathy in the ICU.[8,16] It acts as a sentinel nerve, making it an ideal target for electrophysiological monitoring in critically ill patients.[8] The generalization of a single cutoff

point across all nerves, while appealing for broad screening, may lack the precision necessary for reliable detection of neuromuscular electrophysiological dysfunction in specific areas. A specific threshold for a particular nerve may provide a more accurate and contextualized diagnostic tool. This aligns with findings from Ferris et al.[24] and long-recognized neurophysiological principles that acknowledge nerve-specific distinct thresholds.[25]

SET is presented solely as a diagnostic screening tool and cannot confirm CIP, CIM, or CIPNM or substitute ENMG. However, SET may serve as a surrogate method, as ENMG faces barriers to definitive diagnosis in the early ICU phase due to severe, non-cooperative patients.[5] Reduced CMAPs occur in both axonopathy and myopathy; while reduced sensory nerve action potentials (SNAP) can confirm CIP, they do not exclude CIM and may be masked by ICU conditions.[6] Motor changes often precede sensory changes[5] and n-EMG may present normal or minimal changes in the initial phase common to both conditions.[1] Moreover, CIM and CIP are normally associated, and their differentiation does not appear to be significantly relevant in the ICU.[8,26] In this context, early detection of neuromuscular electrophysiological dysfunction provided by SET might be sufficient for initial screening and follow-up of CIPNM.[9] This claim has gained traction and has already been demonstrated in critically ill patients and in outpatients.[10,11,27] In a prospective study, Silva et al.[9] assessed critically ill patients using SET during mechanical ventilation and demonstrated a significant increase of chronaxie. The presence of neuromuscular electrophysiological dysfunction was associated with a worsening in muscle architecture via ultrasonography. Similarly, Fernandes et al.[27] demonstrated that chronaxie can be a sensitive parameter for monitoring neuromuscular responses in the ulnar nerve after neurorrhaphy in outpatients.

Study Limitations

Among the limitations of the present study, systematic confirmation of CIPNM with n-EMG was not performed, due to a focus on early-phase assessments in non-cooperative patients.[5] However, the diagnosis of neuromuscular electrophysiological dysfunction appears sufficient for monitoring and treatment of critically ill patients.[6] In this context, PENT, which served as the reference test, appears appropriate, as it possesses high sensitivity for diagnosing neuromuscular electrophysiological dysfunction.[6] Finally, the STARD guideline warns that if a test's optimal cutoff is determined post-hoc, its observed diagnostic performance involves risks of generating overly optimistic accuracy estimates.[15]

Future Perspectives

Future multicenter prospective studies, with larger samples and serial assessments, are crucial to further document SET's applicability in the ICU, both as a diagnostic screening test and for neuromuscular electrophysiological dysfunction monitoring.

CONCLUSIONS

The present study demonstrates that a new optimal SET cutoff for the common peroneal nerve can be accurate and highly sensitive for early diagnostic screening of CIPNM. The results should be interpreted with caution, as the optimal cutoff was determined using a post-hoc methodology. Further larger trials are needed to assess the external validity of these findings.

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Author contributions

Concept and Design: JRDM and PES.

Data Acquisition, Analysis, and Interpretation: All authors.

Manuscript Drafting: JRDM, PES, and EFM.

Graphics: JRDM and PES.

Critical Revision of the Manuscript for Important Intellectual Content: All authors.

Supervision: PES, RNMF, and EFM.

All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of HBDF/IGESDF, under protocol number 5.731.715. Written informed consent was obtained from the closest responsible family member for each included participant.

Consent for publication

Written informed consent for publication was obtained.

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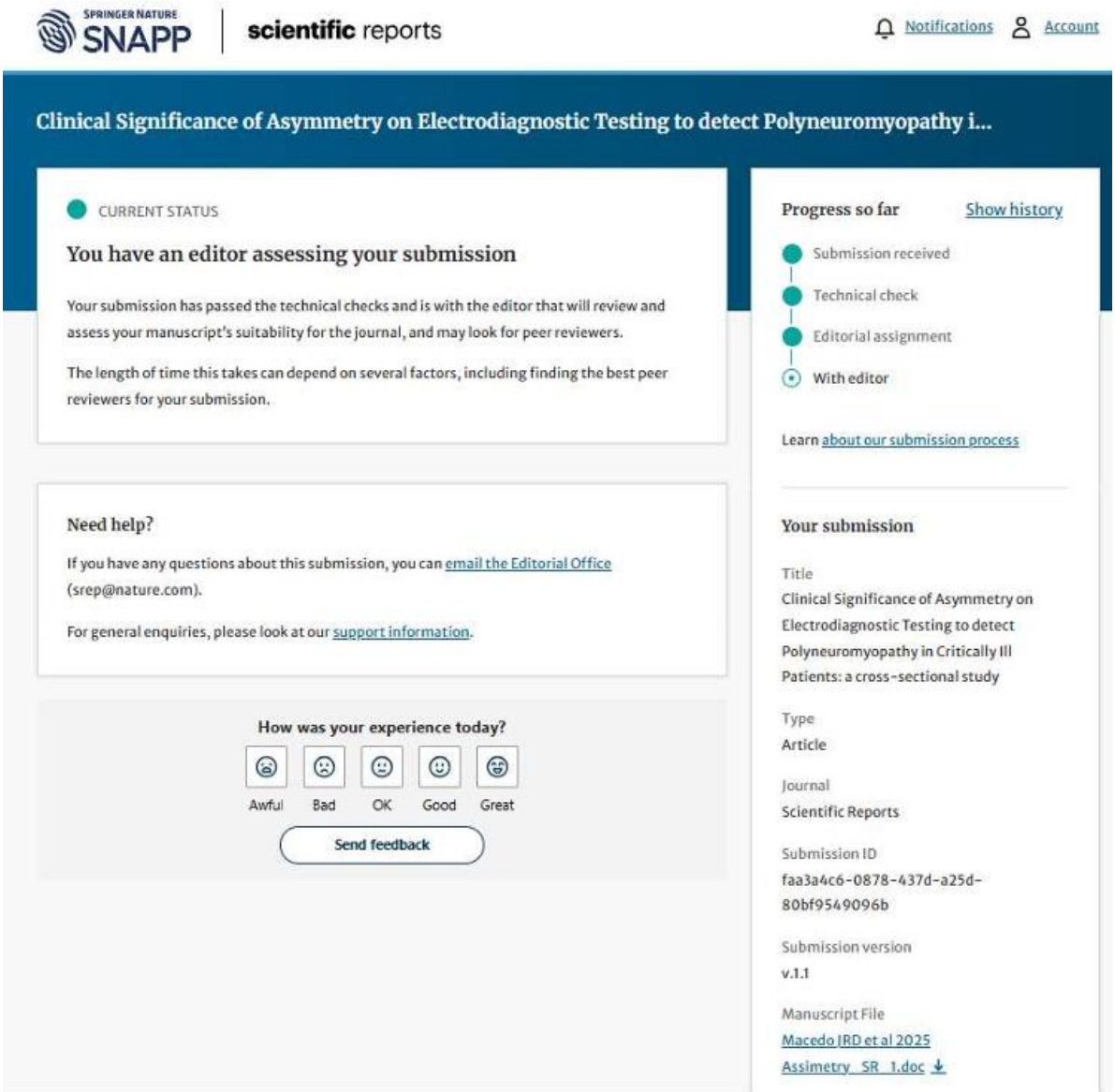

Clinical Significance of Asymmetry on Electrodiagnostic Testing to detect Polyneuromyopathy in Critically Ill Patients: a cross-sectional study

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Abstract

Background: In search of simplified nerve conduction studies as screening electrophysiological tests in Intensive Care Unit (ICU), previous studies have suggested that unilateral electrophysiological evaluations may be sufficient for screening probable critical illness polyneuro and/or myopathy (CIP/CIM) in ICU - also called as neuromuscular electrophysiological disorder (NED) - since quantitative statistical analyses did not detect significant bilateral differences, at first reinforcing its symmetrical manifestation as established. This study aimed to investigate the presence of asymmetry in the onset of NED and the relevance of bilateral electrophysiological assessments for correct screening to avoid diagnostic and analysis errors. We also investigated possible effects of laterality and focal lesions of the central nervous system on NED. **Methods**: From Abril to October 2024, a cross-sectional observational study of critically ill patients admitted in ICU was conducted. All participants underwent bilateral nerve conduction study for the motor peroneal nerve to investigate asymmetry. Different from previous studies, bilateral Compound Muscle Action Potential (CMAP) records were analyzed based on the electrodiagnostic criterion for asymmetry. **Results:** 41 patients were enrolled, in which 82 assessments were carried out. NED was identified in 34 (83%) participants. Based on electrodiagnostic criterion, asymmetries were observed in 12 (29%) participants, with diagnostic divergence in 5 (12%), in which NED could be overlooked if the evaluation were unilateral. Patients with NED had a two-fold odds ratio of asymmetry between bilateral electrodiagnostic assessments compared to patients without NED. We also identified a possible match between brain anatomical landmarks and the worst CMAP on the contralateral side, with an attributable risk of 17% in patients with NED. **Conclusion:** This study suggests that electrodiagnostic screening tests for neuromuscular electrophysiological disorders in critically illness participants in ICU should be performed bilaterally to avoid diagnostic error and analysis bias, due to the clinical relevance of asymmetry in the development of this dysfunction. The impact of cerebral laterality and focal brain lesions on electrodiagnostic asymmetry in the early phase of NED needs to be further studied.

Keywords: Bilateral Evaluation, Asymmetry, Compound Muscle Action Potential, Neuromuscular Electrophysiological Disorders, Clinical Diagnosis, Critical Illness Polyneuropathy, Critically Ill Patients.

BACKGROUND

Critical Illness Polyneuropathy (CIP) is recognized as the most prevalent peripheral polyneuropathy in the Intensive Care Unit (ICU) [1–3]. It manifests as a distal sensory-motor axonopathy symmetrically impacts the limbs and respiratory muscles [2]. In conjunction with Critical Illness Myopathy (CIM), which often occurs concurrently [2,4,5], these conditions are identified as principal contributors to intensive care unit-acquired weakness (ICUAW) [6,7]. In turn, this syndrome is described as the main physical manifestation of Post-Intensive Care Syndrome (PICS) [8,9]. The incidence of ICUAW varies between 40% and 57% [10–12], potentially leading to long-term sequelae and correlating with increased mortality rates even following hospital discharge [2,6]. Evidence of clinical and/or neurophysiological axonopathy can persist for up to five years post-discharge [13], with extreme cases resulting in quadriplegia [14].

Emerging evidence suggests that implementing early rehabilitation within the ICU setting can help maintain physical functionality and potentially enhance outcomes for those suffering from ICUAW [15,16]. However, the successful application of early rehabilitation strategies hinges critically upon early diagnostic capabilities. Nerve conduction study (NCS) and needle-electromyography (nEMG) are tools used to differentiate CIP and CIM, as well as from deconditioning, characterized by muscle weakness in the absence of electrophysiological alterations - all of them with different prognoses [17,18]. Nevertheless, nEMG cannot confirm CIM in unconscious patients - under sedation and/or in coma. Moreover, both NCS and nEMG necessitate considerable time, costly equipment, and specialized expertise [2,18]. To address these challenges, simplified screening tests have been proposed for bedside analysis within the ICU [1,19,20]. The nerve conduction study for the motor peroneal nerve is particularly notable for its high sensitivity in screening for probable CIP/CIM [1] - hereafter referred to as neuromuscular electrophysiological disorder (NED)[20]. Studies have reported an absence of statistically significant differences in electrophysiological findings between the right and left sides of the

body, which reinforces the concept of NED's symmetrical manifestation. Consequently, they recommend that screening tests be conducted unilaterally to optimize the cost-benefit ratio [17,21], a practice already adopted in some studies [1,20].

Nevertheless, since the mid-19th century when Paul Broca and Carl Wernicke [22] introduced the concept of cerebral lateralization, numerous evidence have accrued demonstrating that the nervous system exhibits substantial functional asymmetry. Despite disuse-induced immobility caused by coma or sedation affecting both sides of the body equally, it is conceivable that laterality and unilateral central nervous system lesions (e.g., stroke, trauma) could precipitate an initially asymmetric electrophysiological expression of NED, potentially driven by synergistic interactions among distinct injury mechanisms. The hypothesis was that NED, though established as a symmetrical disease, may initially manifest asymmetrically in critically ill patients and this possibility should not be neglected, due to the risk of analysis errors. This study aimed to investigate the presence of asymmetry in NED development and the relevance of conducting bilateral electrophysiological assessments for its diagnostic screening in critically ill patients in ICU. Moreover, we intended to evaluate the impact of laterality and brain focal lesion on asymmetry.

METHODS

Study design

This research employed a cross-sectional observational study design focusing on critically ill patients admitted to the ICU. It was conducted and reported following the STROBE statement for observational studies [23].

Setting

The study was carried out in a general, surgical and trauma ICU of a tertiary public referral hospital in the Federal District, Brazil. Data collection occurred between April and October

2024. The study received ethical approval from the local ethics committee (HB/IGESDF, Brasília, Brazil, protocol 63620622.2.0000.8153) and adhered to the Declaration of Helsinki. As all participants were intubated and sedated at enrollment, written informed consent was obtained from the closest responsible family member for the patients.

Participants

The study included critically ill participants aged 18 years or older who were admitted to the ICU. All participants had to be sedated and mechanically ventilated for at least three days. Exclusion criteria included pre-existing neuromuscular diseases, detection of peripheral demyelinating neuropathy, use of neuromuscular blocking agents, brain death, pregnancy, a body mass index (BMI) greater than 35 kg/m², orthopedic deformities, or other lower limb conditions (such as edema, fractures, or amputations) that could preclude bilateral nerve conduction studies.

Variables

The primary outcome was to assess the amplitude difference in neuromuscular activation between both sides and detect the presence of asymmetry using electrophysiological criterion. Secondary outcomes involved evaluating whether unilateral anatomical landmarks in the central nervous system - such as ischemia, hemorrhage, or concussion - contributed to asymmetrical reductions in compound muscle action potential (CMAP) and the incidence of NED. Participants' clinical characteristics (age, sex), comorbidities (diabetes, hypertension, chronic obstructive pulmonary disease, etc.), hospitalization diagnosis, severity score - Simplified Acute Physiology Score 3 (SAPS 3), Sequential Organ Failure Assessment score (SOFA), Ramsay Sedation Score, presence of sepsis and septic shock (defined according to Sepsis-3 criteria), and PaO_2/FiO_2 ratio were collected and analyzed.

Nerve Conduction Study of the Motor Peroneal Nerve (PENT)

A purely electrophysiological diagnostic approach for NED was used, via PENT, which has a high sensitivity for detecting NED, ranging from 92% up to 100% [1,17,21,24]. All participants underwent bilateral PENT performed by a single experienced intensivist using a electroneuromyograph (Neuro-MEP-Micro®, Neurosoft, Ivanovo, Russia). The low-pass filter was set at 3Hz and the high-pass filter was set at 10 kHz. Sensitivity and sweep were set at 3 mV and 2 ms, respectively. Stimulation was performed at two sites to record distal motor latencies, record amplitude, and calculate conduction velocity of each nerve. Amplitudes were measured from baseline to negative peak. For testing, surface recording electrodes (Ambu® WhiteSensor 0315M, Ambu, Ballerup, Denmark) were placed over the belly and tendon of the extensor digitorum brevis. The peroneal nerve was stimulated over the anterior region of the ankle slightly lateral to the tendon of the tibialis anterior muscle, 6 to 8 cm from the recording electrodes, and below the head of the fibula for recording motor conduction velocity. Incremental electrical stimulation of the peroneal nerve was applied until the best CMAP amplitudes were obtained, with motor conduction velocity and latency duly recorded.

Diagnostic Criteria for NED

CMAP results 80% below Katirj's normal standard (≥3 mV for age 20-50 years old; ≥2,5 mV for age 51-90 years old) were considered abnormal [25]. Axonopathy-related measures of motor conduction velocity were evaluated by Tan's criteria (80% above lower limit normal, if CMAP <50% of normal; or 90% above, if CMAP >50% of normal)[26]. The expected pattern indicative of NED was axonopathy, characterized by reduction in CMPA amplitude with normal or mildly reduced nerve conduction velocity[2].

Diagnostic Criteria for Asymmetry

We use the electrophysiological criterion for asymmetry which is the CMAP amplitude difference of more than 50% comparing side to side (i.e., a 50% [0,5x] drop from the higher side to the lower or a 100% [2x] increase from the lower side to the higher) [27]. To assess the

bilateral symmetry of CMAPs, we calculated the right/left CMAP records ratio (r/l), and constructed a histogram to visualize the distribution of these ratios and better identify patterns of symmetry and asymmetry. Values in the range between 0.5 and 2 were considered "symmetry" (difference ≤50% between bilateral CMAP records). When the values were exactly the same, we had what we called perfect symmetry (r/l =1.0). Vertical lines were plotted to define a symmetry zone ($0.5 \leq$ ratio ≤ 2) around perfect symmetry (r/l = 1), where the bilateral CMAP amplitudes are considered symmetrical. Thus, "asymmetry" occurred when the ratios were outside this specified interval. Additionally, values outside this range indicate respectively a unfavorable CMAP asymmetry to the right (r/l < 0,5) or left (r/l > 2) side.

All the results were reviewed by an expert neurophysiologist.

Study size

Based on data inferences from our non-publisehd pilot study, a medium effect size (Cohen's d = 0.4) was hypothesized for the difference between groups. An a priori power analysis was conducted using GPower (version 3.1.9.7) for a chi-square goodness-of-fit test on contingency tables. With a significance level (α) of 0.05 and a desired power ($1 - \beta$) of 0.8, the analysis indicated a required sample size of 81 assessments.

Statistical analysis

Given the non-normality of most variables (by the D'Agostino-Pearson test), non-parametric statistical tests were employed. Quantitative results were presented as medians and interquartile ranges, while qualitative variables were described by absolute and relative frequencies of occurrence. To examine differences between quantitative variables was used the Mann-Whitney U test. The Wilcoxon signed-rank test was employed to compare paired quantitative variable data (right versus left sides). Fisher's exact test was used to compare proportions. Statistical differences were considered significant at $p<0.05$.

RESULTS

We enrolled forty-one participants leading to eighty-two assessments (bilateral assessments). Further details are available in the flow diagram (Figure 1).

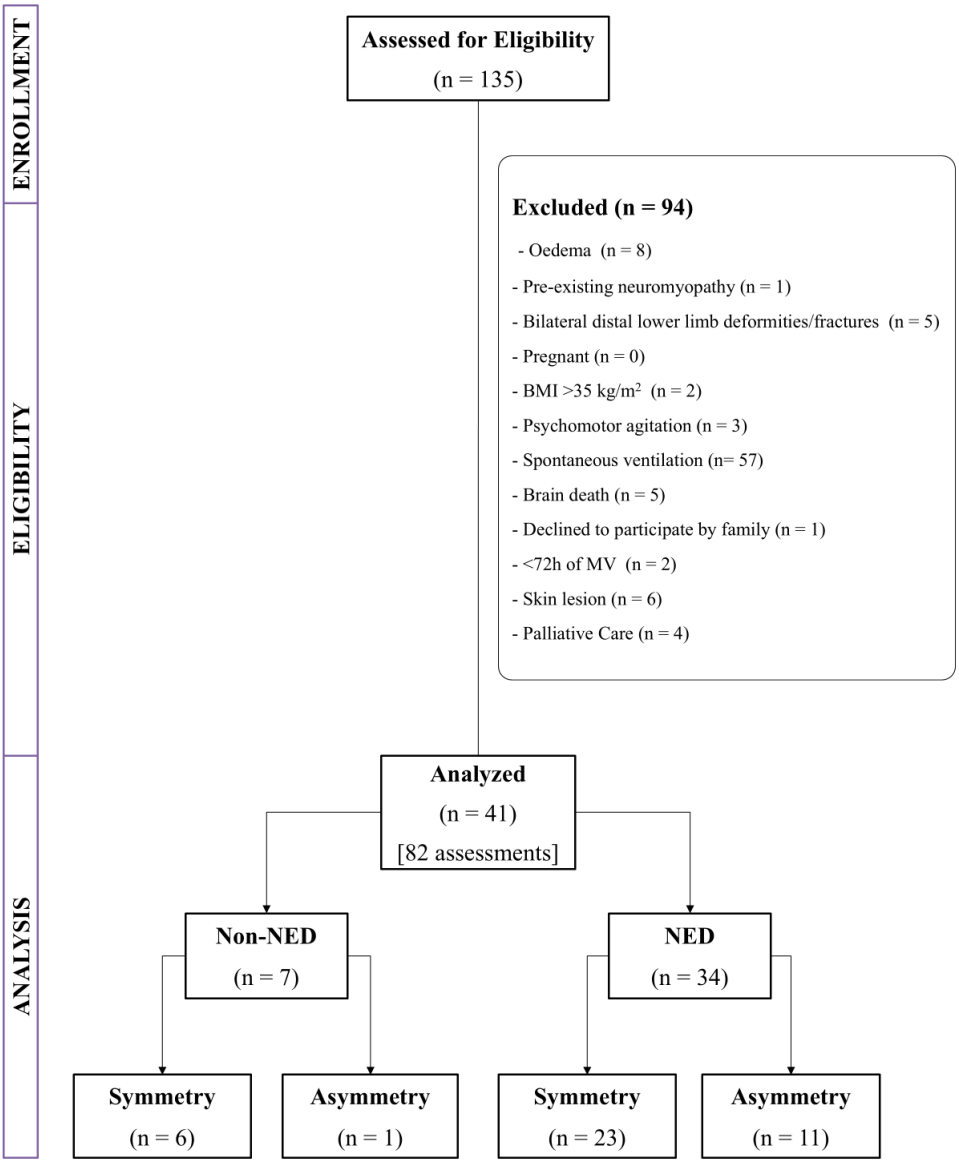


Figure 1. Flowchart. Enrollment, eligibility and analysis.

Legend:
Abbreviations: NED = neuromuscular electrophysiological disorder, Non-NED = without neuromuscular electrophysiological disorder, BMI = body mass index, MV = mechanical ventilation.

Sample characteristics are presented in Table 1.

Table 1. Characterization of the critically ill patients with and without criteria for neuromuscular electrophysiological disorders diagnosis.

Variables	Sample Size (n=41)	Non-NED (n=7)	NED (n=34)
Age (years)	44 (36-59)	37 (25 - 41)	48,50 (40 – 60.50)
Sex - n (%) male	30 (73.17%)	5 (71.43%)	25 (73.53%)
BMI (kg/m^2)	23 (21 - 28)	28 (22 - 30)	23 (20 - 27)
SAPS 3 score, on admission	58 (49 – 66.50)	62 (49 - 67)	58 (49 - 68)
SOFA score, on assessment	7 (6 - 9)	8 (6 - 9)	7 (6 - 8)
Reason for ICU admission - n (%)			
Traumatic brain injury	**14 (34.14%)**	**4 (57.14%)**	**10 (29.41%)**
Hemorrhagic stroke	**5 (12.20%)**	**1 (14.29%)**	**4 (11.76%)**
Ischemic stroke	**2 (4.87%)**	**0 (0%)**	**2 (5.88%)**
Subarachnoid hemorrhage	**2 (4.87%)**	**0 (0%)**	**2 (5.88%)**
Abdominal trauma	2 (4.87%)	0 (0%)	2 (5.88%)
Thoracic trauma	3 (7.31%)	1 (14.29%)	2 (5.88%)
Heart surgery	2 (4.87%)	0 (0%)	2 (5.88%)
Myocardial infarction	2 (4.87%)	0 (0%)	2 (5.88%)
Cancer	3 (7.31%)	1 (14.29%)	2 (5.88%)
Bradycardia	1 (2.44%)	0 (0%)	1 (2.94%)
Others	5 (12.20%)	0 (0%)	5 (14.71%)
Type 2 diabetes - n (%)	2 (4.87%)	0 (0%)	2 (5.88%)
HIV - n (%)	1 (2.44%)	0 (0%)	1 (2.94%)
Drug addiction - n (%)	2 (4.87%)	0 (0%)	2 (5.88%)
Mechanical ventilation days, on assesssment	8 (5 – 12.50)	4 (3 - 9)	9 (6 - 13)
ICU length of stay (days), on assesssment	6 (2 – 10.50)	3 (2 - 7)	7 (3 - 11)
Hospital length of stay (days), on assesssment	9 (5 - 14)	6 (4 - 9)	11 (6 - 15)
Sepsis - n (%)	41 (100%)	7 (100%)	34 (100%)
Lung	35 (85.36%)	7 (100%)	28 (82.35%)
Abdomen	3 (7.31%)	0 (0%)	3 (8.82%)
CNS	2 (4.87%)	0 (0%)	2 (5.88%)
Mediastinum	1 (2.44%)	0 (0%)	1 (2.4%)
Septic Schock - n (%)	14 (34.14%)	4 (57.14%)	10 (29.41%)
GCS - n (%), on admission			

10 – 14	12 (29.27%)	1 (14.29%)	11 (32.35%)
6 – 9	29 (70.73%)	6 (85.71%)	23 (67.65%)
RASS score, on assessment	-5 (-5 - -4)	-5 (-5 - -4)	-5 (-5 - -4)
Using norepinephrine - n (%)	14 (34.14%)	4 (57.14%)	10 (29.41%)
dosage (mcg/kg/min)	0.13 (0.08 – 0.39)	0.1 (0.06 – 0.13)	0.15 (0.07 – 0.52)
Lactate, dosage (mmol/L)	1.4 (1.15 – 1.65)	1.3 (1.2 – 1.4)	1.4 (1.1 – 1.72)
P/F rate, on assessment	284 (234 - 338)	292 (210 - 332)	277 (235 - 344)
Renal failure - n (%), on assessment	4 (9.76%)	0 (0%)	4 (11.76%)

Legend:
The table presents the personal and clinical characteristics of the total sample and the groups with and without clinical criteria for neuromuscular electrophysiological disorders. Qualitative variables are presented as absolute (n) and relative (%) frequencies, and quantitative variables are presented as medians and interquartile ranges (IQR), using non-parametric analysis. The Mann-Whitney U test and Fisher's exact test revealed no significant differences ($p < 0.05$) between NED and Non-NED groups. Items in bold indicate the subpopulation of neurological patients: n=23 (56%). Abbreviations: NED = neuromuscular electrophysiological disorders, Non NED = without neuromuscular electrophysiological disorders, BMI = body mass index, SAPS 3 = Simplified Acute Physiology Score 3, SOFA = Sequential Organ Failure Assessment, ICU = intensive care unit, HIV = human immunodeficiency virus, CNS = central nervous system, GCS = Glasgow Coma Scale, RASS = Richmond Agitation Sedation Scale, P/F = ratio between the partial pressure of arterial oxygen and the fraction of inspired oxygen.

Critical Illness Polyneuromyopathy

Out of the total participants, 34 (83%) individuals were diagnosed with NED. The reason for ICU admission was almost evenly split between neurological and non-neurological conditions, with a slight predominance of neurological conditions, particularly among the Non-NED participants (Table 1).

Electrophysiological Recordings and Bilateral Assessment

The analysis of electrophysiological parameters (Figure 2) revealed a significant decrease in CMAP amplitude in the NED group compared to the Non-NED group; however, conduction velocity and latency remained similar between the groups, consistent with a typical axonopathy pattern.

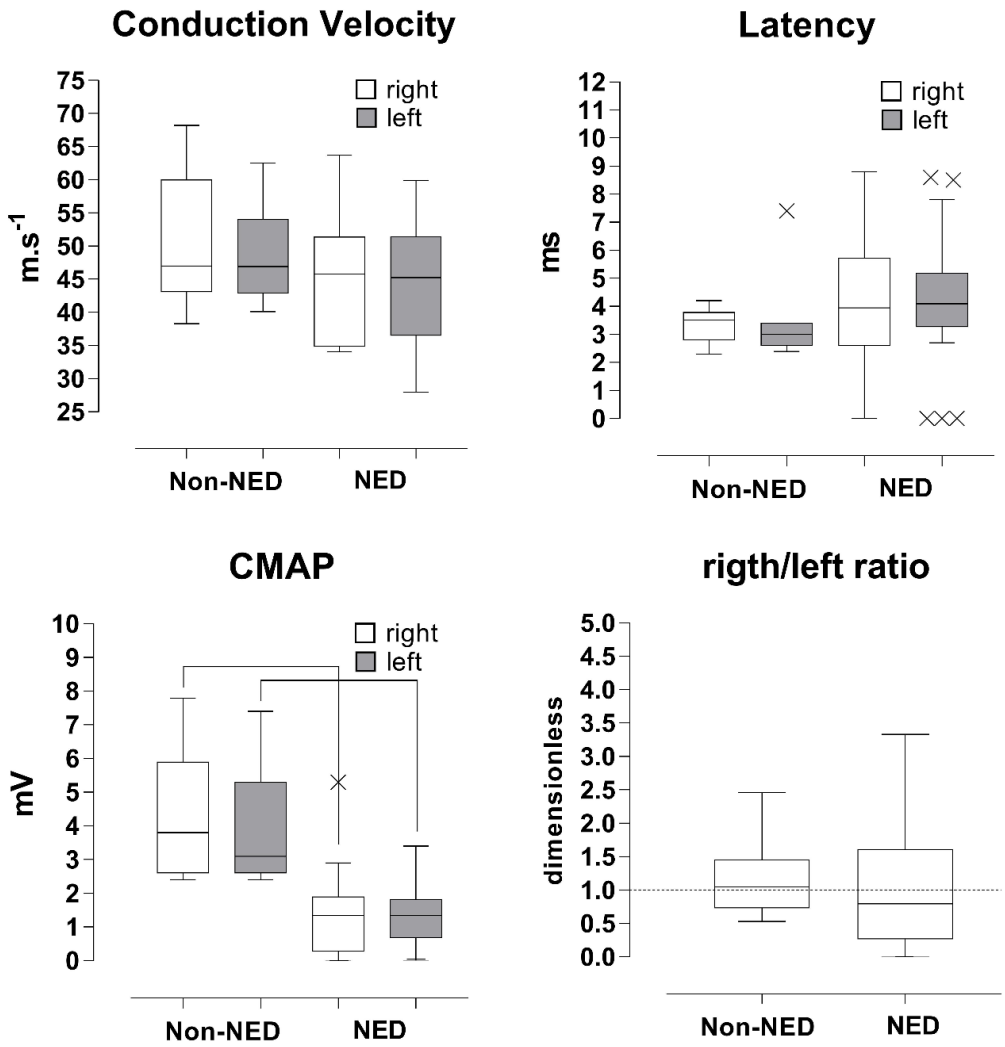


Figure 2. Panel with four graphs showing bilateral recordings of electrical activity in the peroneal nerve.

Legend:
Conduction velocity (top left), latency (top right), and CMAP (bottom left) are presented as box plots of the variables obtained by group (Non-NED *versus* NED) and by right (white) and left (gray) sides. In the bottom right corner, the right-left symmetry ratio for each group is shown, with a horizontal dotted line indicating perfect symmetry between recordings (ratio = 1.00) – an outlier value (r/l = 23) was excluded from the graph to enhance visualization of the box plot. The Mann-Whitney test identified a significant difference ($p<0.05$) between groups for CMAP (indicated by brackets), with no significant difference ($p>0,05$) between the right and left sides as examined by the Wilcoxon matched-pairs rank test. Abbreviations: NED = neuromuscular electrophysiological disorder, Non-NED = without neuromuscular electrophysiological disorder, CMAP – compound muscle action potential.

Regarding the quantitative statistical analysis of bilateral records, statistically significant inter-side differences were absent. Detailed analyses across groups showed a reduction in CMAP amplitude exceeding 50% in the NED group, with a slightly more pronounced reduction on the right side. Specifically, the median CMAP on the right side decreased from 3.8 mV to 1.35 mV

in the NED group - a 64% reduction. On the left side, the median dropped from 3.1 mV in the Non-NED group to 1.35 mV, achieving a 56% reduction.

Bilateral Asymmetries in Electrophysiological Recordings

With regard to the CMAP symmetry ratio (r/l), as depicted in the histogram (Fig. 3), 29 (71%) participants fell within the symmetry zone, which included three participants with no recordable CMAP.

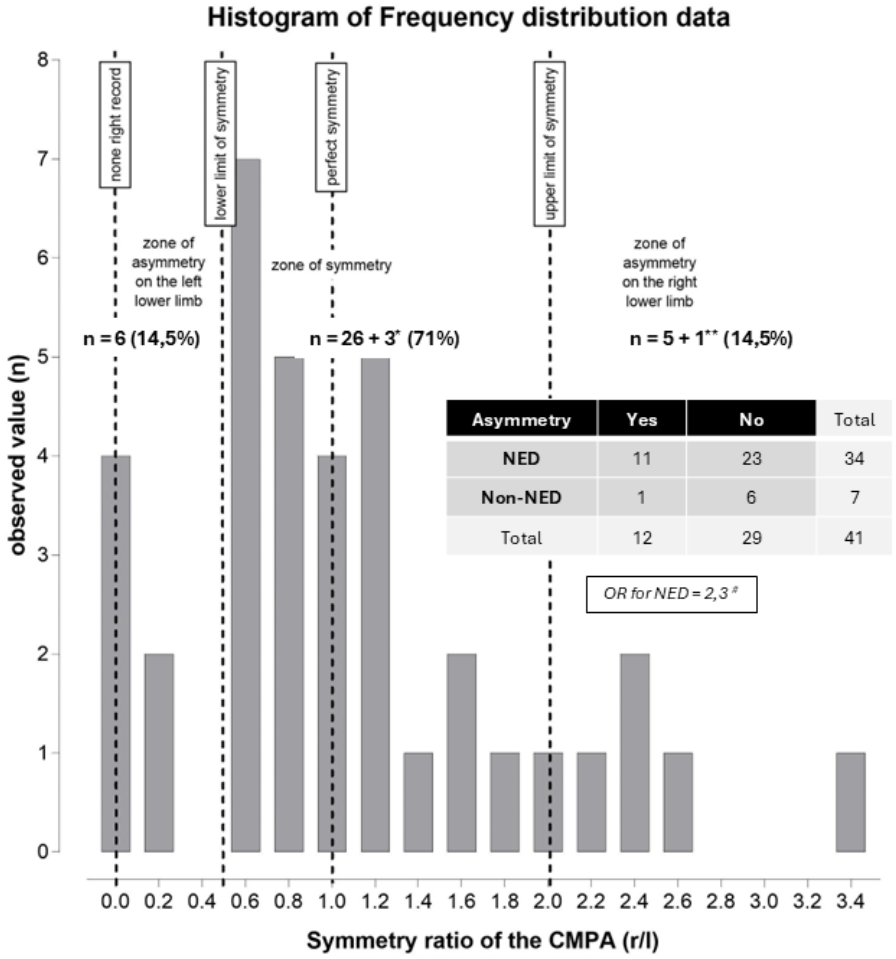


Figure 3. Histogram of the frequency distribution of the symmetry ratio between the bilateral CMAP

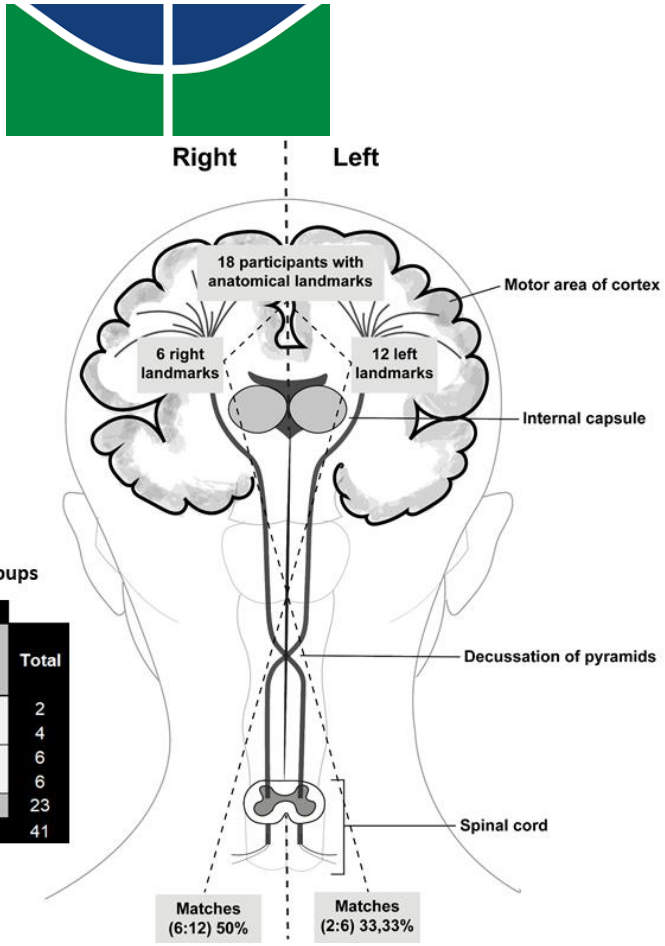
Legend: Distribution of the r/l between the CMAP obtained from the right and left peroneal nerves. The dashed vertical lines highlight the symmetry ratio value corresponding to perfect symmetry (r/l = 1.0), as well as the lower and upper limit values considered as the boundaries of the symmetry zone ($0.5 < r/l < 2$). It also indicates the r/l = 0 value, which corresponds to a symmetry ratio without a CMAP signal recorded on the right side and unilateral CMAP recorded on the left nerve. For algebraic reasons, a CMAP equal to zero on the left peroneal nerve and unilateral CMAP recorded on the right nerve could not be calculated. However, in this sample, there were no participants with this condition, thus avoiding a symmetry ratio value tending to infinite. The dashed vertical lines also delineate the asymmetry zone on the left side of the histogram, indicating a predominance of CMAP signal

intensity in the left lower limb, while on the right side, the upper limit of the symmetry zone marks the beginning of the asymmetry zone with a predominance of the CMAP amplitude in the right lower limb. Four participants from the clinical group were not included in the histogram and were described below the identification of each "zone" in the graph: three participants who did not have CMAP records (*), and one whose symmetry ratio was an upper outlier (r/l = 23) (**). In the table, regarding the distribution of asymmetry in NED versus Non-NED groups, the percentage occurrence of 32% and 14% respectively is verified, resulting in an OR for NED = 2,3 (#). Abbreviations: CMAP = compound muscle action potential, NED = neuromuscular electrophysiological disorder, Non-NED = without neuromuscular electrophysiological disorder, r/l = symmetry ratio, OD = odds ratio.

The histogram indicated that based on electrophysiological criterion, 12 (29%) participants - practically one-third of the sample - exhibited asymmetries in CMAP recordings from bilateral lower limb assessments. Among them, five (12%) had diagnostic divergences: one side indicated NED, while the contralateral side did not. Patients with NED had a two-fold odds ratio of asymmetry compared to the Non-NED group. The median of the symmetry ratio in the Non-NED group was very close to 1 (r/l = 1.05), whereas it was 0.79 in the NED group (Figure 2, bottom right corner). This suggests a tendency towards a more pronounced reduction in CMAP on the right side in the NED group - below the perfect symmetry line where r/l = 1.

Matches between Anatomical Landmarks and Electrophysiological Recordings

We explored potential correlations between cerebral anatomical landmarks due to hemispheric injury and CMAP reduction in contralateral muscles - under corticospinal influence (Figure 4).



Matches separated by NED and Non-NED groups

Landmark in cerebral hemisphere (side and occurrences)		Matches	NED	non-NED	Total
Right	6	Yes	2	0	2
		No	4	0	4
Left	12	Yes	4	2	6
		No	2	4	6
None			22	1	23
Total			34	7	41

Figure 4. Corticospinal matches between the worst record of bilateral CMAP and a brain anatomical landmark.

Legend: Schematic representation of the corticospinal tract and its decussation to illustrate the possibility of an anatomical landmark worsening the NED condition in muscles under its corticospinal influence. Of the 18 participants in the sample with anatomical landmarks, 6 had landmarks in the right cerebral hemisphere and 12 in the left. These anatomical landmarks corresponded to 6 (50%) and 2 (33%) of the worst records on right and left sides respectively (6 from the left hemisphere with the muscle on the right side, and 2 from the right hemisphere with the muscle on the left side, making a total of 8 (44%) matches in 18 observations. When separating the matches by groups with or without clinical criteria for NED diagnosis, we observed 6 (50%) matches in 12 observations in the NED group, compared to 2 (33%) matches in 6 observations in the non-NED group. This indicates an attributable risk of 17%, favorable to the NED group, that there is such a match between the hemispheric anatomical landmark and the contralateral side of the muscle where the worst electrophysiological recording occurred. This results in an indicator of the number needed to match (NNM) of 6, that means that for every 6 participants with a brain anatomical landmark, one participant would be expected to have a match between the side of the focal lesion in the NCS and the worst electrodiagnostic recording of NED on the corresponding corticospinal side. Abbreviations: NED = neuromuscular electrophysiological disorder, Non-NED = without neuromuscular electrophysiological disorder.

Among the eighteen neurological participants in the sample with anatomical landmarks from trauma or stroke, twelve were in the left cerebral hemisphere and six in the right. Corticospinal correspondence between focal hemispheric lesion and the side of the body with the most pronounced electrophysiological impairment was observed in 50% of cases (6:12) and 33% of

cases (2:6), respectively (Figure 4). Splitting the matches by groups, we found the same proportions: 6 matches (50%) out of 12 observations in the NED group, compared to 2 matches (33%) out of 6 observations in the Non-NED group (Figure 4). This suggests a 17% attributable risk in the NED group for a match between the hemispheric anatomical landmark and more pronounced contralateral peripheral electrodiagnostic dysfunction - corresponding corticospinal side. From this 17% attributable risk, we derived an indicator called the number needed to match (NNM), calculated as 6. This implies that for every 6 participants with a brain anatomical landmark, one participant is expected to exhibit a match between the side of the focal brain injury and the worst peripheral electrodiagnostic record on the contralateral body side.

DISCUSSION

This study highlights the presence of clinically relevant electrophysiological asymmetry at the onset of NED among critically ill patients. Recognizing this asymmetry in diagnostic screenings is crucial, as neglecting it can lead to diagnostic errors and inaccurate research findings. Our results reinforce the high incidence of NED in critically ill patients with sepsis and multi-organ dysfunction syndrome; and underscore the potential influence of laterality and focal CNS lesions on NED progression.

Symmetry vs Asymmetry

Our findings initially align with previous research that did not identify statistically significant differences in bilateral CMAP records of peripheral nerves [17,21]. In neurophysiology, the assessment of neuromuscular electrical dysfunction via bilateral CMAP comparison is fundamentally determined by the identification of asymmetry, which is established on electrophysiological criteria instead of relying solely on statistical parameters [27]. Unlike the previous ones, this study used the electrophysiological criterion for asymmetry adopted by

neurophysiology: difference in CMAP amplitude greater than 50% inter-sides [27]. It revealed a high occurrence of CMAP asymmetry, identified in 12 (29%) participants, with diagnostic divergence between sides in 5 (12%) cases - where one side was NED compatible and the other, normal. Supporting our observations, Latronico (2022) [24] similarly observed diagnostic divergence of 12%, advocating for contralateral nerve assessment only after a normal initial PENT. The clinical significance of our findings supports using clinical parameters alongside statistical analysis to evaluate effects [28], strengthening the recommendation for bilateral electrodiagnostic evaluations in critical illness research, to avoid diagnostic errors and reduce analysis bias.

Influence of laterality and focal CNS lesions

Our findings also indicate an increased risk of spinal-cortical correspondence between focal CNS lesions and worsening CMAP recordings among NED participants. This is coupled with a slightly more pronounced reduction in neuromuscular electrical activity on the right side for those with NED compared to unaffected patients. The intricate interplay between the central nervous system (CNS) and peripheral system involves complex scientific challenges, not yet explored in the CIP/CIM scenario, particularly the potential for asymmetrical development of this condition. While not the primary etiological factor, laterality, driven by cerebral dominance, potentially predisposes one hemisphere to structural and metabolic fragilities, which could modulate disease progression and affect otherwise symmetrical peripheral nerve damage [22]. This aligns with existing research on asymmetries in neurodegenerative disorders [22]. Axonal transport, essential for the proper function of the nervous system, allows the CNS to exert significant control over the maintenance and functional integrity of peripheral nerves [29]. The CNS modulates peripheral axonal neuroregeneration through trophic signaling, mirroring the reciprocal influence of peripheral axonal stimuli on CNS neuroplasticity [30]. Schweickert et al. (2009) [31] correlated early motor rehabilitation in the ICU with reduced duration of delirium

and more ventilator-free days, suggesting a negative interaction between ICU-induced delirium and ICUAW. Prospective studies in ICU indicate that both septic encephalopathy and CIP occur together in 70% of cases, septic encephalopathy appearing first, suggesting an association between both dysfunctions [32]. Recent evidence suggests that central nervous system involvement with failure of coordinated repetitive firing within the motor neurons can be a very early event, preceding electrical failure in axons and muscle fibers, strengthening CNS engagement with NED [33]. In PICS, the interplay of physical (ICUAW), cognitive (dementia), and mental (depression and delirium) impairments may underline the close relationship between brain dysfunctions and peripheral axonopathy [8]. Despite the scarcity of robust scientific evidence, all these distinct entities may provide clues into the interaction of the laterality and focal brain with the asymmetric progression of NED, possibly by disproportionately affecting contralateral descending pathways [34].

NED incidence

Our study reported an 83% incidence of NED, significantly higher than the 47% reported in a systematic review of ICUAW [12]. This higher incidence can be justified by the sample, which included neurological patients with sepsis and multiple-organ dysfunctions [35], with reports of incidences approaching 100% as severity and organ failures increase [5]. Berek et al. (1996) [36] and Latronico et al. (2022) [24] described a CIP frequency of 82% and 79% respectively among similar populations.

Study limitations

Some limitations should be addressed in our study. There was no diagnostic confirmation of ICUAW, since we worked with uncooperative participants - under sedation or coma [11]. Nevertheless, electrophysiological disorders are associated with deleterious outcomes in critically ill participants, even in the absence of weakness [18,37]. We applied only bilateral assessment of motor peroneal nerve by PENT, without sensory evaluation of the sural sensitive

nerve to confirm CIP diagnosis [17,21]. Indeed, reduced CMAP is observed in both axonopathy (CIP) and myopathy (CIM). However, although reduced sensory nerve action potential (SNAP) confirms CIP, it does not exclude CIM and may be blunted or masked due to local oedema, low surface temperatures, or electromagnetic interference [1]. Motor changes precede sensory changes, so that normal SNAP does not rule out axonopathy at the onset of dysfunction [1,38]. Moreover, CIM and CIP are normally associated [1] and several researchers argue that the differentiation between them is not very relevant in ICU [1,17,39]. The limited setting and cross-sectional nature reduce generalizability to other contexts.

Future perspectives

Future multicenter studies with larger cohorts are needed to further document neuropathological asymmetry in NED progression and its clinical implications. Research should explore advanced neurophysiological tools [34] to track CNS dysfunction and assess peripheral axonopathies in critically ill patients, extending follow-up beyond hospital discharge.

CONCLUSIONS

Electrodiagnostic screening tests for neuromuscular electrophysiological disorders in critically illness patients in ICU should be performed bilaterally to avoid diagnostic error and analysis bias, due to the clinical relevance of asymmetry in its development. The impact of cerebral laterality and focal brain lesions on electrodiagnostic asymmetry in the onset of critical illness polyneuromyopathy needs to be further studied.

Abbreviations

NED	Neuromuscular electrophysiological disorder
Non-NED	Without neuromuscular electrophysiological disorder
CMAP	Compound muscle action potential
SNAP	Sensory nerve action potential
r/l	Right/left CMAP ratio
PENT	Nerve conduction study for the motor peroneal nerve
NCS	Nerve conduction study

EMG	Needle-electromyography
CIP	Critical illness polyneuropathy
CIM	Critical illness myopathy
CIP/CIM	Critical illness polyneuro and/or myopathy
ICUAW	Intensive care unit-acquired weakness
PICS	Post-intensive care syndrome
CNS	Central nervous system
ICU	Intensive care unit
SAPS 3	Simplified Acute Physiology Score 3
SOFA	Sequential organ failure assessment
BMI	Body mass index
GCS	Glasgow Coma Scale
RASS	Richmond Agitation Sedation Scale
MV	Mechanical ventilation
OR	Odds ratio

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Author contributions

Concept and Design: JRDM and PES. Aquisition, analysis and interpretation of the data: all authors. Drafting the manuscript: JRDM, PES and EFM. Graphics: JRDM, PES and EFM. Critical revision of the manuscript for important intellectual content: all authors. Supervision: RNMF and EFM. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of HB/IGESDF, under protocol number 63620622.2.0000.8153. Written informed consent was obtained from the closest responsible family member for each included patients.

Consent for publication

Written informed consent for publication was obtained.

Competing interests

All authors declare no competing interests.

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ORIGINAL ARTICLE

Towards innovative electrodiagnosis tests to investigate neuromuscular excitability dysfunction in critically ill patients: an agreement study

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Abstract

Purpose Early diagnosis of ICU-acquired weakness can support the ICU team in applying appropriate interventions which may lead to better results at clinical and functional outcomes. Thus, interest has increased in non-invasive and more feasible methods to diagnose neuromuscular dysfunction, such as the stimulus electrodiagnosis test (SET) and strength-duration test (SDT). The aim of the present study was to assess the agreement of the SET and SDT carried out automatically using an innovative method.

Methods We performed a prospective observational study to determine the agreement of SET and SDT, performed automatically using a biofeedback circuit to detect muscle contractions, comprised of an accelerometer module connected to an electrical stimulator. These tests were applied in healthy and critically ill participants.

Results Twenty-one participants were analyzed in the study, and 168 assessments of SET and SDT were performed. The Bland-Altman analysis of automatic SET and SDT in the control group showed a low bias of −25 (95% CI, −94.3 to 44.3 µs) and 0.6 (95% CI, −1.9 to 3.1 µC) respectively. In the critically ill group, automatic SET and SDT presented a low bias of −104.5 (95% CI, −1716 to 1507µs) and −12.6 (95% CI, −119.4 to 94.1 µC) respectively.

Conclusions We demonstrated that an innovative method to carry out SET and SDT automatically presents low agreement bias and good to excellent reliability.

Keywords Agreement · Chronaxie · Intensive care unit-acquired weakness · Neuromuscular electrical stimulation · Strength-duration test

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Introduction

Intensive care unit-acquired weakness (ICUAW) is a prevalent neuromuscular dysfunction that often arises during a patient's stay in the intensive care unit (ICU). Its origin appears to be closely tied to the critical illness itself and the treatments administered, with no other readily identifiable causes (Vanhorebeek et al. 2020). Its prevalence is around 43% and ranges from 25 to 75% (Fan et al. 2014), which can be explained by the tool used to assess, the timing of the evaluation and the cause of ICU admission (Hermans and Van den Berghe 2015). The presence of ICU-acquired weakness is related to worse clinical outcomes and impairs short and long-term functional results (Hakiki et al. 2020; Latronico and Bolton 2011). Early diagnosis can support the ICU team in applying appropriate interventions, such as neuromuscular electrical stimulation, which may lead to better clinical and functional outcomes such as decrease ICU length of stay and increase of muscle strength (Moss et al. 2014; Silva et al. 2019).

Nerve and muscle biopsy, as well as electroneuromyography, are validated tools to detect neuromuscular dysfunction caused by ICU-acquired weakness (Latronico and Bolton 2011; Moss et al. 2014). However, carrying out these exams is not always feasible in the ICU. A biopsy is a surgical procedure, and the ICU is an electrically unfriendly setting for electroneuromyography (Lacomis 2013). Moreover, electroneuromyography requires appropriate devices and a specialized team that are commonly unavailable in the ICU.

In this context, there has been increased interest in non-invasive and more feasible surrogate methods to diagnose neuromuscular dysfunctions, such as the stimulus electrodiagnosis test (SET) and the strength-duration test (SDT) (Fagoni et al. 2021; Silva et al. 2018). The SET provides variables such as rheobase and chronaxie which are the minimum intensity and minimum pulse duration needed to excite a given tissue, respectively (Silva et al. 2018). The sensitivity of the SET to detect muscle denervation can reach 100% in the acute phase, compared to electroneuromyography in outpatients (Paternostro-Sulga et al. 2002).

The use of the SDT has been described for more than a century to guide neurophysiologists regarding neuromuscular excitability (Lapicque 1909). It plots the lowest intensities required for stimulation versus pulse durations through predefined steps. The SDT is useful because it describes how the current required changes when the pulse duration is modified, providing information about neuromuscular excitability (Geddes and Bourland 1985); the less excitable the tissue is, the higher the intensity and pulse duration necessary to excite the tissue. The lack of appropriate devices in the ICU and the absence of SDT validation in critically ill patients has hindered the widespread use of SDT in clinical practice.

Recently, the feasibility of the SET and SDT to assess critically ill patients was demonstrated; however, many points still require further clarification (Fagoni et al. 2021; Silva et al. 2018).

The inter-rater reproducibility of the SET is fair in some conditions, and SDT reproducibility has not yet been evaluated. The critical point related to the reproducibility of these exams is that both depend on the visual and subjective detection of muscle contraction. Thus, in the present study, we propose an innovative method for automatically performing the SET and SDT to detect neuromuscular excitability. This may improve reproducibility and solve inter-rater incongruent diagnoses.

The main aim of the present study was to assess the agreement and reliability of the SET and SDT carried out automatically using an innovative method. Secondarily, we aimed to determine the safety and feasibility of the SET and SDT in critically ill patients.

Methods

Study design

We performed a prospective observational study to assess the agreement of the SET and SDT, performed automatically using a new medical device. The present study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies (von Elm et al. 2007).

Setting

The research was carried out at the department of rehabilitation and at the neurotrauma ICU in a tertiary public reference hospital in the Federal District of Brazil. We conducted our study according to the Declaration of Helsinki, and approval for the project was obtained from the local ethics committee (IHBDF, Brasília, Brazil, protocol 3.629.265). Written consent was obtained from healthy participants in the control group and from the closest responsible family member in the critically ill group, since all participants were intubated and sedated at enrollment. Data collection was conducted between November 2020 and March 2022.

Participants

The control group was composed of healthy male and female participants, aged 18 to 60 years, without a clinical history of orthopedic and neuromuscular disease. The critically ill

group was composed of traumatic brain injured participants, of both sexes, aged 18 to 60 years, sedated for at least 6 days on mechanical ventilation. Participants with bone fractures, skin injuries at the assessment location, and pregnant women were excluded. In both groups, participants were recruited consecutively.

Variables

All participants were assessed by SET and SDT. Two manual and two automatic assessments were performed for every test (i.e., SET and SDT). The manual assessments were performed by a single expert examiner (PES). We used a new innovative device, Recare® (Visuri, Belo Horizonte, Brazil), to achieve both manual and automatic assessments.

The automatic assessments were performed using a biofeedback circuit to detect muscle contractions, comprised of an accelerometer module (STMicroelectronics STEVAL-MKI211V1K) connected to the Recare® by an I^2C serial protocol. The weight of the printed circuit board was 5.5 g, and the plastic encapsulation weighed 10 g, resulting in a final weight of 15.5 g. The Recare® Scientific Mode (RSM) was configured to start the stimulation and progressively increment the pacing parameter values until a contraction was detected. At this moment, the device automatically interrupts the stimulation and saves the final parameter values on the hardware memory. To determine the contraction, the accelerometer Z-axis was positioned perpendicularly to the surface of the skin, over the muscle belly. The RSM was configured to acquire accelerometer data at a 100 Hz sample rate. The RSM algorithm calculated the standard deviation (SD) for 500 ms of Z-axis data obtained before and after each stimulation. A contraction event was determined every time the Z-axis SD value after the stimulus exceeded 1.2 times the previously calculated value. The value of 1.2 times was defined based on a previous study (Bispo et al. 2019).

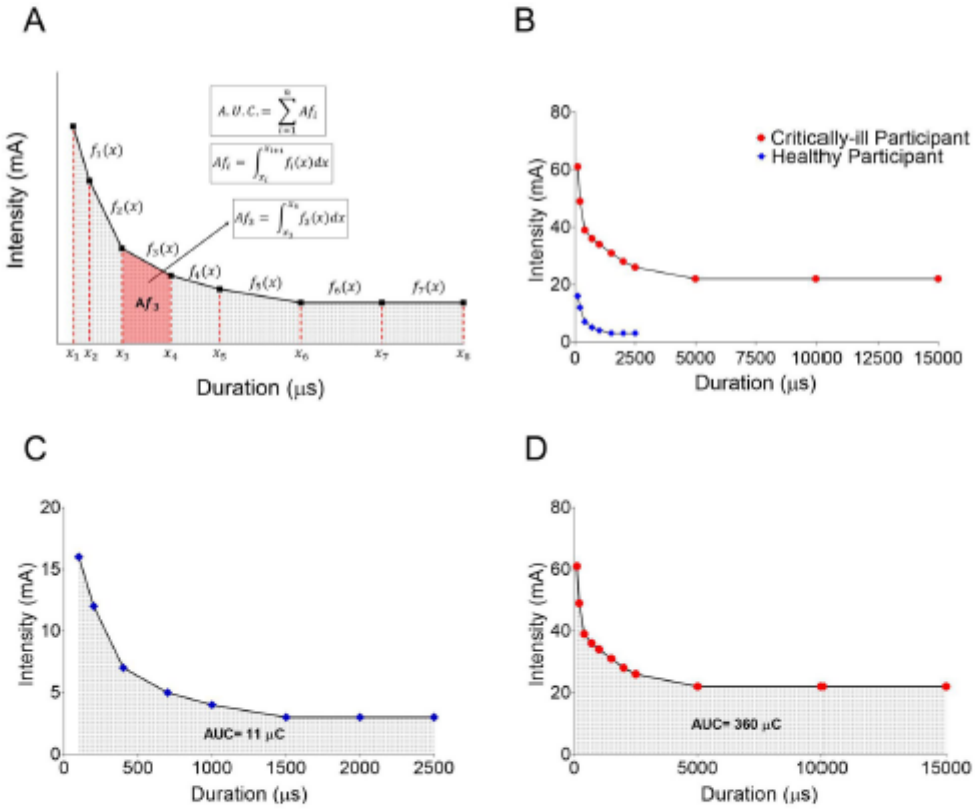


Fig. 1 Calculation of the area under the curve from the strength-duration test. **A** presents the function used to calculate AUC. **B**, **C**, and **D** show examples of the strength-duration test plotted automatically by the device in two representative participants of both groups. The AUC was calculated according to the equations shown in **A**. **B** presents two curves plotted in the same graph from a healthy and a critically ill participant. **C** and **D** present the AUC values from healthy and critically ill participants respectively. AUC, area under the curve; μC, microcoulomb; SDT, strength-duration test

Primary outcomes

The primary outcomes of the present study were the agreement and reliability of chronaxie and area under the curve, measured automatically during two repetitive tests from the SET and SDT respectively.

Stimulus electrodiagnosis test (SET)

The SET was performed using two electrodes positioned proximal over the right tibialis anterior muscle, 1/4 of the distance between the inferior border of the patella and the lateral malleolus. All participants were in a supine position with 30° bed elevation.

Neuromuscular excitability was assessed by rheobase and chronaxie. Rheobase is the minimal current intensity necessary to reach the neuromuscular excitability threshold applied with a rectangular pulse with an infinite duration. Chronaxie is the shortest pulse duration required to reach the neuromuscular excitability threshold by a current with twice the intensity of rheobase (Silva et al. 2018).

Rheobase and chronaxie were measured with a single-biphasic pulse. For rheobase assessment, the intensity was increased from 1 to 240 mA, with individual 1 mA increments until eliciting a slight and visible muscle contraction. The evaluation was performed with a pulse duration of 500 ms and intervals of 2 s between pulses. For the assessment of chronaxie, the current amplitude was set to twice the rheobase value. Subsequently, the pulse duration was increased from 50 µs to 500 ms in increments of 50 µs, until eliciting a slight but visible muscle contraction (Silva et al. 2018).

The examiner performed the SET manually and automatically, twice each, separated by 5-min intervals.

Strength-duration test (SDT)

The SDT was carried out 5 min after the SET. Patients and electrodes were maintained in the same position as the SET. A

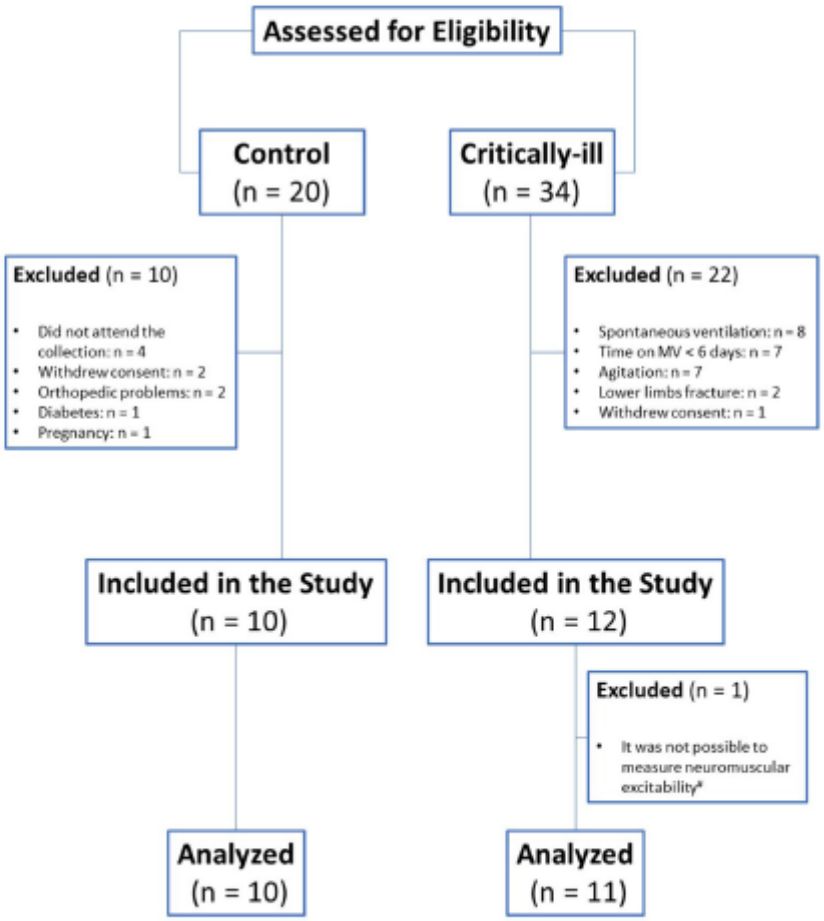


Fig. 2 Flow Diagram. MV, mechanical ventilation; The number sign (#) means that this participant was excluded because he had significant swelling that prevented contraction detection even using the maximal allowed current output (intensity of 240 mApp with pulse duration of 500 ms)

rectangular, biphasic, and symmetric pulse was used with different pulse durations: 100 µs, 200 µs, 400 µs, 700 µs, 1000 µs, 1500 µs, 2000 µs, 2500 µs, 5000 µs, 10 ms, 15 ms, 20 ms, 50 ms, 100 ms, 200 ms, up to 500 ms. For every pulse duration, the examiner (manual) or the device (automatic) was required to find a minimal muscle contraction using an intensity ranging from 1 to 240 mApp. The assessment was stopped when a plateau was reached in the intensity axis in three incremental steps of pulse duration.

First, the examiner manually performed the SDT twice, with a 5-min interval. In sequence, the device automatically performed the SDT twice with 5-min intervals.

The total charge applied in the SDT was measured by the area under the curve (AUC). Before calculating the AUC, the curve was determined by joining the "n" straight lines between the "$n+1$" subsequent points on the graph obtained by the pulse duration (x-axis, µs) and intensities (y-axis, mA) from each SDT. The AUC (Fig. 1A) was obtained by calculating the sum of the areas under the "n" functions $f_i(x)$, which represent the "n" equations of straight lines between points x_i and x_{i+1}, with i ranging from "1" to "n." Each of the "n" section areas was calculated by the respective definite integrals of $f_i(x)$ from x_i to x_{i+1}. According to the International System of Units, the unit of area used was µs × mA, equivalent to the electrical charge in microcoulombs (µC). The AUC calculations were carried out in Matlab R2022b.

Secondary outcomes

Safety and feasibility

Safety was assessed by the incidence of a skin burn and feasibility by the time spent performing the assessments.

Study size

Sample size was calculated a priori using the formula proposed by Walter et al. (Walter et al. 1998) for reliability studies. Initially, 30 subjects were proposed in the critically ill group; however, due to the SARS-CoV-2 pandemic, the present study needed to be stopped with 12 participants. Thus, the post hoc power (1-β) was calculated, demonstrating a mean value of 83%. This calculation was carried out taking into account 11 subjects, a number of observations of 2, significance level of 0.05, acceptable reliability of 0.8, and a mean of measured reliability of 0.96 in the AUC analysis.

Statistical methods

The normality of the data was tested with the Shapiro-Wilk test, and parametric and non-parametric tests were used, given the characteristics of the variables. The variables were described as mean and standard deviation or median and interquartile range. Agreement was assessed by the Bland-Altman method and reliability by the intraclass correlation coefficient. The correlation coefficients were classified as suggested by Mukaka (2012): > 0.9, excellent; 0.7 to 0.9, good; 0.5 to 0.7, moderate; 0.3 to 0.5, fair; 0 to 0.3, slight.

Differences in SDT, SET, and time spent during the test were analyzed using the unpaired Student T-test. Statistically significant differences were assumed when $p < 0.05$. Data were analyzed using the software Graphpad Prism version 8.3 (Graphpad Software, Inc., San Diego, California, USA).

Results

From the fifty-four participants assessed for eligibility, twenty-two were included in the study. The recruitment process is described in the flow diagram (Fig. 2). Participants' characteristics are presented in Table 1.

Stimulus electrodiagnosis test (SET)

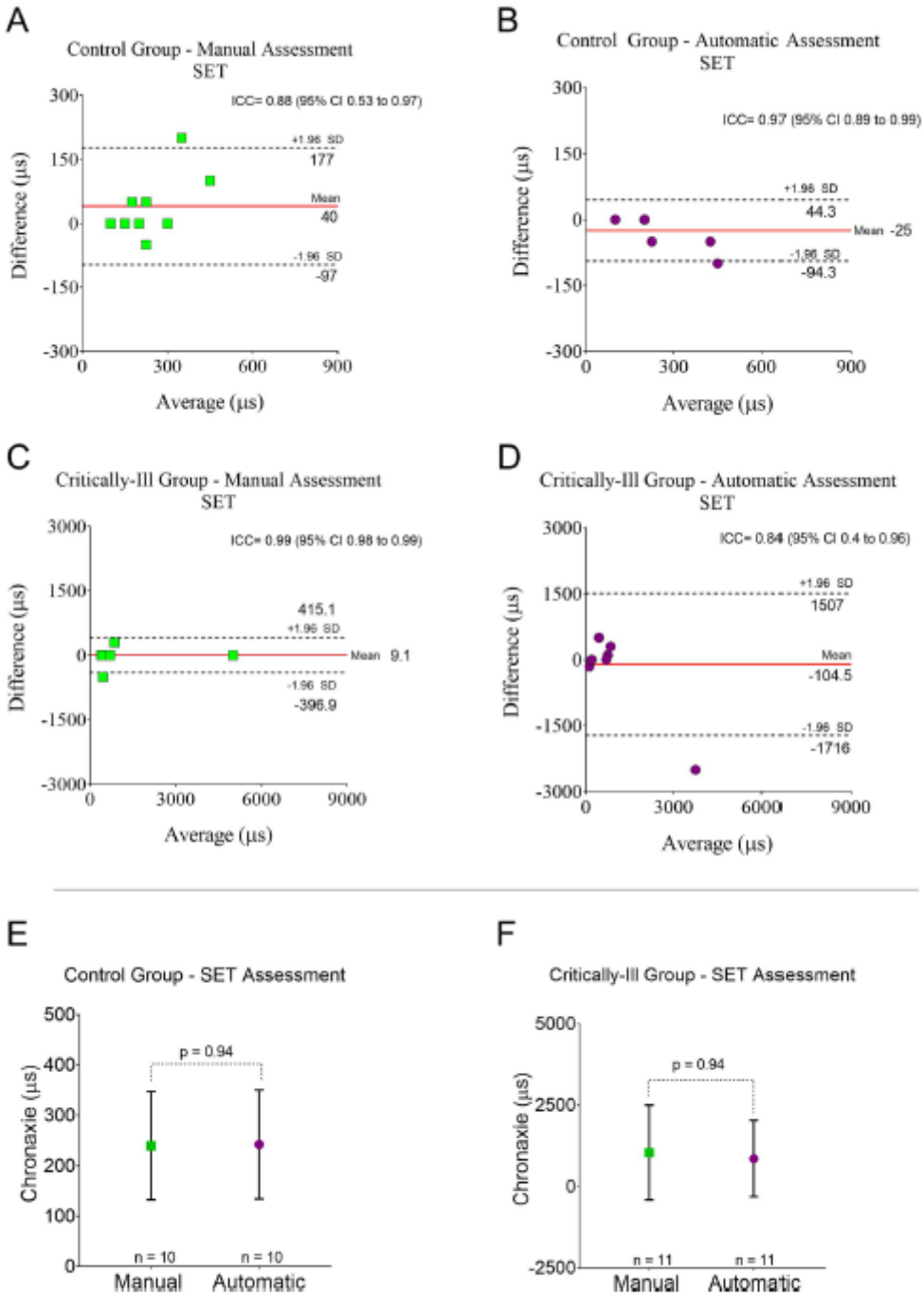
The SET agreement was calculated using chronaxie, as this parameter is used to define neuromuscular excitability

Table 1 Participants' characteristics

Variable	Control	Critically ill
n	10	11
Sex, *n*, male (%)	5 (50%)	8 (73%)
Age, years	36.9 ±6.5	44.1 ±11.5
AIS (head)	-	5 [5–5]
Cause of injury		
Motorcycle, *n* (%)	-	2 (18%)
Beating, *n* (%)	-	1 (9%)
Gunshot, *n* (%)	-	1 (9%)
Fall, *n* (%)	-	6 (55%)
Pedestrians, *n* (%)	-	1 (9%)
Penetration Trauma mechanism, *n* (%)	-	1 (9%)
Operative Intervention, *n* (%)	-	11 (100%)
SAPS III	-	38 [36–43]
MV, days at the collection	-	9.4 ±5.8
Sedation, days at the collection	-	8.2 ±3.9
Use of sedative drugs, *n* (%)*	-	11 (100%)
ICU stay, days at the collection	-	8.3 ±5.7
Use of vasopressor drugs, *n* (%)	-	6 (55%)
Use of carbapenem antibiotics, *n* (%)	-	2 (18%)

AIS Abbreviated Injury Scale, *MV* mechanical ventilation, *SAPS 3* Simplified Acute Physiology Score 3

Variables are reported as mean and (± standard deviation), median and [interquartile range], or absolute frequency and (relative frequency). The asterisk symbol (*) means all patients were sedated with fentanyl and midazolam


A
Control Group - Manual Assessment
SET
ICC= 0.88 (95% CI 0.53 to 0.97)
+1.96 SD
177
Mean
40
-1.96 SD
-97
Difference (µs)
Average (µs)
B
Control Group - Automatic Assessment
SET
ICC= 0.97 (95% CI 0.89 to 0.99)
+1.96 SD
44.3
Mean -25
-1.96 SD
-94.3
Difference (µs)
Average (µs)
C
Critically-Ill Group - Manual Assessment
SET
ICC= 0.99 (95% CI 0.98 to 0.99)
415.1
+1.96 SD
Mean 9.1
-1.96 SD
-396.9
Difference (µs)
Average (µs)
D
Critically-Ill Group - Automatic Assessment
SET
ICC= 0.84 (95% CI 0.4 to 0.96)
+1.96 SD
1507
Mean
-104.5
-1.96 SD
-1716
Difference (µs)
Average (µs)
E
Control Group - SET Assessment
p = 0.94
Chronaxie (µs)
n = 10
n = 10
Manual
Automatic
F
Critically-Ill Group - SET Assessment
p = 0.94
Chronaxie (µs)
n = 11
n = 11
Manual
Automatic

◂**Fig. 3** Intra-rater agreement of chronaxie measured from stimulus electrodiagnosis test, manually and automatically. The Bland-Altman plot of the intra-rater comparison between two repeated measures of chronaxie during the SET taken by the examiner manually and the device automatically. Differences and averages were calculated from the repeated measures recorded on the tibialis anterior muscle. Upper and lower discontinuous traces show respectively the bounds of a 95% range of the LOA; the continuous line presents the bias mean. The ICC between repeated measures is indicated for each graph. Squares in the graphs represent manual assessments, and circles represent automatic assessments. ICC, intraclass correlation coefficient; LOA, limit of agreement; SET, stimulus electrodiagnosis test

dysfunction (Paternostro-Sulga et al. 2002; Silva et al. 2018). The results of these assessments in the control and critically ill groups performed manually and automatically are presented in Fig. 3A to D. There were no statistical differences in the chronaxie assessed manually by the examiner and automatically by the device in both groups (Fig. 3E and F). The overall mean chronaxie in the control group and in the critically ill group were respectively 236 ±106 µs vs. 851 ±1159 µs ($p < 0.0028$).

Strength-duration test (SDT)

The agreements of the SDT carried out manually and automatically are presented in Fig. 4A–D. There was no statically difference in the AUC plotted by manual and automatic assessments in both groups (Fig. 4E–F). The overall mean (manual and automatic) of the AUC in the control group and the critically ill group were respectively 10.5 ±3.5 µC vs. 71.6 ±100.9 µC ($p < 0.0002$).

Safety and feasibility

In total, 168 SET and SDT were performed manually by the examiner and automatically by the device. No cases of skin burns or any side effects were detected. There were no statistical differences between the time spent in the manual or automatic assessments to perform the SET: automatic, mean (±SD) of 1.76 ±0.42 min vs. manual, 1.6 ±0.3 min respectively, $p = 0.13$. The automatic assessment spent more time than the manual to assess SDT: mean (±SD) of 4.98 ±2.52 min vs. 3.35 ±0.87 min respectively, $p = 0.0076$.

Discussion

The present study demonstrated low agreement bias in the automatic assessment of SET and SDT. The agreements of the SET and SDT were similar when performed manually and automatically. Both presented a good to excellent reliability, and there was no significant difference between the absolute values of these two forms of assessment of SET and SDT. Moreover, it was shown that both the manual and automatic assessments are feasible and safe.

Electrodiagnostic tests in the ICU, such as nerve conduction studies and needle electromyography, can be a difficult task due to the electrically unfriendly environment (Lacomis 2013). Thus, the SET can be viewed as a surrogate screening test that can be used to detect neuromuscular abnormalities (Paternostro-Sulga et al. 2002; Silva et al. 2019).

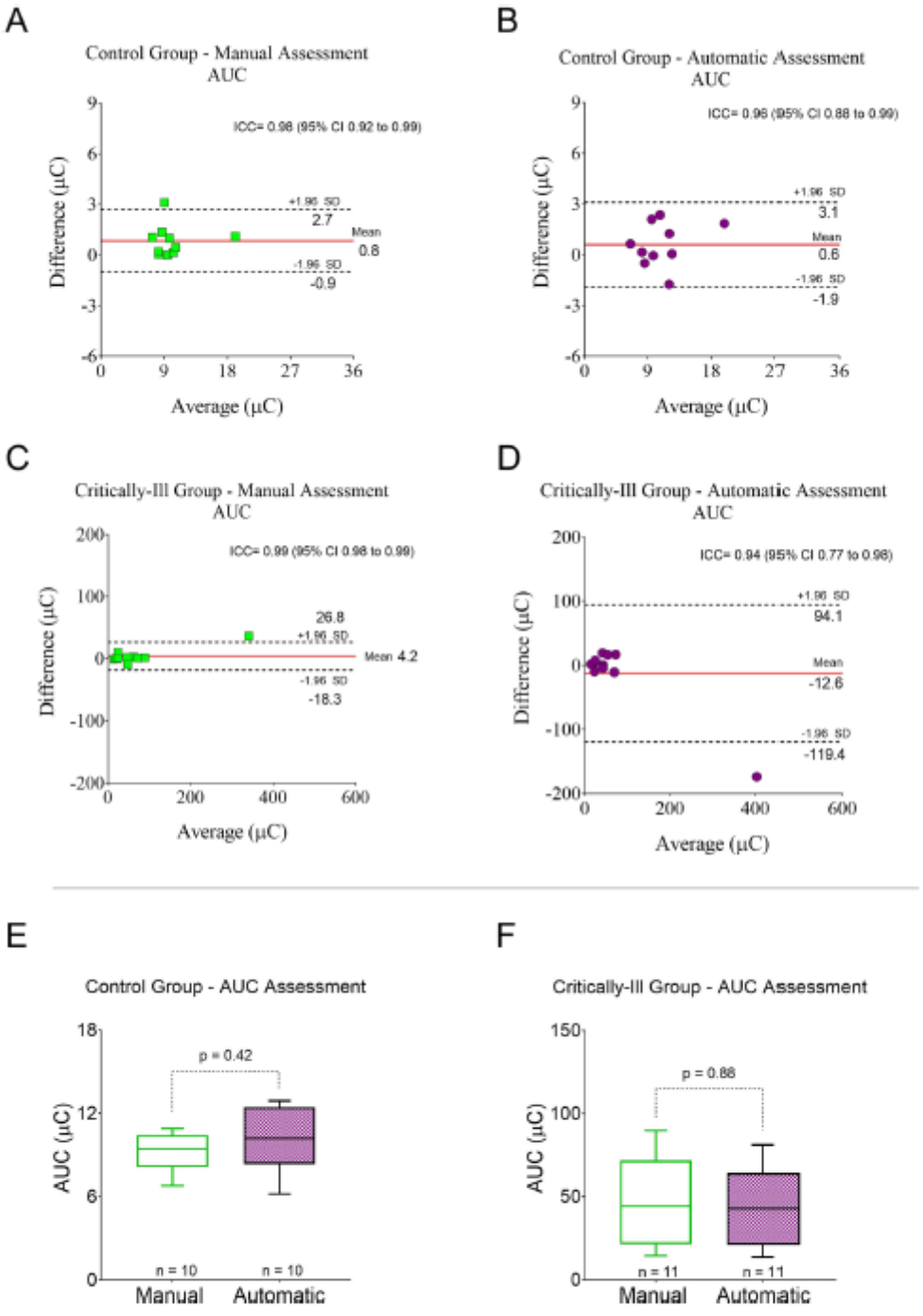
The assessment of chronaxie by the SET seems to be fundamental not only for diagnosis, but also for the prescription of neuromuscular electrical stimulation (NMES) (Silva et al. 2019, 2018). Chronaxie defines the minimal level of neuromuscular excitability, and its value should be applied to pulse duration to evoke effective contractions, in order to avoid muscle atrophy (Silva et al. 2017). The precise definition of chronaxie could be the starting point for an adequate diagnosis of neuromuscular excitability and NMES treatment.

A previous study found that SET has a sensitivity of 100% in the acute phase and 86% in the subacute/chronic phase of muscle denervation in outpatients, compared to needle electromyography (Paternostro-Sulga et al. 2002). However, these authors did not assess all clinimetric properties of this test. A more recent study showed that the SET can present fair agreement in the inter-rater evaluation in an ICU setting when the tibialis anterior is assessed (de Araujo et al. 2019).

The level of reproducibility (reliability and/or agreement) of a test can be related to the previous training of the professionals (Brooks and Thomas 1995). Furthermore, both the SET and SDT have another critical point: the subjectivity of visual detection of the muscle contractions (de Araujo et al. 2019). Thus, the heterogeneity in the expertise of the ICU team and the subjectivity can preclude adequate levels of inter-examiner reproducibility in these tests. Accordingly, the use of new automated technology that does not need a human decision can improve the clinimetric properties of SET and SDT. Consistent with the previous assertion, the present study showed that automatic SET assessment achieved high reliability in both the control and critically ill groups.

It has been advocated that SDT may be more robust to detect neuromuscular excitability dysfunctions than SET (Paternostro-Sulga et al. 2002). Chronaxie, in fact, is a point in the SDT curve. However, since the first studies that described SDT (Lapicque 1909; Ritchie 1944), few advances have been made to improve its assessment and decrease the subjectivity. The analysis of the SDT curve has been performed visually, meaning that clinicians can provide subjective and imprecise descriptions.

The current study presented a novel way to objectively measure the movement of the curves using the calculation of the AUC. Thus, it is possible to numerically assess signals of worsening or improvement in neuromuscular excitability; the higher the AUC, the worse the neuromuscular excitability. Moreover, it was demonstrated that the automatic SDT


A
Control Group - Manual Assessment
AUC
ICC= 0.98 (95% CI 0.92 to 0.99)
+1.96 SD
2.7
Mean
0.8
-1.96 SD
-0.9
Difference (µC)
Average (µC)
B
Control Group - Automatic Assessment
AUC
ICC= 0.96 (95% CI 0.88 to 0.99)
+1.96 SD
3.1
Mean
0.6
-1.96 SD
-1.9
Difference (µC)
Average (µC)
C
Critically-Ill Group - Manual Assessment
AUC
ICC= 0.99 (95% CI 0.98 to 0.99)
26.8
+1.96 SD
Mean 4.2
-1.96 SD
-18.3
Difference (µC)
Average (µC)
D
Critically-Ill Group - Automatic Assessment
AUC
ICC= 0.94 (95% CI 0.77 to 0.98)
+1.96 SD
94.1
Mean
-12.6
-1.96 SD
-119.4
Difference (µC)
Average (µC)
E
Control Group - AUC Assessment
p = 0.42
AUC (µC)
n = 10
n = 10
Manual
Automatic
F
Critically-Ill Group - AUC Assessment
p = 0.88
AUC (µC)
n = 11
n = 11
Manual
Automatic

◂**Fig. 4** Intra-rater agreement of the area under the curve measured in the strength-duration test, manually and automatically. The Bland-Altman plot of the intra-rater comparison between two repeated measures of area under the curve from SDT taken by the examiner manually and the device automatically. Differences and averages were calculated from the repeated measures recorded on the tibialis anterior muscle. Upper and lower discontinuous traces show respectively the bounds of a 95% range of the LOA; the continuous line presents the bias mean. The ICC between repeated measures is indicated for each graph. Squares in the graphs represent manual assessments, and circles represent automatic assessments. ICC, intraclass correlation coefficient; LOA, limit of agreement; SDT, strength-duration test

assessment has a low agreement bias, which allows different examiners to carry out this test.

Recently, Fagoni et al. (2021) carried out the SDT in critically ill patients and concluded that this is a feasible tool to assess neuromuscular excitability dysfunctions. Moreover, SDT can provide additional information to that obtained by electroneuromyography. The authors performed a manual assessment and used a low charge protocol, with a pulse duration ranging from 50 up to 450 µs. This protocol can limit the assessment of patients with neuromuscular excitability dysfunctions as demonstrated by the authors. It has been shown that patients with neuromuscular excitability dysfunctions need high values of charge in SDT to be assessed (Ritchie 1944; Silva et al. 2018). Classically, therefore, this test has been carried out using pulse duration ranges up to infinite values (i.e., >200 ms) as in the present study (Geddes and Bourland 1985).

A possible application of the SDT, beyond diagnosis, is to guide the treatment of neuromuscular dysfunctions. It has been demonstrated that many patients in the ICU are "non-responders" to NMES, i.e., their muscles are unexcitable with traditional protocols: pulse width up to 500 µs and intensity up to 120 mA (Grunow et al. 2019; Segers et al. 2014). The present results reinforce that neuromuscular excitability depends on the charge applied and that the SDT, like the SET, can guide the ICU team on the more precise dose to be used during NMES.

Our results demonstrate that manual and automatic assessments of both tests are safe and feasible, overall requiring less than 5 min to perform. The major complication of this type of test is the incidence of skin burns, caused in this context by the high current density (i.e., values > 50 $\mu A/mm^2$) (Scheiner et al. 1990). No cases of skin burns were documented in the present study, which could be due to the safety algorithm applied in this new technology. The device is programmed to avoid a current density > 35 $\mu A/mm^2$; the examiner is required to inform the electrode size, and the intensity is limited based on that cut-off. Due to this safety tool, one participant in the critically ill group could not be completely assessed. The participant presented generalized edema, and to perform SDT, it would have been necessary to overcome the safety limits of current density.

Some limitations should be addressed in our study. This was a single-center observational study with healthy participants and critical traumatic brain injury patients; thus, the findings may not be generalizable to different settings and patients. As a result of the SARS-CoV-2 pandemic, the study needed to be stopped before reaching the established sample size. Nevertheless, the power post hoc analysis demonstrated a β error < 20%. Finally, the weight of our sensor (15.5 g) exceeded the recommendation by Ahn et al. (2016) of 13 g as ideal for mechanomyography measurements. However, for the proposed application in our work, which uses accelerometry to determine whether a muscle contraction has occurred or not, the high-frequency components present in the mechanomyography signal were not necessary.

Further studies are required to define the cut-off of the SET and SDT to diagnose ICU-acquired weakness. The use of electroneuromyography may be an adequate tool to be used as the gold standard.

Conclusion

The current study demonstrated that the novel technology used to perform the SET and SDT automatically presents low agreement bias and good to excellent reliability. Furthermore, the results have shown its feasibility and safety. Further studies in different settings with larger sample sizes are necessary to confirm the present findings.

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Author contribution PES and HRS designed the study and drafted the article. PES was responsible for applying the SET and SDT. JRDM, AVQ, and AU selected participants and conducted primary data extraction. EFM participated in the interpretation of results, and PES performed the statistical analysis. All authors revised the article and approved the final manuscript.

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Data Availability The datasets generated and/or analyzed during the current study are available from the corresponding author on request.

Declarations

Ethics approval The study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards approved the protocol (IHBDF, Brasília, Brazil, protocol number 3.629.265).

Consent to participate Participants in the control group signed the informed consent form, and the consent form of participants in the critically ill group was signed by their legal guardian.

Consent for publication This manuscript has not been published elsewhere and is not under consideration by another journal.

Competing interests The authors PES and HRM have patents in neuromuscular electrical stimulation as inventors. They also have equity in Visuri SA and serve as scientific advisors. The remaining authors have no relevant conflicts to disclose.

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6. DISCUSSÃO

Os artigos que compõem o cerne desta tese de doutoramento abordam, de forma coletiva, o desafio persistente e crítico do diagnóstico precoce e preciso de distúrbios eletrofisiológicos neuromusculares (PNDC e/ou MDC), em pacientes críticos adultos, mecanicamente ventilados em UTI. O objetivo primordial desta pesquisa foi refinar métodos eletrodiagnósticos alternativos existentes para triagem de PNMDC, e introduzir abordagens inovadoras para superar as limitações intrínsecas das técnicas tradicionais (p.ex. eletroneuromiografia), pavimentando, em última análise, o caminho para abordagem precoce e melhoria dos desfechos dos pacientes críticos. Esta discussão sintetiza as principais descobertas apresentadas nos quatro artigos, destaca sua interconexão, discute suas implicações para a prática clínica e para pesquisas futuras e, finalmente, enquadra a contribuição significativa desta tese para o campo da abordagem neuromusculoesquelética, diagnóstico, prevenção e reabilitação precoces em cuidados críticos, aproximando mais os médico intensivistas e equipe multiprofissional, sobretudo fisioterapeutas e nutricionistas, do contexto da disfunção neuromuscular da doença crítica, que progride silenciosamente no conjunto das demais disfunções orgânicas das condições graves, em desfavor dos pacientes.

A jornada iniciou-se abordando o artigo principal - *Manuscrito 1 "Diagnostic performance of the Strength-Duration Test for bedside screening of Critical Illness Polyneuromyopathy: a prospective, cross-sectional study"*, que explorou o potencial do TFD como uma ferramenta de avaliação mais abrangente, comparado ao TEDE "convencional" (ponto de corte de cronaxia = 1 ms). Nesse estudo, o TFD exibiu um desempenho diagnóstico clinicamente relevante (AUC = 0,8) para a triagem de PNMDC, com um ponto de corte ótimo de carga elétrica de 600 mC (baseado na área sob a curva ID), e emergiu como um teste mais equilibrado com maior especificidade e acurácia em comparação ao TEDE. A capacidade do TFD de avaliar múltiplos pontos ao longo da curva força-duração, incluindo a cronaxia (portanto o TEDE), oferece uma avaliação mais ampla da excitabilidade neuromuscular, o que se expressa no aumento importante da especificidade e projeta o SDT como ferramenta que deve ser considerada não apenas para triagem diagnóstica de PNMDC, mas também para guiar protocolos personalizados de estimulação elétrica neuromuscular. Essas descobertas validam o TFD como uma promissora ferramenta não-invasiva, customizada, de triagem à beira do leito, oferecendo uma avaliação abrangente que complementa e expande a utilidade do TEDE, posto que o engloba. Ainda, inaugura a necessidade de avaliar limiares eletrodiagnósticos

possivelmente distintos para nervos específicos, em consonância com o racional da neurofisiologia.

Avançamos ainda mais o arsenal diagnóstico com o *Manuscrito 2 "Chronaxie as a diagnostic screening tool for critical illness polyneuromyopathy in ICU: an analysis of diagnostic accuracy in critically ill patients"*, onde nos debruçamos sobre a aplicabilidade diagnóstica da cronaxia - parâmetro chave do TEDE, em ambiente de UTI. Historicamente, os valores de cronaxia para diagnóstico de "denervação muscular" foram estabelecidos em populações ambulatoriais, com um limiar generalizado de 1 ms; e a despeito da amostra analisada por esse estudo primordial (Paternostro-Sluga, 2002), esses resultados vêm sendo aplicados em ambiente de UTI, sem a devida validação. Esse estudo, ancorado em metodologia rigorosa de estudo de acurácia diagnóstica, preenche essa lacuna: percorre amplamente as métricas diagnósticas do TEDE, aplicado em ambiente de UTI (acurácia, sensibilidade, especificidade, valores preditivos e taxas de verossimilhança); avalia a performance do método; e estabelece com rigor estatístico ponto de corte positivo ótimo para a cronaxia do nervo fibular profundo de melhor equilíbrio sensibilidade/especificidade para a triagem de PNMDC em UTI, muito acima do anterior (1.8 ms versus 1 ms). Esta descoberta é transformadora, enfatizando que o complexo meio fisiopatológico da doença crítica altera significativamente a excitabilidade neuromuscular, exigindo limiares diagnósticos específicos para a UTI. Este artigo não apenas validou o TEDE como uma ferramenta de triagem diagnóstica de PNMDC com desempenho aceitável (AUC=0.7), mas, mais importante, forneceu as métricas diagnósticas específicas tão necessárias para sua adequada aplicação em pacientes críticos.

Introduzimos uma mudança de paradigma em nossa compreensão da manifestação da PNMDC no *Manuscrito 3 "Beyond Symmetry: The Clinical Significance of Bilateral Assessments in Critically Ill Patients with Neuromuscular Electrophysiological Disorders"*, no qual desafiamos a descrição categórica de apresentação simétrica dessa disfunção neuromuscular. Através dos registros bilaterais de PAMC, nosso estudo revelou uma incidência clinicamente significativa de assimetria (39%) na fase inicial de estabelecimento dessa enfermidade, com base em critério eletrodiagnóstico (e não apenas estatístico, como em estudos anteriores). Documentamos divergência diagnóstica ocorrendo em 12% dos participantes, nos quais a disfunção neuromuscular poderia ter sido ignorada por uma avaliação unilateral, retardando a identificação e abordagem precoces. Além disso, apontamos possível conexão entre lateralidade e lesões focais do SNC com axonopatia assimétrica, sugerindo um risco atribuível de 17% de assimetria da axonopatia nesse perfil de pacientes. Esta descoberta

inovadora ressalta a importância clínica da obrigatoriedade de avaliações eletrofisiológicas bilaterais em pacientes de UTI, alterando fundamentalmente os protocolos de triagem recomendados em função de economicidade, a fim de prevenir erros diagnósticos e fornecer uma imagem mais precisa do estado neuromuscular do paciente.

Finalmente, a questão fundamental da subjetividade e reprodutibilidade nas avaliações eletrodiagnósticas em função da dependência do operador na aplicação dessas ferramentas alternativas – TSD e TEDE foi abordada no *Manuscrito 4 "Towards innovative electrodiagnosis tests to investigate neuromuscular excitability dysfunction in critically ill patients: an agreement study"*. Nessa publicação, documentamos o sucesso da automatização do TFD e do TEDE, com robusta concordância e confiabilidade de método inovador para a realização desses testes, com menor dependência do operador, anulando vieses de subjetividade e reprodutibilidade interexaminadores. Este avanço é crucial, pois mitiga a variabilidade em função da subjetividade e dependência do examinador para detectar contrações mínimas durante o teste, particularmente no ambiente desafiador da UTI, onde a cooperação do paciente representa uma barreira. Ao apresentar e validar um sistema automatizado, objetivo e factível de avaliação eletrodiagnóstica, este estudo documentou uma opção tecnológica para triagens diagnósticas mais precisas de excitabilidade neuromuscular na doença crítica.

Em conjunto, esta tese oferece consideráveis avanços na triagem eletrodiagnóstica precoce, não-invasiva e beira-leito da PNMDC em UTI. Em primeiro lugar, oferece e valida, com rigor metodológico, o TFD como ferramenta eletrodiagnóstica alternativa, estabelecendo métricas diagnósticas completas, ponto de corte de carga elétrica e performance do teste em UTI comparado ao TEDE, enfrentando questões de subjetividade e reprodutibilidade, por meio da automação do teste (possibilidade ainda não tangenciada na eletroneuromiografia). Em segundo lugar, redefine os parâmetros diagnósticos do TEDE, descrevendo as métricas diagnósticas para além da sensibilidade e definindo ponto de corte de cronaxia em UTI, transcendendo os valores generalizados de pacientes ambulatoriais. Em terceiro lugar, sinaliza atenção quanto ao fundamento central da manifestação simétrica característica à clínica da PNMDC, defendendo necessariamente a avaliação bilateral pela possibilidade de assimetria e divergência diagnóstica no estabelecimento inicial dessa enfermidade; abrindo ainda, novo campo de investigação sobre a complexa interação entre patologias do SNC e manifestações neuromusculares periféricas em pacientes críticos. Por fim, em quarto lugar, não menos relevante, trabalhamos especificamente com testes eletrodiagnósticos aplicados a nervo específico, no caso, ao nervo fibular profundo, propondo alinhamento dessas alternativas

propedêuticas com o racional da neurofisiologia, bem estabelecido para a eletroneuromiografia (referência).

As **implicações clínicas** imediatas desta pesquisa são substanciais, a começar por fornecer meios de atenção assistencial à disfunção neuromuscular, até o momento ainda despretigiada dentre as prioridades da miríade de cuidados e vigilância em UTI, em função de barreiras substanciais quanto a sua identificação precoce e monitoramento. As ferramentas TFD e TEDE validadas (automatizadas ou manuais), juntamente com as métricas diagnósticas específicas para o nervo fibular profundo em pacientes críticos, oferecem aos profissionais ferramentas objetivas, não invasivas, beira-leito e custo-efetivas para a triagem diagnostica precoce da PNMDC. Dessa forma, facilita o diagnóstico precoce e oportuno, crucial para iniciar intervenções de reabilitação precoces, potencialmente reduzindo a duração da VM, acelerando a recuperação funcional e mitigando o ônus de longo prazo da FA-UTI, com inestimáveis ganhos assistenciais, humanos, familiares, trabalhistas e financeiros para todos os partícipes (paciente, família, equipe, operadoras de saúde, empregadores, etc.). Além disso, o imperativo da avaliação bilateral, destacado pela prevalência até então desconsiderada de assimetria no desenvolvimento inicial da PNMDC, com possibilidade de divergência diagnóstica, garante uma triagem mais abrangente e precisa, prevenindo diagnósticos perdidos (falsos negativos), que poderiam afetar profundamente o cuidado e seguimento desses pacientes.

Embora esta tese apresente avanços significativos, é importante complementar **limitações** já exploradas nos manuscritos. O projeto foi unicêntrico e transversal, o que limita a generalização dos resultados, impede o seguimento longitudinal da doença e o impacto direto do diagnóstico precoce nos desfechos clínicos de médio e longo prazo (por exemplo, mortalidade, tempo de internação hospitalar, tempo de VM, manifestações da SPCI). Além disso, o diagnóstico definitivo de PNMDC, seja por ENMG ou por biópsia nervosa e/ou muscular não foi sistematicamente realizado, sendo mesmo inviável, posto os desafios de conduzir tais procedimentos em pacientes não cooperativos e criticamente enfermos; baseando-se estritamente no PENT - modelo de ECN simplificado, como padrão-ouro.

Perspectivas futuras devem incluir a reprodutibilidade desses achados de acurácia diagnóstica por meio de estudos prospectivos multicêntricos, em larga escala, em diferentes populações de UTI, mesmo em diferentes possibilidades diagnósticas, para a melhor validação das métricas e limiares diagnósticos propostos para essas duas ferramentas eletrodiagnósticas. Estudos longitudinais são essenciais para rastrear as mudanças dinâmicas nos parâmetros de

carga elétrica (TFD) e cronaxia (TEDE) ao longo do tempo, correlacionando esses perfis com desfechos clínicos importantes e trajetórias de recuperação funcional. Outros nervos, em membros superiores e inferiores, devem ser somados à avaliação e aplicabilidade dessas alternativas de triagem eletrodiagnóstica, estabelecendo limiares eletrofisiológicos específicos, em consonância com o racional da neurofisiologia para a ENMG. Uma exploração mais aprofundada dos mecanismos subjacentes à apresentação assimétrica da axonopatia na PNMDC, particularmente a interação entre lateralidade e lesões do SNC, e o estabelecimento da disfunção neuromuscular em pacientes críticos. A integração dessas ferramentas eletrodiagnósticas com outras tecnologias emergentes, como imagens avançadas ou biomarcadores, também poderia fornecer uma compreensão mais holística da neuromiopatia da doença crítica. Em última análise, a próxima fronteira envolverá a demonstração do impacto direto dessas estratégias alternativas aprimoradas de diagnóstico precoce, nos desfechos centrados no paciente e na utilização de recursos de saúde, otimizando a prevenção, o diagnóstico e o cuidado precoce da disfunção neuromuscular nos primeiros dias de internação em UTI.

7. CONCLUSÃO

1. O Teste de Força Duração de Estímulo, baseado na análise de área sob a curva intensidade/duração de estímulo (carga elétrica), apresenta-se como alternativa eletrodiagnóstica viável para triagem precoce, não invasiva, beira-leito de PNMDC em UTI, com métricas diagnósticas mais favoráveis, comparado ao TEDE, que aliás complementa, posto que o TEDE representa ponto único da curva ID – a cronaxia;
2. O Teste Eletrodiagnóstico de Estímulo, baseado na análise de cronaxia, constitui ferramenta eletrodiagnóstica viável para triagem precoce, não invasiva, beira-leito de PNMDC em UTI, tendo suas métricas diagnósticas amplamente descritas e com ponto de corte ótimo positivo estabelecido em valor bem acima do validado previamente em pacientes ambulatoriais;
3. Os métodos simplificados ou alternativos de avaliação eletrodiagnóstica periférica em pacientes críticos internados em UTI para triagem de PNMDC, devem necessariamente ser realizados bilateralmente, devido relevância clínica da assimetria eletrodiagnóstico na fase inicial dessa síndrome, mesmo se tratando de enfermidade conceitualmente de manifestação clínica simétrica;

4. O TFD e o TEDE podem ser automatizados pelo uso de dispositivo inovador, com resultados semelhantes à aplicação manual por operador especializado, contornando viés de reprodutibilidade de resultados e intersubjetividade.

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9. ANEXOS

9.1. ANEXO 1. Normas Editoriais Manuscrito 1

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